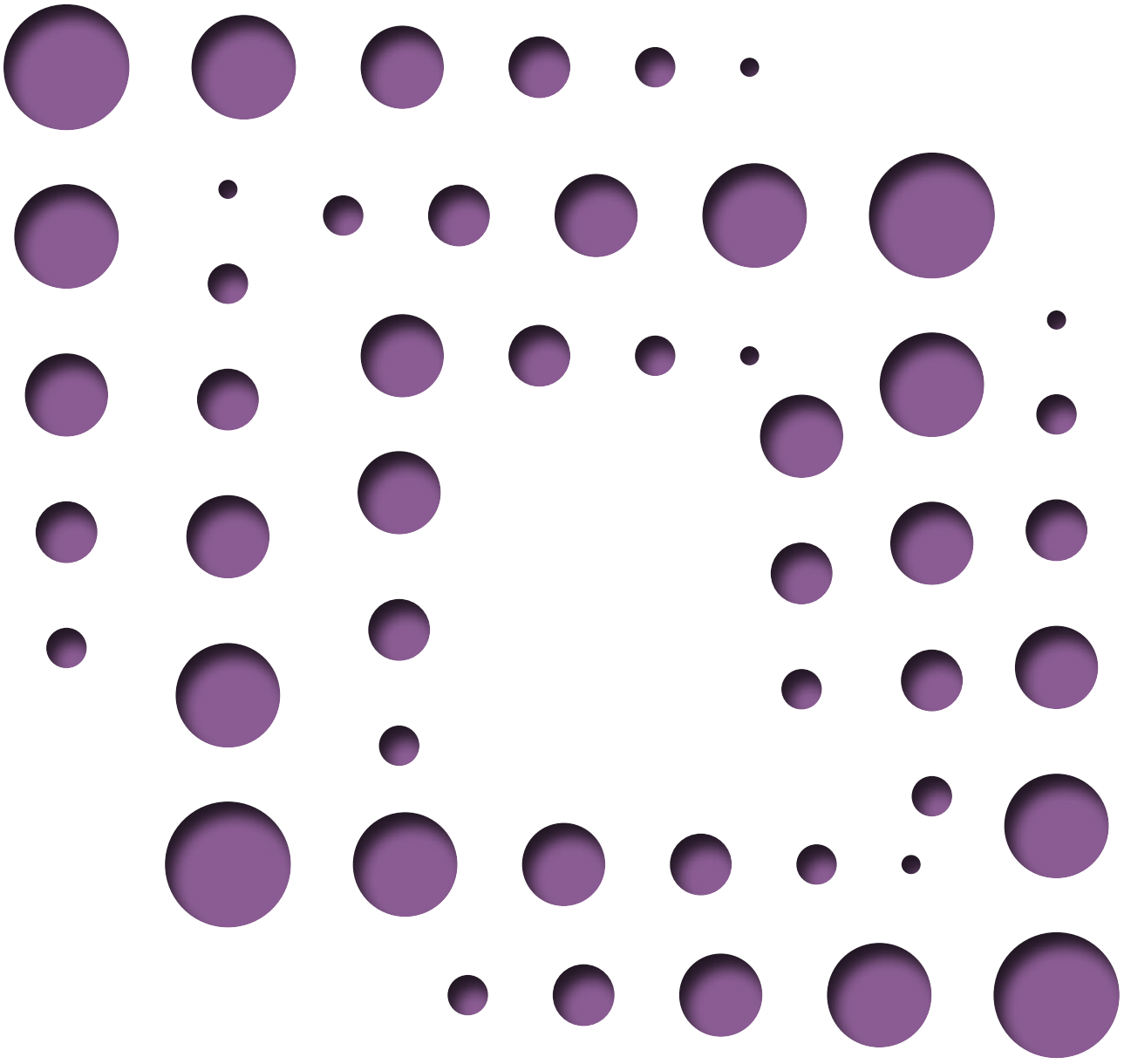

Scientific Annual Report 2017

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

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Contents

Scientific Annual Report 2017

Director of Research
René Medema

Introduction

I am pleased to present our Scientific Annual Report that contains an overview of the scientific achievements of the Netherlands Cancer Institute in 2017. More background information on our research programs and principle investigators can be found on our website (www.nki.nl) or in our Scientific Brochure that is available for download on our website.

The Netherlands Cancer Institute is a Comprehensive Cancer Center, and the only Dutch center to officially carry this title. We combine a dedicated cancer hospital and cancer research institute in a single organization. Our hospital currently has 220 beds, 12 state of the art operation theatres, an outpatient clinic that received approximately 110.000 patient visits in 2017, a large radiotherapy department and an extensive infrastructure for clinical research that includes clinical data management and a large array of diagnostic facilities. Over the years, the hospital has built a large repository of patient data and a large collection of tumor and normal tissues. Our clinical research spans across medical, surgical and diagnostic oncology, radiotherapy, pharmacology, epidemiology, psychosocial oncology and research into cost effectiveness of health care and efficiency of planning and organization. Our hospital has seen steady growth in patient numbers over the last years, with an average annual growth of 4%.

To accommodate this growth, we have in recent years been expanding. Our building activities have increased the capacity of our outpatient clinic and intensive care, as well as the number of operation rooms. In 2017, we opened our new Center for Survivorship and Supportive Care to centralize all of our in-house activities for treatment-related health problems. Of the 35000 patient we treat annually, about 9000 need additional care (for anxiety, fatigue, cognitive functions, etc.) for treatment-related health issues. To continue to accommodate our overall growth, we will need to plan additional expansions of our clinical capacity and will commence the construction of a new Pharmacy and Pharmacological Research Center in 2018.

We again managed to end 2017 with a profit for the hospital. But it is clear that the current workload is a serious challenge for our personnel. Our excellent reputation is attracting more patients than we can possibly treat due to limitations in physical space and personnel. This, combined with tighter budgets from health insurance companies, is putting an increasing strain on all of our activities. Our clinical research program suffers from the limited time that clinicians can dedicate to research, and this remains a serious challenge for our institute. We currently lack resources to invest in all of the opportunities for improved patient benefit that present themselves each year. In 2017, we have invested all of our available resources in our research themes, and again made a number of strategic recruits to enforce them. We are very thankful to the Dutch Ministry of Health, Welfare and Sport and to the Dutch Cancer Society (KWF Kankerbestrijding) for their generous institutional funding (figure 1). Our funding is still in large part (~63%) coming from external project grants, donations and short-term research agreements with third parties. This is possible because our principal investigators continue to be very competitive in obtaining this type of funding, but the relatively low ratio of core funding for our institute provides us with big challenges to maintain sufficient manpower in the underlying infrastructure.

HIGHLIGHTS

It is impossible to provide a complete overview of the total impact generated by our institute in 2017 in this introduction. Many of the highlights can be found in reports of the individual group leaders further on in this annual report and on our website. I have chosen to mention a few highlights of our 5 research themes below.

As for the institute as a whole, I am very pleased that our accreditation as Comprehensive Cancer Center by the Organization of European Cancer Institutes (OECI) (http://www.oeci.eu) was renewed in 2017 after a successful audit. The Netherlands Cancer Institute is the only center in the Netherlands that has received this accreditation, and this was the second time we successfully applied for it. In addition, our institute successfully applied for the designation "Comprehensive Cancer Center of Excellence" at the European Academy of Cancer Sciences (www.europeancanceracademy.eu). The Cancer Research UK Cambridge Cancer Center and the Netherlands Cancer Institute were the first two centers in Europe to receive this designation.

MOLECULAR ONCOLOGY

The Estrogen Receptor reprogrammed

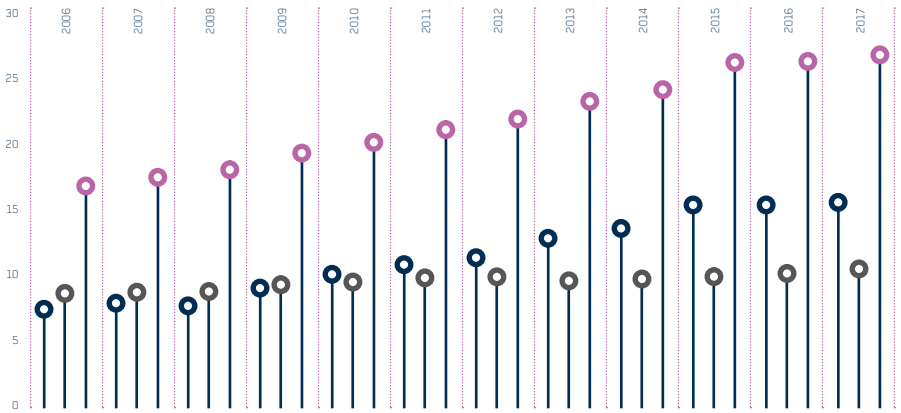
A side effect of breast cancer treatment with the drug tamoxifen is the stimulation of endometrial cancer development in some patients. The group of Wilbert Zwart identified a potential explanation for this undesired phenomenon. With drug treatment, the Estrogen Receptor in the endometrial tissue is reprogrammed to DNA sites normally only found in breast cancer, activating a 'breast cancer-like' phenotype in these tamoxifen-induced endometrial tumors (PNAS, February 2017).

Coining a term: epi-transcriptomics

Using genome-wide approaches of gene expression measurements, Boris Slobodin and Ruiqi Han from the oncogenomics group of Reuven Agami uncovered a strong link between RNA production in the nucleus and protein production in the cytosol of cells.

FIGURE 1

CORE RESEARCH FUNDING THE NETHERLANDS CANCER INSTITUTE - ANTONI VAN LEEUWENHOEK HOSPITAL BY THE DUTCH CANCER SOCIETY AND THE MINISTRY OF HEALTH, WELFARE AND SPORT IN THE PERIOD 2006 – 2017 IN MILLION EUROS.



- DUTCH CANCER SOCIETY
- MINISTRY OF HEALTH, WELFARE & SPORT*
- TOTAL

* EXCLUDED ARE THE REIMBURSEMENT FOR INTEREST AND DEPRECIATION OF BUILDINGS

This newly-discovered form of communication involves specific RNA modifications and was therefore coined epi-transcriptomics. As cancer is a disease of aberrant gene expression, the team speculates that epi-transcriptomics is used by cancer cells to promote aggressive tumor behavior (Cell, April 2017).

Cohesin puts limits to loop formation

The labs of Benjamin Rowland and Elzo de Wit discovered that WAPL-mediated cohesin release limits the degree to which chromatin loops can be enlarged. Cohesin turnover on DNA hereby allows the 3D genome to be highly dynamic through the constant formation, loss, and reformation of loops. While cohesin plays a key role in the formation of these loops, it rather counteracts the separation of the nucleus into active and inactive compartments (Cell, May 2017).

Unraveling the mechanisms of drug addiction

Cancer cells can become addicted to the drugs that are supposed to eliminate them and studies have suggested that this dependency can be used against them because drug-addicted cells massively die when treatment is suddenly stopped. Postdoc Xiangjun Kong in the laboratory of Daniel Peeper in the new Division of Molecular Oncology & Immunology now unraveled the mechanistic principles of drug addiction in cancer. His findings may guide therapies that exploit the addiction phenotype, particularly alternating therapies whereby the drug holiday is immediately followed by a second, rational treatment (Nature, October 2017).

New technique solves old riddle

Marcus Brockmann, in the group of Thijn Brummelkamp, has developed a powerful new approach to study cellular processes using DNA sequencing that enables efficient inactivation of human genes by a single mutation (Nature, May 2017). The new technology was immediately put to use by Joppe Nieuwenhuis and Vincent Blomen to address a 40-year old question in cell biology. They found the long-sought enzyme that cuts a tyrosine off the microtubules, which is the initiating event of the cycle that modifies the building blocks of the cell skeleton. (Science, November 2017). Brummelkamp: 'This knowledge could be relevant to further understand the processes of mitosis, cell migration and cancer development. It is already found that the invasive front in some tumor tissues, where cells are migrating most actively, contains a high amount of detyrosinated tubulin.'

PRECISION MEDICINE

When is breast cancer not really cancer?

Women with a precancerous stage of breast cancer, DCIS (Ductal carcinoma in situ), are now all treated as if they have cancer. However, in the majority of cases, DCIS will not progress to breast cancer. The big problem is: at present, we cannot distinguish between the women with DCIS who will develop cancer, and those who will not. Pathologist Jelle Wesseling has received a multimillion grant (GBP 15 million) from Cancer Research UK and KWF (Grand Challenge Award) to learn how to how to distinguish harmless from hazardous DCIS, thus saving thousands of women from an unnecessary, burdensome treatment.

Identifying biomarkers for colorectal cancer

The fecal immunochemical test for detecting hemoglobin is used widely for noninvasive colorectal cancer screening, but its sensitivity leaves room for improvement. The group of Gerrit Meijer aims to identify novel protein biomarkers in stool that outperform or complement hemoglobin in detecting colorectal cancer and advanced adenomas. Mass spectrometry of stool samples identified novel candidate protein biomarkers for CRC screening. Proof of concept that such proteins can be detected with antibody-based assays in small sample volumes indicates the potential of these biomarkers to be applied in population screening. (Annals of Internal Medicine, November 2017).

Getting the dose right in every patient

Fluoropyrimidines are widely used in the treatment of a variety of cancer types, and research from the groups of Schellens and Beijnen has demonstrated that dosing of fluoropyrimidines should be adjusted based on the genotype of the individual patient. Based on their work a modification of the medical standards was approved in 2017 by the Netherlands Medicines Regulatory Agency (College ter Beoordeling van Geneesmiddelen; https://www.cbg-meb.nl) and the European Medicines Agency (EMA; www.ema.europa.eu/ema/).

High dose chemotherapy for breast cancer

Based on research performed by Sjoerd Rodenhuis and Sabine Linn, the Ministry of Health, Welfare and Sports provisionally authorized high dose chemotherapy for stage 3 BRCA-like breast cancer. In the Netherlands alone, approximately one hundred young women are diagnosed with this form of cancer. Using conventional treatments only 30-40% of them remains disease-free at 10 years after start of treatment, while the high-dose chemotherapy brings that percentage up to almost 85%.

IMMUNOTHERAPY

PD-L1 turns out to have a buddy

Because of its central role in controlling T cell activity, PD-L1 on cancer cells has become the centre of attention in immunotherapy, and treatments that block this checkpoint are already used widely in patients. Ton Schumacher and others now discovered that this well-studied protein turns out to be controlled by a partner, CMTM6, a previously unexplored molecule that is now suddenly also a potential therapeutic target. Immunotherapy is an exciting new way of treating cancer. Schumacher: 'You can imagine that blocking CMTM6 could reactivate immune cells just like the currently used PD-L1 blockers can. Blocking both molecules could even be superior. It remains to be seen whether it will eventually deliver a therapy, but this is clearly something we are eager to test.' (Nature, August 2017).

ERC Advanced Grant for Ton Schumacher

Ton Schumacher received an ERC Advanced Grant of 2.4 million euros for his research into the sensitivity of human tumors to T cell attack. Schumacher will use the grant to investigate different attack mechanisms that are employed by tumor-specific T cells. He suspects that, next to an already well-known mechanism, T cells can also kill cancer cells by secreting compounds called cytokines. Schumacher will look at the interactions between T cells and cancer cells in both untreated tumors and in tumor tissue of patients who have received immunotherapy. In addition, this project will focus on resistance against immunotherapy with checkpoint inhibitors. Such therapy resistance can arise because of changes in the T cells, but also because of changes in the cancer cells. Schumacher is interested in the latter. He suspects that his research will uncover a number of thus far unknown resistance mechanisms. Next to this, he wants to elucidate the role of a protein complex called PD-L1M1 that he has recently identified in therapy resistance against PD-L1 checkpoint inhibitors.

IMAGE-GUIDED INTERVENTIONS

Radiotherapy guided by real-time tumor imaging

In 2017, the radiotherapy group of Marcel Verheij started its first clinical study on MRI-sequence optimization and workflow development for treatment guidance, using the integrated MRI scanner of the MRI-Linac system, which combines radiotherapy and real-time imaging.

Transcriptomics-guided radiotherapy

At the ESTRO meeting in May in Vienna, Paul Essers, bioinformatics postdoc in the Verheij/Vens group, received the prestigious Donal Hollywood Award for his research on

prediction of DNA repair defects in head and neck cancer. Paul uses machine learning to predict treatment response and discover tumor sub-types from transcriptomics data of head and neck squamous cell carcinoma patients.

Implementing the Papillon

In December, our hospital introduced the Papillon brachytherapy in the clinic, as first center in the Netherlands. The Papillon delivers high local and superficial doses of radiation for the organ-preserving treatment of small, residual or recurrent rectal tumors.

Chair of adaptive radiotherapy

On August 1st, Jan-Jakob Sonke was appointed professor in adaptive radiotherapy at the University of Amsterdam. This chair was established on behalf of the Netherlands Cancer Institute.

SURVIVORSHIP

Predicting heart failure risk in Hodgkin lymphoma survivors

In a case-control study, Rianne van Nimwegen in Flora van Leeuwen's group examined treatment factors explaining the increased risk of heart failure in survivors of Hodgkin lymphoma. In a case-control study, a nonlinear radiation dose-response relationship with upward curvature was derived for mean heart dose (MHD). These findings will now be used to predict CVD risk for HL patients before treatment, during RT planning and during follow-up.

Online cognitive behavioral therapy works

Breast cancer survivors who suffer from serious sexual dysfunction can benefit from internet-based cognitive behavioral therapy. This is demonstrated in a study of the research team of behavioral scientist Prof. dr. Neil Aaronson (Journal of Clinical Oncology, February 2017).

QUALITY OF RESEARCH

The quality of our research can be monitored in several ways. First of all, objective bibliometric parameters (citations and impact of scientific articles published by NKI staff) demonstrate that our scientific productivity, as measured in numbers of citations, is steadily increasing over time (table 1). It is therefore gratifying to note that we manage to maintain our position at the international forefront of cancer research.

Secondly, our prominent international standing in cancer research is reflected by the frequency with which our staff members are invited to present at international meetings and in the awards and grants that they obtain. We score high on all of these accounts. See the 'honors and appointments' section for the most prestigious grants and awards our researchers received in the past year. The NKI is also a member of a number of European networks for the most excellent centers in the field of cancer research and life sciences, including CancerCoreEurope and EULife.

HONORS AND APPOINTMENTS

The NKI cannot award university degrees, but many of our staff members hold honorary part-time chairs at Dutch universities. This allows them to award PhD degrees to graduate students who receive their training at the Netherlands Cancer Institute. Currently, 36 staff members have professorships at one of the Dutch universities. Secondly, our prominent international standing in cancer research is reflected by the frequency with which our staff members are invited to present at international meetings and in the prestigious appointments, awards and grants they obtain.

Jelle Wesseling received a Grand Challenge award from Cancer Research UK and the Dutch Cancer Society to solve the clinical problem affiliated with DCIS. Reuven Agami, Wilbert Zwart and Lodewyk Wessels of the Netherlands Cancer Institute received a ZonMW TOP grant for genetic research. Agami and Zwart got 675.000 Euro to search for enhancer elements that influence gene activity in hormone-sensitive tumor. Wessels received, together with Mark van der Wiel of the VU Medical Center, 675.000 Euro to implement Big Data techniques in the search for new biomarkers. Thijn Brummelkamp received a Vici-grant of 1.5 million Euro with the ultimate goal to build a 'phenotype map', that shows the complex network of genes and their influence on distinct phenotypical properties of human cells. The European Research Council awarded Ton Schumacher with an ERC Advanced Grant and awarded both Tineke Lenstra and Fabricio Loayza-Puch with an ERC Starting grant. Lenstra will study a phenomenon called transcriptional bursting. Loayza will use his grant to investigate the tumor microenvironment (TME). Martijn Stuiver, physiotherapist in our clinic and researcher in the field of supportive care and revalidation after cancer, was appointed as lector at the Amsterdam University of Applied Sciences. Jan-Jakob Sonke was appointed Professor by special appointment of Adaptive Radiotherapy at the University of Amsterdam-Academic Medical Center (UvA-AMC).
Jan Schellens received the Saal van Zwanenberg Honorary Award from the Royal Holland Society of Sciences and Humanities (KHMW). Lotte Elshof, from Jelle Wesseling's group, was awarded the Jan Hendriks Prize for her research into DCIS. Newly appointed biophysicist Jacco van Rheenen won the Jozef Steiner Award, a prestigious scientific award consisting of 1 million Swiss Franc, and microscopy expert Bram van den Broek won the Nikon Small World Competition.

Next to the special grants mentioned above several other NKI postdocs and group leaders have received competitive grants from national and international organizations. Staff of the NKI also fulfilled numerous functions in national and international organizations, on boards of scientific journals, as members of study sections, of site visit committees, and as organizers or co-organizers of scientific meetings, workshops and conferences.

TABLE 1

SHORT TERM CITATIONS AND IMPACT OF SCIENTIFIC ARTICLES PUBLISHED BY THE NETHERLANDS CANCER INSTITUTE RESEARCH STAFF 2002 - 2016

PUBLICATION YEAR	PUBLICATIONS	CITATIONS	CITATIONS/ PUBLICATIONS	IMPACT
2003	366	5094	13,9	2122
2004	348	5267	15,1	1882
2005	405	6350	15,7	2461
2006	435	6336	14,6	2608
2007	430	5605	13,0	2969
2008	442	5657	12,8	2590
2009	511	7904	15,5	3074
2010	481	8788	18,3	2841
2011	459	8651	18,8	3110
2012	573	9268	16,2	3333
2013	512	8989	17,6	3228
2014	596	9599	16,1	3935
2015	659	19618	29,8	5234
2016	795			5373
2017	740**			5927**

* SINCE 2014 A NEW STANDARD WAS USED TO PERFORM THE CITATION AND IMPACT FACTOR ANALYSES. CONSEQUENTLY THE NUMBERS CAN DIFFER FROM THE PREVIOUS YEARS.

** ANALYSIS WAS PERFORMED IN FEBRUARY 2018. DATA CAN BE SUBJECT TO CHANGE.

TABLE 2

CLINICAL TRIALS PERFORMED AT THE NETHERLANDS CANCER INSTITUTE THAT WERE BASED ON THERAPEUTIC CONCEPTS DEVELOPED FROM OUR OWN FUNDAMENTAL AND TRANSLATIONAL RESEARCH PROGRAM (SELECTED FROM CLINICAL TRIALS THAT WERE ONGOING IN 2014 AND ONWARDS).

AVL CODE	REFERENCE	NOVEL TREATMENT	TUMOR TYPE
M06CRI	1-3	Chemoradiotherapy + Surgery	Resectable Gastric Cancer
P06OVH	4,6	Secondary Debulking with HIPEC	Ovarian Canc
P07CB	7,8	Cognitive Behavioral Therapy & Physical Exercise	Breast Cancer
P08TIM	9	Rapid Genetics	BRCA mutant Breast Cancer
M08PBI	10	Partial Accelerated Preoperative Irradiation	Early Stage Operable Breast Cancer
M09TNM	11-13	Neo-adjuvant Chemotherapy	Triple-Negative Breast Cancer
P09PHY	14	Physical Exercise	Breast & Colon Cancer
M09PBO	15	FDG-PET-based Boosting RT	Inoperable NSCLC
N10DMY	16	Dose reduction of preoperative RT	Liposarcoma
N11ORL	17	Radiotherapy ± Cisplatin + PARPi	Locally Advanced NSCLC
M11ART	18	Cisplatin + Adaptive High Dose Radiotherapy	Locally Advanced Oropharynx, Oral Cavity or Hypopharynx SCC
M11VOL	19	MLD-based SBRT	Inoperable + Peripheral NSCLC
P11SIG	20,21	Problem checklist	Breast & Colon Cancer
M11TCR	22	MART-1 TCR gene therapy	Metastatic Melanoma
M12LGX	23	EGFRi + BRAFi ± PI3Ki	Mutant BRaf Colorectal Cancer
M12PHA	24	Hippocampus Avoidance PCI	SCLC
N12HYB	25	Combined Stereotactic and Conventional Fractionated RT	Stage II-III NSCLC
N12RES	26	In vivo response assessment	Liver and Colorectal Cancer
N12IGP	27	Intra-operative fluorescence during prostate surgery	Prostate
M13DPT	23	EGFRi + BRAFi ± MEKi	Mutant BRaf Colorectal Cancer
M13DAP	28	Pan-HERi + MEKi	Mutant KRas Colorectal Cancer
N13ORH	17	Radiotherapy + PARPi	Laryngeal and HPV-Negative Oropharyngeal SCC
N13ORB	17	Radiotherapy + PARPi	Locally Advanced Triple-Negative Breast Cancer
M13TNB	11-13,29-33	Paclitaxel ± VEGFi	BRCA1-like Breast Cancer
M13PSN	34	ICG-99mTc-nanocolloid for sentinel node surgery	Prostate Cancer
N13NAV	35	Surgical Navigation	Colorectal Cancer
M14TIL	36	TIL vs. Ipilimumab	Metastatic Melanoma
M14LTK	28	Pan-HERi + MEKi	Mutant KRas Colorectal Cancer
M14REV	37-39	Carboplatin + PARPi	Advanced BRCA- Breast Cancer
M14POS	40,41	Tamoxifen + PI3Ki	ER/PR+ and HER2- Breast Cancer
N14HPV	42,43	DNA vaccination	HPV16+ Vulvar Neoplasia
N14RCS	44	Smart tools during surgery	Colorectal Cancer
M14AFS	28	Afatinib + Selumetinib	Advanced Mutant KRas, PIK3CA wildtype Colorectal, NSCLC or Pancreatic Cancer
M14WLC	23	WNT974 + LGX818 + Cetuximab	Mutant BRAF Colorectal Cancer with Wnt Pathway mutations
N14OPC	45	Ipilumimab + Nivolumab	Melanoma
M14PDP	46,47	Genotype-directed dosing of Fluoropyrimidines	Various Neoplasms
N14SUS	48,49	Sentinel node mapping using SPECT	Head and Neck Cancer
N14LMN	34,35,50,51	Lymphatic mapping of the neck with ICG-nanocolloid	Oral Cavity Malignancies
M14HSN	34,35,50,51	Sentinel node mapping with ICG-99mTc-nanocolloid	Bladder Cancer
M14SEA	52	Strengtening Exercises using the Swallowing Exercise Aid	Head and Neck Cancer
M14HUM	53	Organoid Biobank for drug discovery	Solid Tumors
M14PRT		Premolizumab + SBRT vs. premoluzimab	Advanced/metastatic NSCLC
M15CRI	1-3	Preoperative chemo vs chemoradiotherapy vs chemo + chemoradiotherapy	Resectable Gastric Cancer
M15PAP	10	Pre- vs postoperative accelerated partial breast irradiation	Early stage breast cancer
N15MML	54	Magnetic Marker localization to guide surgery	Non-palpable breast cancer

M15PAS	55,56	Panopanib + RT	Non-metastatic Sarcoma
M15MSR	57	DNA-PKi + Radiotherapy	Advanced Solid Tumors
N15DOP	58	ModraDoc + hormone treatment + intensity-modulated RT	Early stage prostate cancer
M15 OLY	59	Hypofractionated focal ablative radiotherapy	Prostate cancer
N15 IMP		Pembrolizumab vs intermittent dual MAPK inhibition + pembrolizumab	B-Raf muant melanoma
N16PZN	60	Novel formulation of pazopanib	Solid tumors
M16HFL	59	Hypofractionated focal ablative radiotherapy	Prostate cancer
M16OPN	45	Neo-adjuvant Ipilumimab and Nivolumab	Melanoma
N16UMB		MR guided Adaptive Radiation Therapy.	Solid tumors
N16PRB		Preoprative breast irradiation	Breast Cancer
N16STS		Biobank of patient-derived xenografts of soft tissue sarcomas	Soft tissue sarcomas
N16NEON		Personalized adaptive T-cell therapy	Various solid tumors
N17MRB		Monitoring RT-induced MRI changes of Brain Tumors	Brain Tumors
M17SDM		Decision aid for breast cancer and DCIS patients	Breast Cancer

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OUTLOOK AND ACKNOWLEDGEMENTS

For the last decennia, our Institute has been at the international forefront in cancer research and innovative cancer treatments. It has demonstrated to be able to maintain that position, despite the difficult economic situation of the last few years. We have been very successful in obtaining external grants for our research and I am convinced that we will continue to do so. Provided that we can match this with a healthy ratio of core funding, I am convinced that the Netherlands Cancer Institute can continue to deliver important breakthroughs that will prove beneficial in the treatment of cancer. Particularly in a time when our ever-growing molecular understanding of cancer meets up with a new generation of anti-cancer drugs that target well-defined nodal points in the cancer cell. This calls for a more individualized treatment of cancer, in which molecular pathology in the form of a genetic and/or immunological fingerprint of the tumor is extensively used in making clinical decisions how to treat the individual patient. Success in this area will critically depend on a close collaboration between basic and clinical research; where basic research can provide the concepts for new drug combinations that can be taken to the clinic, and vice-versa, where response failure of a genetically and immunologically defined tumor in the clinic can be taken to the lab to identify alternative strategies. Success in this area requires that we further optimize the links that exist between research and clinic. The fact that the Netherlands Cancer Institute has integrated research and clinic in a single Comprehensive Cancer Center provides us with the ideal setting to facilitate this collaboration, and the examples of therapeutic concepts that we have brought to the clinic (table 2) provide solid proof of the added advantage of this integral model. We are actively recruiting new principal investigators with highly creative and innovative research programs aimed at groundbreaking research to continuously improve ourselves for the benefit of our patients. To uncover new insights in cancer biology, develop new tools to study cancer, and to develop novel therapeutic strategies that can benefit patients.

I want to end by thanking all of our employees and everyone that supported us. Ever since our creation in 1913 our organization has received enormous support from our highly-motivated employees, volunteers and sponsors. I also want to thank the Dutch Cancer Society (KWF Kankerbestrijding), that has been a very significant sponsor of our research ever since its creation in 1948; the Ministry of Health, Welfare and Sport, that provides a substantial core grant to our Institute and has provided the funds to renovate our research facilities; and all of those individuals that provided us with financial, moral and practical support. Their support is making it possible for us to continue to strive for better treatments to improve the outlook of cancer patients. And last but not least, I would like to extend my sincere gratitude to all of our patients willing to participate in our clinical studies; they are vital to the progress that we can make.

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Key publications

Agasi-Idenburg SC, Thong MSY, Stuiver MM, Aaronson NK. Comparison of symptom clusters associated with fatigue in older and younger survivors of colorectal cancer. J Supp Care Cancer 2017; 25:625-632

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Hummel SB, van Lankveld JJDM, Oldenburg HSA, Hahn DEE, Kieffer JM, Gerritsma MA, Kuenen MA, Bijker N, Borgstein PJ, Heuff G, Lopes Cardozo AMF, Plaisier PW, Rijna H, van der Mei S, van Dulken EJ, Vrouenraets BC, Broomans E, Aaronson NK. Internet-based cognitive behavioral therapy realizes long-term improvement in the sexual functioning and body image of breast cancer survivors. J Sex Marital Therapy 2017 (in press)

Behavioral interventions in clinical oncology and Health-related quality of life assessment

This research line has two primary foci: (1) development and testing of behavioral and psychosocial interventions to reduce symptom burden and improve the HRQL of patients with cancer; and (2) development and use of health-related quality of life (HRQOL) assessments in clinical research and clinical practice.

Factors associated with specific DSM-IV sexual dysfunctions in breast cancer survivors: a study of patients and their partner

Using baseline data from a clinical trial of online cognitive behavioral therapy for sexual dysfunction among women with breast cancer survivors, we evaluated: 1) patient-related and clinical factors that are associated with a) specific DSM-IV sexual dysfunctions and b) the level of sexual functioning and sexual distress as reported by BCS; and 2) the association between the sexual functioning of BCS and that of their partners. In this sample of 169 BCS, the most prevalent female sexual dysfunctions were hypoactive sexual desire disorder (HSDD; 83%), sexual arousal disorder (40%) and dyspareunia (33%). Endocrine therapy was associated with HSDD (p=.003), and immunotherapy with dyspareunia (p=.009). Higher age was associated with lower sexual distress (p<.001). Depressive symptoms were highest among women with sexual arousal disorder (p=.004). Among the 69 partners, two-thirds had erectile dysfunction. Lower overall partner sexual satisfaction was associated with lower overall BCS sexual functioning (p=.001), lower female arousal (p=.002), and lower female sexual satisfaction (p=.001). Poorer male erectile function was related to higher female sexual pain (p=.006). Our findings indicate that the sexual functioning of both the women and their partners is affected, underscoring the importance of involving both partners in sexual counseling after BC.

The accuracy pf patients' perceptions of the risks associated with localized prostate cancer treatments

In this prospective, longitudinal study, we assessed newly diagnosed localized prostate cancer (PC) patients' (N=426) understanding of the differences in outcomes and risks of radical prostatectomy (RP), radiotherapy (RT), and active surveillance (AS). Patients' pretreatment perceptions of differences in adverse outcomes of treatments were compared to those based on the literature. Approximately two-thirds (68%, n=211) of the patients did not understand that the risk of disease recurrence is comparable between RP and RT. More than half of the patients did not know that RP patients are at greater risk for incontinence (65%, n=202) and erectile dysfunction (61%, n=190), and less at risk for bowel problems (53%, n=211) than RT patients. Many patients overestimated the risk of requiring definitive treatment following AS (45%, n=157), and did not understand that mortality rates following AS, RP, and RT are comparable (80%, n=333). Consulting a radiotherapist or a clinical nurse specialist was positively associated with,

and emotional distress was negatively associated with better understanding of risks ($p<0.05$). Greater efforts should be made to better understand why these misperceptions occur and, most importantly, how they can be corrected.

Prevalence and correlates of mental health problems in prostate cancer survivors: a case-control study comparing survivors with general population peers

In this observational case-control study we evaluated: (1) differences in the prevalence of mental health (MH) problems between prostate cancer survivors (PCs) alive ≥5 years after diagnosis of a stage I-IV carcinoma (n=644) and age-matched men from the general population (GenPop) (n=644); and (2) correlates of MH in PC survivors. MH was assessed with the SF-36 questionnaire. We observed clinically relevant MH symptoms in 14% of the PC survivors and 6% of the GenPop controls ($p<0.01$, OR=2.45 [1.66-3.62]). The most important correlates of lower MH scores in the PC survivors were being widowed, lower education, poorer general health perceptions, more bodily pain and urinary bother, and less sexual satisfaction. Our results indicate that long-term PC survivors have poorer MH than men of a comparable age from the general population without a history of PC. Attention to potentially modifiable factors associated of MH problems in PC survivors, such as urinary function and its related bother, bodily pain and sexual satisfaction, may help to prevent or limit MH problems in this survivor population.

Cost-utility and cost-effectiveness of physical exercise during adjuvant chemotherapy

We previously demonstrated that a home-based, low intensity physical activity program (Onco-Move) and a supervised, moderate-to-high intensity, combined resistance and aerobic exercise program (OnTrack) were effective in maintaining physical fitness and reducing fatigue among breast cancer patients undergoing adjuvant chemotherapy. This study evaluated the cost-utility and cost-effectiveness of the two interventions. Patients (N=230) were randomized to Onco-Move, OnTrack, or usual care (UC). Health outcomes included quality-adjusted life years (QALYs), general and physical fatigue, and physical fitness measured at baseline, end of chemotherapy, and 6-month follow-up. Societal costs included professional and informal health care, work absenteeism and unpaid productivity costs. Cost data were based on 3-monthly questionnaires, supplemented by medication data obtained from pharmacies. The results in indicated that Onco-Move is not likely to be cost-effective due to the relatively high willingness-to-pay necessary to reach reasonable probabilities of cost-effectiveness (QALY, general and physical fatigue). Incremental cost-effectiveness ratios for OnTrack compared to UC were €26,916/QALY, €788/1-point decrease in general fatigue and €1,402/1-point decrease in physical fatigue. The probability of OnTrack being cost-effective ranged from 31% at a willingness-to-pay (WTP) of €0 to 79% at a WTP of €80,000/QALY, 97% at a WTP of €15,000/1-point decrease in general fatigue, and 86% at a WTP of €24,000/1-point decrease in physical fatigue. Both interventions had a low probability of being cost-effective for physical fitness.

Online cognitive behavioral therapy (CBT) for climacteric symptoms in breast cancer patients experiencing treatment-induced menopause

In this randomized controlled study we are evaluating the (cost-) effectiveness of an internet-based cognitive behavioral therapy (CBT) program for climacteric problems in women treated for breast cancer (EVA-Online). Women have been recruited from 10 hospitals in the Netherlands and randomized to one of 3 study arms: (1) guided internet-based CBT; (2) self-managed internet-based CBT; or (3) a waiting list control group. Questionnaires are administered at baseline, post-intervention, and at 6-month follow-up. Primary outcomes are climacteric symptoms. Secondary outcomes include psychological distress, sexuality problems, sleep quality and health related quality of life. In 2017, we completed all data collection (N =248) and initiated the primary statistical analyses.

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Publications

Elkon R, Agami R. Characterization of noncoding regulatory DNA in the human genome. Nat Biotechnol. 2017;35(8):732-746

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Identifying and characterizing novel vulnerabilities of cancer

Our main research objective is to identify novel cellular vulnerabilities that can be exploited for cancer therapies. For this purpose, we develop innovative genomic and genetic tools. Key targets are non-coding RNAs, mRNA translation, and enhancers. In particular, we employ novel unbiased functional genetic screening approaches, perform mechanistic studies to understand their connection with the cancerous phenotype, and use this information for the development of innovative cancer therapeutic approaches.

We report the following advance in 2017

(A) Tumour-specific amino acid vulnerability uncovered by differential ribosome codon reading

Cancer cells modulate their metabolic networks to support cell proliferation and a higher demand of building blocks. These changes may restrict the availability of certain amino acids for protein synthesis, which can be utilized for cancer therapy. However, little is known about the amino acid demand changes occurring during aggressive and invasive stages of cancer. Recently, we developed *diricore*, an approach based on ribosome profiling that can uncover amino acid limitations. Using *diricore* we already uncovered shortage in proline in breast cancer cell lines expanded in vivo, and in human kidney tumors. Intriguingly, proline shortage has been linked to high levels of PYCR1, a key enzyme in proline production, and PYCR1 knockout compromised tumor growth in vivo, demonstrating the importance of identifying amino acid shortages in growing tumors. We are developing various approaches to assess whether PYCR1 inhibition and proline deprivation are good strategies in combating cancer.
Furthermore, we applied *diricore* to a cellular model of metastasis and tumor resistance to chemotherapy, and uncovered a shortage of leucine in the aggressive cells. Further analyses indicated that reduced uptake of leucine - caused by down-regulation of its transporter limits cell proliferation of the aggressive tumors (figure 1). Thus, we identified a specific amino acid limitation that can serve as a vulnerability point to target aggressive cancers.

Altogether, the identified cancer-associated amino acid shortages and their links to changes in metabolic pathways will serve as signatures for diagnosis and guidelines for therapy.

(B) Functional genetic screens of regulatory DNA elements

Enhancers are genomic domains that regulate transcription of distantly located genes through chromatin looping. They function as binding platforms for transcription factors and are characterized by specific chromatin signatures of histone methylation and acetylation. Only a small subset of all enhancers is active at a given space and time during development,

indicating a tight regulation of enhancer activity to control gene expression. Intriguingly, recent studies have indicated that single nucleotide polymorphisms, large-scale genomic rearrangements and somatic mutations can affect enhancer activity and by that contribute to tumor development and its aggressiveness.

So far, systematic identification of enhancer functions was hampered by the lack of tools to perform unbiased functional genetic screens. We therefore devised a novel approach for this purpose by utilizing the genome editing CRISPR tool. We presented two proof-of-concept genetic screens to identify and characterize functional enhancers in their native environment. As a result, we identified potential tumor suppressive and oncogenic enhancers that are targets of p53 and estrogen receptor (ER). Additionally, we showed that this technology is suitable for *de novo* identification of novel enhancer elements using a genomic CRISPR-Cas9 tiling approach. Altogether, our results allow for the first time to expand the utility of CRISPR-Cas9 to explore the functions of the non-coding genome under normal and pathological conditions (figure 2).

(C) Transcription impacts the efficacy of mRNA translation via co-transcriptional N6-adenosine methylation

Studying mRNA translation and transcription (parts A and B, respectively) we hypothesized that these processes are linked via epi-transcriptomic changes in mRNA. This link, we suggest, will make responses to intrinsic and extrinsic cues more robust. To investigate such a connection, we performed an unbiased screen of multiple human promoters, and uncovered a positive general coupling between mRNA expression and translational efficacy. Using CRISPR-Cas9-mediated approach, genome-wide analyses and in vitro experiments, we showed that the rate of transcription regulates the efficacy of translation. Most significantly, we provided a mechanistic explanation for this link in the form of mRNA methylation. We demonstrated that methyl-6-Adenine (m6A) modification of mRNAs is co-transcriptional and depends upon the dynamics of the transcribing RNA polymerase. Suboptimal transcription rates lead to elevated m6A content, which may result in reduced translation. Altogether, our study uncovered a general and widespread link between transcription and translation that is governed by epigenetic modification of mRNAs (figure 3). Although this is a very fundamental study, our conclusions open up new prospects in understanding changes in gene regulation in genetic diseases such cancer.

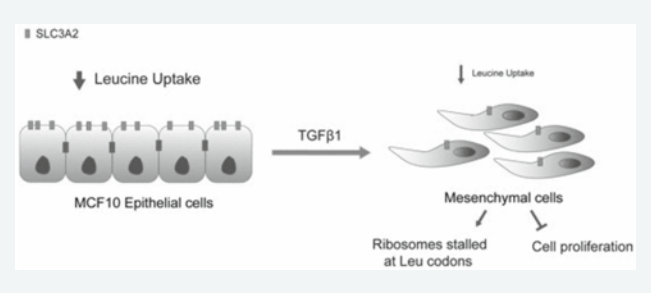

Figure 1: *Diricore*, a platform for the discovery of novel amino acid vulnerabilities in aggressive cancer. Transformation of human breast epithelial cells to aggressive mesenchymal ones reduces the expression of SLC3A2, a subunit of the leucine transporter, which diminishes leucine uptake, impacts on mRNA translation, and limits cell proliferation.

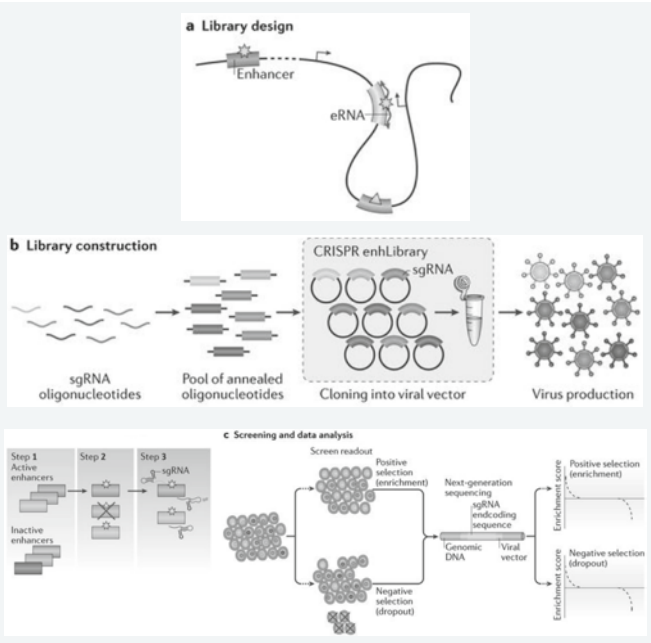

Figure 2: Functional genetic screens of active enhancers using the CRISPR–Cas system. (A) Bioinformatics design of the CRISPR libraries. (B) Library construction. (C) Screening approaches.

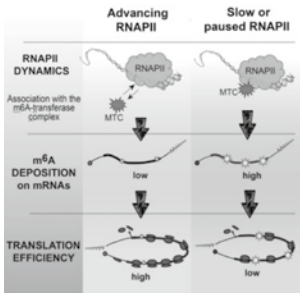

Figure 3: Transcription impacts the efficacy of mRNA translation via co-transcriptional N6-adenosine methylation. A schematic model showing how transcription rates of mRNAs positively correlate with rates of their translation. How the dynamics of RNA polymerase impact the deposition of m6A on mRNAs. And finally, how excessive m6A modification is detrimental for the translation process.

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Publications

Carmona-Fontaine C, Deforet M, Akkari L, Thompson CB, Joyce JA, Xavier JB. Metabolic origins of spatial organization in the tumor microenvironment. Proc Natl Acad Sci U S A. 2017;114(11):2934-2939

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Macrophage Dynamics in Cancer Response to Treatment

Our laboratory focuses on the role of macrophage populations in solid tumors, to identify vulnerabilities in cancer cell/stroma heterotypic communication that can be targeted therapeutically. We study the microenvironment-mediated mechanisms of tumor maintenance, therapeutic resistance and recurrence in brain and liver malignancies. In particular, we investigate the acquired resistance mechanisms resulting from dynamic alterations in the activation and recruitment of macrophages and their mediators in response to standard of care treatment. We utilize cancer mouse models of glioma and hepatocellular carcinoma combined with lineage tracing systems to unravel the functions of resident versus infiltrating macrophages in sheltering tumor cells during cytotoxic therapy response.

Targeting myeloid cells during glioma therapeutic response to standard of care therapy

The consequences of cancer cell death induced by radio- or chemotherapy include the release of endogenous immune adjuvants in the tumor microenvironment (TME) that may influence macrophage activation status and their recruitment to the tumor site. Our laboratory studies the role of tumor infiltrating bone marrow derived macrophages (BMDM) and tissue resident microglia (MG) in glioblastoma multiforme response to standard of care treatment (SoC), using multiple murine models of the disease.

The GEMMs we employ develop tumors from *nestin*+ glial progenitors, and are based on loss of the tumor suppressors *p53*, *Pten* or *Cdkn2a* combined with PDGFR signaling activation, mirroring mutations found in human gliomas. We have found that therapeutic intervention with radiotherapy and temozolomide has different, albeit limited effect on prolonging survival of these animals depending on the genetic make-up of cancer cells. Resistance mechanisms involve differences in macrophage and neutrophil recruitment from the periphery, and activation of the tissue resident macrophage population, microglia. Both populations of BMDM/MG undergo transcriptional changes in the course of treatment and acquire novel pro-tumorigenic functions linked to immune suppression and M2-alternative activation. Our work focuses on identifying the signaling pathway activation underlying these changes in order to enhance the early response to SoC.

Microenvironmental regulation of glioma quiescence and relapse

Not all cells are equally malignant within a glioma tumor. Certain subpopulations are particularly prone to drive disease recurrence post therapeutic intervention. We identified that recurrent glioma post-SoC displayed an altered immune phenotype compared to primary tumors, with increased content of infiltrating monocyte, macrophages and neutrophils. We are now developing mouse models that will enable to trace the cell

of origin of recurrent disease and its local immune environment. We use the *Prom1*C-L; *Rosa*ZsG mice to trace glioma stem-like cells (GSCs) in treated gliomas. *Prom1*C-L mice express both CreER2-recombinase and LacZ from the endogenous *Prom1* (Cd133) locus, and the *Rosa*ZsG floxed allele is activated by tamoxifen-induced recombination, allowing us to follow these cells with GFP in dormant or recurrent glioma, and to analyse their local environment using CLARITY brain imaging and flow cytometry. In this GSC tracing model, RFP-mediated labelling of differentiated cancer cells distinguishes GFP^+ GSCs, which tracing can be induced at different time point post-tumor growth or treatment. Using these tools and immune cell specific markers, we are currently analysing the stage-dependant regulation of GSC and glioma cell activation mediated by BMDM/MG. Our goal is to identify and target the niche-regulated changes in recruited and resident immune cells that favor glioma recurrence.

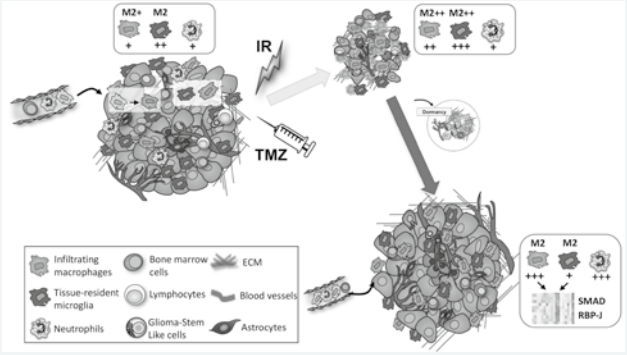
Functional investigation of BMDM and MG phenotypes at recurrence

We performed RNA sequencing on infiltrating BMDM and tissue-resident MG sorted from murine glioma recurrent tumors post SoC, and compared it to untreated gliomas. We identified a convergence of the transcriptional signature of these two subpopulations of macrophages, associated with tumor relapse. The transcription factors (TF) SMAD and RBPJ are at the center of this acquired signature, and these TF are not active in untreated GBM or in early phases of IR response, suggesting a rewiring of microglia and infiltrating macrophage programming at recurrence.

Importantly, we collaborate with Dr Dieta Brandsma and neurosurgeons at the MC Slotervaart to obtain primary and recurrent human GBM, and our preliminary results support these observations. In our glioma GEMMs, using promoter specific, inducible deletion of SMAD and RBPJ in either microglia or infiltrating macrophages, we now plan to abrogate their recurrent-specific, acquired signature in dormant or recurrent gliomas. In parallel, we identified additional alterations in the immune contexture of recurrent disease, including T cell phenotype. In collaboration with Dr Gerben Borst, we are now targeting these cells in combination with radiotherapy.

Characterize the tumor microenvironment dynamics in hepatocellular carcinoma (HCC) initiation and progression

HCC typically develop in the context of inflamed, injured livers that share traits with chronic regeneration, in which infiltration of innate immune cells occurs and contributes to hepatocarcinogenesis. In order to reproduce the diversity of oncogenic events found in HCC, we used hydrodynamic gene delivery and Sleeping Beauty (SB)-mediated somatic integration for long-term *in vivo* gene expression in mouse hepatocytes. Among the oncogenes and tumor suppressors with documented roles in human HCC we have used two genetic combinations to generate and characterize the HCC tumor microenvironment: either N90 b-catenin (constitutively active) or NRasV12, co-injected with a CRISPR-mediated knock out of the tumor suppressor PTEN. We found that the adaptive and innate immune cell content was affected by the cancer cell's genetic background. Interestingly, macrophages showed the largest differences in content in these two models of HCC. These findings are encouraging us to therapeutically target macrophage populations in liver cancer. We now concentrate on developing these HCC models in a necro-inflammatory environment, as seen in HCC patients, using the *fah-null* mouse model of liver injury.



Evolution of macrophage content and phenotype in the course of GBM response to standard of care treatment:
Infiltrating macrophages and tissue resident microglia are present in primary GBM. Their content increases in the early onset of therapeutic response to radio and chemotherapy in glioma, when they acquire a pronounced M2-like pro-tumorigenic phenotype.
Treatment leads to tumor regression, however glioma inevitably relapse, with different latency depending on the cancer cell genetic make-up. Increased neutrophil numbers are found in the recurrent immune environment, and the ratio of macrophage subpopulations is altered in recurrent disease. They acquire a common, recurrent specific transcriptional program independent of the M2-protumorigenic phenotype, with the transcription factor SMAD and RBP-J at its core. Targeting the different stages of macrophage subpopulation evolution represent novel and attractive therapeutic strategies to durably enhance GBM response to cytotoxic treatment.

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Genotype specific dependencies

Our research continues to evolve around the discovery of genotype specific dependencies and synthetic lethal interactions that can be explored as drug targets in precision therapy. To achieve these goals, we use functional genomic technologies including large scale RNAi screening, CRISPR based gene-editing, CRISPR based transcriptional activation and repression and high throughput technologies to study the consequences of pathway inhibition in large panels of cancer cell lines harboring specific genetic alterations. In addition, we characterize the consequences on gene expression and protein modification upon perturbation of components of signaling pathways. This integrated approach allows for the identification of specific dependencies in the context of tumor- and patient-specific alterations that can be explored for cancer therapy and lead to the development of predictive models and biomarkers for therapy response to pathway-targeted therapeutics in cancer.

Understanding sensitivity to mTOR inhibitors in breast cancer

The understanding of the complex dynamic circuitry of signaling pathways in the context of targeted inhibition is highly valuable not only to identify novel targets but also for identifying biomarkers to stratify patients, to understand resistance and to enable the identification of more effective combination therapies.
Using drug sensitivity screening, genomic analyses (copy number variation, mutations, gene expression profiles) and (phospho)protein analysis, combined with computational modeling (with Lodewyk Wessels group) we previously found that the protein expression levels of 4E-BP1, a downstream target of mTOR involved in regulating cap-dependent protein synthesis, correlated with response to PI3K inhibitors. We have extended this integrated approach to study the sensitivity of a panel of HER2 positive human breast cancer lines to combination therapies including HER2 inhibitors and chemotherapy. With this effort, we will attempt to generate a predictive model for sensitivity to combination therapy that will be validated in patient samples for clinical response.

Correlated gene essentiality and functional relationship in cell line panel CRISPR screens

CRISPR based screening provides a powerful way to identify cell line specific dependencies. We have screened a panel of 10 different cell lines for genotype specific dependencies using a sgRNA library targeting more than 450 genes involved in DNA modification. Apart from genotype specific dependencies, the output of such a panel of cell lines also provides the opportunity to identify genes that display a similar pattern of gene essentiality across the different cell lines, known as correlated gene-essentiality. Using our data, we identified a strong correlation between UHRF1 (ubiquitin-like, containing PHD and RING finger domains protein 1) and DNMT1 (DNA

methyltransferase 1) (figure 1). UHRF1 targets DNMT1 for DNA methylation providing evidence for a functional relationship displayed as correlated gene essentiality. Furthermore, we identified a correlation between PRMT1 (Protein-Arginine-Methyl-Transferase-1), ASH2L (Absent-Small-Homeotic-2- Like protein) and the H3K4 methyl-transferase SETD1A. Similar to the first example, this correlated gene essentiality is supported by functional relationships where PRMT1 methylates ASH2L, which is a shared component of the SET1/ASH2 histone H3K4 methyl-transferase complex. The cell line panel screening platform for gene essentiality has allowed us to identify novel potential genotype specific dependencies and also novel functional correlations among the genes interrogated in the cell line panel CRISPR screens. We are currently studying these novel interactions in more detail.

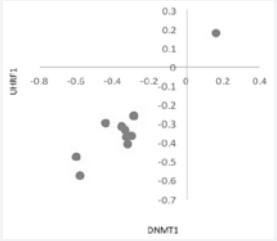
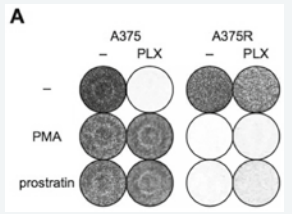


Figure 1. Correlated gene essentiality for UHRF1 and DNMT1. Plotted are the essentiality scores for the DNMT1 (x-axis) and UHRF1 (y-axis) in 10 different cell lines. Essentialty scores are the average of 10 sgRNAs targeting either UHFR1 or DNMT1.

MAPK pathway hyper-activation as strategy to treat resistant cancers

Drug resistance is the largest factor limiting the success of targeted treatment. $BRAF^{V600E}$-mutant melanomas are strongly driven by MAPK signaling. This dependency is illustrated by the effectiveness of MAPK pathway inhibition using either single (BRAF) inhibitors or combinations of BRAF and MEK inhibitors. However, treatment with MAPK pathway inhibitors almost invariably leads to outgrowth of resistant disease. It has been shown that both genomic and non-genomic mechanisms cooperate to maximize MAPK pathway output to compensate for the targeted therapy with BRAF and MEK inhibitors. Interestingly, recent reports have shown these resistant melanoma cells can become sensitive to withdrawal of the inhibitor(s), a phenomenon referred to as drug addiction. This suggests that hyper-activation of the MAPK pathway in these resistant tumors represents a vulnerability that is exposed upon drug withdrawal. However, melanoma cells are able to adapt, survive and resume proliferation after drug withdrawal. We have explored the possibility to enhance the drug withdrawal phenotype by exogenous activation of the MAPK pathway. Treatment of BRAF inhibitor resistant and BRAF/MEK double-resistant BRAF-mutant melanoma cells after drug withdrawal with Prostratin results in enhanced cell death upon drug withdrawal (figures 2A and 2B). Prostratin, developed as an HIV drug is a PKC and MAPK pathway activator but lacks the tumorigenic effects of other PKC activators such as PMA (phorbol-12-myristate-13-acetate). The effect of Prostatin can be reverted by treatment with a MEK inhibitor (PD0325901) indicating that indeed MAPK pathway hyperactivation is essential for the effect on cell proliferation and survival (figure 2B). This acquired vulnerability to MAPK hyper-activation is characterized by cell cycle defects, arrest and cell death. Importantly, introduction of oncogenic Ras in BRAF-mutant melanoma, representing a common resistance mechanism to BRAF inhibitors in patients, directly imparts sensitivity to MAPK pathway hyper-activation. Our work implies that repurposing of an HIV drug could provide a novel therapeutic solution for MAPK inhibitor resistant tumors. We are currently studying the effectiveness of this strategy *in vivo* for the treatment of BRAF/MEK inhibitor resistant melanoma.



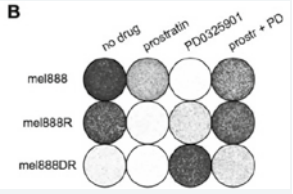


Figure 2. MAPK hyper-activation in BRAFV600E mutant melanoma cells resistant for the BRAF inhibitor PLX4032 induces cell death.
A. Colony formation assays of parental (-) and resistant (R) A375 cells in the presence of 2 µM PLX4032, 10 nM phorbol-12-myristate-13-acetate (PMA) or 2 µM Prostratin.
B. Colony formation assays of parental, resistant (R) and double-resistant (DR) mel888 cells after drug withdrawal in the presence of no durg, 2 µM prostratin, 100 nM PD0325901 or the combination of 2 µM prostratin and 100 nM PD0325901.

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Pharmaceutical research: drug manufacturing – bioanalysis – pharmacokinetics

The research programs of our department deal with different themes but generally falls under the common denominator of optimization of cancer treatment with medicines including cellular immunotherapies. We have both preclinical and clinical projects ongoing for which we work closely together with the Schellens, Schinkel and Van Tellingen groups. This year we have formed together the Division of Pharmacology.

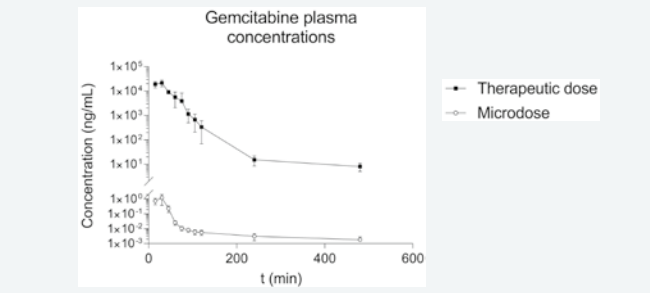
Drug manufacturing

We support >20 mono- and (international) multi-center clinical trials (*e.g.* DRUP, POSEIDON, REPOSIT) with drug manufacturing, packaging and distribution. Novel pharmaceutical formulations have been designed and tested clinically. An example is PazSol, an alternative formulation of pazopanib (Votrient®) which showed a significant increase in solubility and bioavailability as compared to the marketed formulation. Development and manufacture of vorinostat capsules enabled a clinical study in advanced resistant BRAF V600 melanoma. Oral solid dispersion tablet formulations of docetaxel (ModraDoc006) and paclitaxel (ModraPac005) are manufactured for ongoing studies.
The Biotherapeutics Unit (BTU) is a biotech facility within our department. Currently, Tumor Infiltrating Lymphocytes (TIL) infusions are produced for melanoma patients participating in a multi-center, randomized phase III trial. So far 45 patients have been treated with TIL *or* ipilimumab therapy. In 2017 BTU also manufactured MART-1 T cell receptor modified T cells for 5 patients. Future clinical trials with TCR modified T cells and innovative T cell therapies directed against patient specific neo-antigens are now prepared. DNA vaccines have been manufactured for HPV induced malignancies, in the context of the FP7 RAIDs program. BTU is also partner in the FP7 TargetAMD consortium for which clinical grade pDNA for the *ex vivo* transfection of retina cells, is produced.
The radiopharmaceutical ^{177}Lutetium-PSMA for imaging and treatment of prostate cancer is under development.

Bioanalytical method development + implementation in pharmacokinetic studies

Our therapeutic drug monitoring (TDM) service for the optimization of drug treatment, particularly with the new tyrosine kinase inhibitors (TKIs), has been extended past year and now includes more than 30 agents. The number of samples grows annually from 100 samples in 2010 to 3,500 in 2017.
To handle this big increase of samples we have developed liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods where we quantify more than 10 different oral drugs in a single run. We have also set up a specific assay for Δ(4)-abiraterone (D4A), a newly discovered active metabolite of abiraterone. In general, our extensive data sets combining laboratory values (drug concentrations in plasma) and clinical observations (antitumor activity / toxicity) greatly aids to define and to advise the right drug dose for each patient: the ultimate

form of personalized medicine. Lurbinectedin (PM01183) is currently investigated in a mass balance clinical trial. Patients receive 5 mg of ^{14}C-PM01183 (100 µCi), after which plasma, urine and feces samples are collected. So far, four patients have been included in the trial. Recovery of radioactivity was nearly complete, with a mean (±SD) total cumulative recovery of 96.9 (±9.9)%. Feces is clearly the main route of excretion with a mean total recovery of 91.4 (±11.9)%. The mass balance trial with SGI-110, a prodrug of decitabine exhibits rapid metabolism with renal excretion. We conducted a proof-of-concept trial, in which a gemcitabine micro dose, being >10,000-fold lower than the therapeutic dose, was administered to determine drug pharmacokinetics. We were able to measure plasma concentrations in the low picogram per mL range with our ultrasensitive LC-MS/MS (API 6500) platform (see figure). For other studies we routinely measure paclitaxel, docetaxel, capecitabine and its metabolites, vorinostat, olaparib and platinum. To screen for dihydropyrimidine dehydrogenase (DPD) deficiency, we analyze the DPD substrates uracil (U) and dihydrouracil (UH_2) in plasma.



Plasma concentration-time curves of gemcitabine after i.v. administration of a microdose (100 µg) (○) and a therapeutic dose (1,000 – 1,250 mg / m²) (■)

Pharmacokinetic and Pharmacodynamics (PK/PD) modelling and simulation

Research on population PK/PD modelling and simulation was focused on drug trial optimization. We found pazopanib trough concentrations (20 mg/L) to be related with efficacy in both renal cell cancer and soft tissue sarcoma. Furthermore, switching from 800 mg once daily to 400 mg twice daily optimized PK.

The relationship between left ventricular ejection fraction (LVEF), trastuzumab and anthracycline exposure was evaluated using population PK/PD modeling. High troponin T levels after anthracycline treatment and before trastuzumab treatment are predictive for the larger decreased in LVEF.

We are currently involved in various clinical trials taking place in East Africa, Colombia, and South Asia on the neglected tropical parasitic disease leishmaniasis, mainly focusing on the repurposed anticancer PI3K/Akt inhibitor miltefosine. A relationship between disease relapse and miltefosine exposure was found and demonstrated that children were underexposed and require a higher drug dose. We developed an optimized allometric dosing regimen for pediatric patients, which is currently being evaluated in a clinical trial in Kenya and Uganda. Current research focuses on integrated modelling of parasitic and immunological biomarkers in relation to treatment response and drug exposure. Our group is partner in the recently awarded H2020 consortium Afri-KA-Dia, which will investigate efficacy and PK/PD of combination therapies for leishmaniasis in East Africa.

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Publications

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The role of the microenvironment in prostate carcinogenesis

Our lab has an interest in the exploration of the interaction between normal prostate cells and prostate cancer. The prostate cancer microenvironment consists of both resident stromal and immune cells and immune cells recruited to the microenvironment. There is abundant evidence that these cells play a crucial role in the initiation and progression of prostate caner. In contrast to the tumor cells, the stroma and infiltratred immunecells in the tumor microenvironment consists of normally regulated cells and might hold promise for clinical valuable biomarkers and drug targets.

Functionality of Androgen Receptor expression in human prostate cancer associated fibroblasts

Androgen Receptor (AR) signaling is essential for the development of the prostate and for prostate cancer development. Not only normal and malignant epithelial prostate cells express the AR, but also cells in the prostate cancer microenvironment, including fibroblasts. Fibroblasts have shown to contribute to prostate cancer development and are named Cancer Associated Fibroblasts (CAFs) when associated with prostate cancer. Therefore, the functionality of the AR in these cells is of interest. CAFs were isolated from biopsies of cancer-affected areas in prostatectomies and cultured in vitro. The isolated cells express various CAF markers and the AR. The AR bound to the chromatin upon testosterone, which suggests transcriptional activity. Exposure of prostate cancer cells to medium of testosterone stimulated fibroblasts, resulted in decreased migration mediated by CCL2 and CXCL8.

Androgen Receptor signaling in prostate cancer associated macrophages

Multiple macrophage differentiations have been described, including inflammation associated M1 and cancer promoting M2 macrophages. The amount and differentiation of infiltrating macrophages proved to be prognostic factors for prostate cancer development. Prostate cancer cells express the AR and its ligand testosterone is the main driver of prostate cancer cell growth. Moreover, CD163+ and CD206+ (M2) macrophages, in vitro generated from the peripheral blood lymphocyte fraction also expressed AR. Since macrophages differentiation might dictate prostate cancer development, we assessed the occurrence of AR expression in native human prostate cancer associated macrophages and the role of AR in differentiation of macrophages. Immunohistochemical double staining for the pan-macrophage marker CD68 and AR of paraffin embedded human prostate cancer specimen showed co-localization. Moreover, mRNA sequencing of myeloid (CD14+) cells isolated from human prostate cancer biopsies showed AR expression. Both results suggest AR expression in native human prostate cancer associated macrophages. In in vitro stimulated M1 macrophages, AR translocated to the nucleus and CD163 and CD206 were expressed upon testosterone exposure, suggesting a direct

involvement of AR in the differentiation of the macrophages. Simultaneous exposure to testosterone and the androgen receptor inhibitor RD162 restored the initial M1 phenotype. Maintaining macrophages in M1 differentiation might be a novel mechanism of action of androgen receptor inhibitors.

Lesion of origin of metastatic prostate cancer

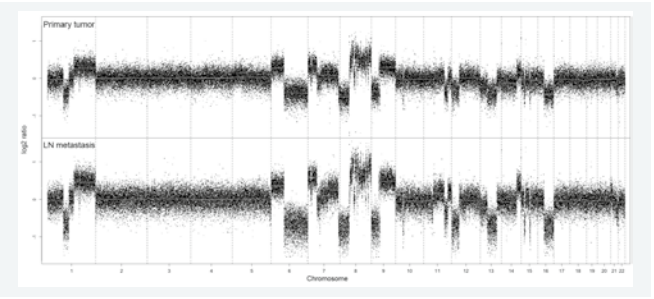
The prostate of a patient diagnosed with prostate cancer, contains an average of five genetically different prostate cancer lesions. It is commonly assumed that the largest lesion is also the one that metastasizes and therefore is the source of potential lethal disease. Various focal therapies aim to destroy the largest prostate cancer lesion only, as an organ sparing curative treatment. However, there is no data supporting this assumption. We selected FFPE prostatectomy specimen with associated pelvic lymph node metastases. The various prostate cancer foci in the prostatectomy specimen and the lymph node metastases were identified and DNA was isolated. Copy number aberrations, allowed us to identify the prostate cancer lesion of origin of the metastasis with great certainty (Figure 1). A significant number of metastases did not originate from the largest prostate cancer lesion, but from smaller lesions.

Androgen receptor genomics as a biomarker of responsiveness to anti androgen drugs

Chip-seq was employed to identify Androgen Receptor (AR) responsive genes with classifier properties for sensitivity of human prostate cancer to antiandrogen drugs. We have shown that AR chromatin binding patterns can separate anti hormonal treatment-sensitive prostate cancers from resistant disease. A gene set with predictive properties is selected and its prospective value is currently investigated. Moreover, in a clinical trial, biopsies are taken from a metastatic lesion and submitted for AR Chip-seq. Outcome of treatment with the antiandrogen enzalutamide will be correlated with AR chromatin binding patterns. In another clinical trial patients with localized prostate cancer are treated with enzalutamide for three months prior to prostatectomy. AR Chip-seq will be performed on pretreatment biopsies and prostatectomy specimen, which will allow us to assess changes in AR regulation as a result of AR signaling inhibition.

Myeloid cell populations in human prostate cancer

Macrophages are among the most abundant non-cancerous cells in the tumor microenvironment and relatively recent studies introduced the concept of different subtypes of macrophages that are able to influence tumor progression. The overall aim of this project is to assess the phenotype of the myeloid cells compartment and their secreted factors in the tumor microenvironment of human prostate cancer. Myeloid cell populations are quantified in human prostate cancer specimen. Moreover, macrophages are isolated from biopsies from the cancer affected peripheral zone of human prostates and phenotypically characterized by single cell sequencing.



Copy Number Abberation profiles suggesting clonality between the primary tumor tissue (upper panel) and malignant lymph node tissue (lower panel). Black dots represent log2 ratios of probes along genomic locations, red line represents segmented CGHcall values. Low-coverage NGS data (<1x coverage), generated from DNA isolated from archival FFPE prostate cancer tissue.

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Functional Genomics

My group uses genome-wide functional genetic approaches to identify powerful drug combinations, new drug targets and mechanisms of resistance to cancer drugs. We bring our discoveries to the clinic in close collaboration with the division of Clinical Pharmacology.

Collateral sensitivity of drug resistant cancers

BRAF mutant melanomas typically respond for some 6-8 months to combinations of selective MAPK pathway inhibitors, after which very few treatment options remain for such patients. Moreover, subsequent therapies tend to become increasingly less effective. It is a well-established principle that drug resistance comes at a "fitness cost" for the cancer cell that in turn can lead to novel vulnerabilities of the drug resistant cells. We therefore searched for new vulnerabilities that are acquired when *BRAF* mutant melanomas become resistant to the combination of BRAF and MEK inhibitors. We found that resistance to BRAF+MEK inhibitors is associated with increased levels of reactive oxygen species (ROS). Subsequent treatment of BRAF-inhibitor resistant melanoma cells with the histone deacetylase inhibitor vorinostat suppresses *SLC7A11*, leading to a lethal increase in the already elevated levels of ROS in drug-resistant cells. This causes selective apoptotic death of only the drug resistant tumor cells. Consistently, treatment of BRAF inhibitor-resistant melanoma with vorinostat in mice results in a dramatic tumor regression (figure 1). In collaboration with professors Jos Beijnen and Jan Schellens, we launched a clinical study in which patients with advanced BRAF+MEK inhibitor resistant melanoma were treated with the HDAC inhibitor vorinostat. Preliminary results from this study indicate that vorinostat can selectively ablate BRAF inhibitor-resistant tumor cells, providing clinical proof of concept for the novel therapy identified in the laboratory. More generally, our data highlight that studying how cancer cells acquire resistance to targeted cancer drugs may be fruitful to identify novel vulnerabilities that can be exploited therapeutically.

Senescence inducing therapies for the treatment of cancer

Senescence is a stable proliferation arrest characterized by absence of proliferation markers, expression of growth-inhibitory tumor suppressor genes, senescence associated β-galactosidase and nuclear heterochromatin foci. Senescent cells also secrete a variety of inflammatory cytokines and chemokines, collectively referred to as the "Senescence-Associated Secretory Phenotype". We have used both functional genetic- and compound screens in cancer cells harboring a reporter gene that is activated during senescence to find targets to induce senescence selectively in cancer cells. We found that suppression of the SWI/SNF component SMARCB1 induces senescence in melanoma through super-activation of the MAP kinase pathway. From the compound screen, we identified multiple aurora kinase inhibitors

as potent inducers of senescence in *RAS* mutant lung cancer. We also found that senescent melanoma and lung cancer cells acquire sensitivity to the BCL2 family inhibitor ABT263. Our findings suggest the possibility to treat cancer through a one-two punch approach in which a first drug is used to induce senescence in cancer cells and the second drug is used to kill senescent cancer cells (figure 2).

PTPN11 as a drug target in RAS mutant cancers

RAS gene mutations are frequent in human cancer, especially in pancreatic, colorectal and non-small cell lung cancers (NSCLC). Inhibition of the RAS oncoproteins has proven difficult, and attempts to target downstream effectors have been hampered by the activation of compensatory resistance mechanisms. It is also well-established that *KRAS* mutant tumors are insensitive to inhibition of upstream growth factor receptor signaling. Thus, EGFR antibody therapy is only effective in *KRAS* wild type colon cancers. Consistently, inhibition of the protein tyrosine phosphatase non-receptor type 11 (PTPN11), which links receptor tyrosine kinase signaling to the RAS-RAF-MEK-ERK pathway, was shown to be ineffective in *KRAS or BRAF* mutant cancer cell lines. Our data also indicate that PTPN11 inhibition in KRAS mutant NSCLC cells under normal cell culture conditions has little effect. In contrast, our data indicate that PTPN11 inhibition under growth factor-limiting conditions in vitro results in a senescence response. In vivo, inhibition of PTPN11 in *KRAS* mutant NSCLC also provokes a senescence response, which is exacerbated by MEK inhibition. Our data identify PTPN11 inhibition as an unexpected vulnerability of *KRAS* mutant NSCLC cells that remains undetected in cell culture, which can be exploited therapeutically.

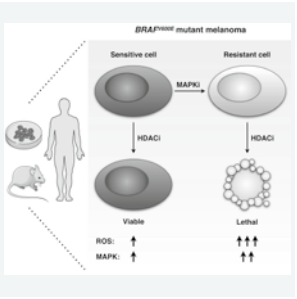

Figure 1. An acquired vulnerability of BRAF inhibitor resistant melanoma with therapeutic opportunities. Development of resistance to BRAF inhibitors in BRAF mutant melanoma results in a hyper-activation of the MAP kinase pathway, which in turn causes an increase in Reactive Oxygen Species. Treatment of resistant cells with Histone Deacetylase Inhibitors (HDACi) leads to a further increase in ROS, which is lethal to the drug resistant cells, but not to the parental drug sensitive cells. Thus, HDACi selectively kill BRAF inhibitor-resistant tumor cells.

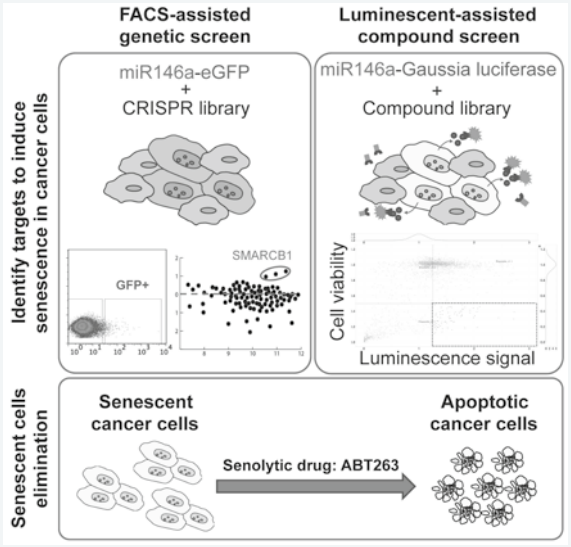

Figure 2. A one-two punch model for cancer therapy based on induction of senescence. CRISPR-mediated genetic screens and chemical screens can serve as two types of high-throughput methods to identify senescence inducers in cancer cells. Senescent cancer cells can be killed selectively by the BCL2-family inhibitor ABT263, providing a potential sequential drug treatment strategy for cancer.

B

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Mouse models for cancer

We use the mouse as a model organism for establishing the role of oncogenes and tumor suppressor genes in tumor development. By utilizing recombination-mediated switching and taking advantage of somatic gene transfer methods we can alter the expression of multiple oncogenes and tumor suppressor genes in a tissue-specific and temporal fashion permitting accurate modeling of tumorigenesis as it is observed in man. In this way we can study genotype-phenotype correlations and determine the synergistic activity of proto-oncogenes and tumor suppressor genes in tumor development and metastatic spread. Furthermore, we exploit these models for testing new intervention strategies.

Functional analysis of oncogenes and tumor suppressor genes

Our emphasis is on lung cancer and mesotheliomas. We use Adenovirus or Lentivirus-mediated somatic gene transfer to introduce new genes, to inactivate genes by Crispr/Cas9 or to switch conditional oncogenes and tumor suppressor genes on or off at a defined time in the appropriate target cell by Cre/Lox recombination. Subsequently, tumor initiation and progression is monitored over time using a variety of *in vivo* imaging techniques.

Small Cell Lung Cancer

When *Rb* and *p53* are inactivated specifically in lung, small cell lung cancer (SCLC) ensues in almost all mice. These tumors closely resemble human SCLC. We have studied whether different cells in the lung can give rise to these tumors. We found that depending on the combination of driver mutations we can initiate tumors more effectively from different locations in lung. Intriguingly, mice developed peripheral neuroendocrine lesions which resembled Large Cell Neuro Endocrine Carcinoma (LCNEC) when we used a generic CMV promoter to target lung cells instead of the extensively charachterized CGRP promoter, suggesting the contribution of a different cell of origin for this subclass of Neuroendocrine tumors. None of the major lung cell subtypes was capable to generate these peripheral tumors, suggesting that a new peripheral progenitor cell lacking these differentiation markers, serves as the cell of origin of these peripheral tumors.
These lesions show high expression of E-cadherin and are relative refractory to CisPt treatment. Interestingly, also the "typical" SCLC that develops in the central lung initially shows high expression of E-cadherin. Upon progression, often catalyzed by amplification and overexpression of Nfib, SCLC becomes more invasive and metastatic but also more responsive to CisPt treatment. Treatment of SCLC with CisPt very effectively eliminates these more advanced lesions but not the E-cadherin positive lesions that then cause the tumor to quickly relapse.
A high throughput drug combination screen performed in

collaboration with the Sanger Institute (WTSI) in the mouse SCLC cell lines has yielded a couple of drug combinations that are now further explored for their effectiveness. In particular drug combinations with inhibitors of the NAD salvage pathway, on which specifically SCLC almost exclusively depends for supplying NAD, shows promise in vitro and will be tested now in vivo in mice.

Next to these drug combination screens we have further pursued drug combinations that impact on DNA damage response genes and genes involved in chromosome segregation. The promising effects observed in vitro are currently being tested in vivo.

We have also now validated in cell lines a number of tumor drivers that were found in an insertional mutagenesis screen in mice. The most significant one is currently tested in vivo.

The screen was originally set up to assess whether SCLC can originate from different cell types in lung and whether this requires different driver mutations. Although we have shown using other approaches that the neuroendocrine tumors in lung can originate from different cell types and that this depends on the driver lesions present, the PiggyBag mutagenesis screen has not identified new, not previously recognized driver lesions that can cause this.

Squamous cell carcinoma of lung

We have generated a mouse model of lung squamous cell carcinoma (SCC) based on the biallelic deletion of Cdkn2ab and Pten in combination with Sox2 overexpression. It very closely resembles the human counterpart but the latency period is still relatively long. We have been attempting to further accelerate SCC development by including additional drivers to obtain a model that can be effectively used for testing new intervention strategies. Progress has been hampered by the transition to a new animal facility in which tumor development was attenuated, likely as a result of different environmental conditions.

Trichoblastic carcinoma with SCC differentiation of skin

Concomitantly with the above studies we noted that Cdkn2ab null mice exhibit a high incidence of skin tumors, which was lost upon further backcrossing to the FVB strain. We have now elucidated the underlying mechanism by mapping a "wild-type" locus in the 129 background (the origin of the ES cells) that very strongly predisposes to trichblastic carcinoma but only when it is combined with Cdkn2ab deletion. Differential regulation of Wnt7b expression from the 129Ola locus appears to be the primary culprit. We have further explored how Wnt7b influences cell growth and cell transformation in vitro to better understand the synergy between the loss of the Cdkn2ab locus encoded genes and Wnt signaling. We have shown that this converges to Cdk6 which appeared to play a critical role in integrating the signaling of Wnt and Ink4b.

Mesotheliomas

Previously we have generated mouse models for mesotheliomas by the inactivation of Nf2, p53 and Cdkn2a in the intra-thoracic mesothelium of mice. These lesions can give rise to tumors that closely resemble the mesothelioma subtypes observed in man. Factors that define the tumor subtypes are the cell-of-origin and how descendants of a defined cell-of-origin become stabilized in a mesothelioma subtype. Our data indicate that mesothelioma subtypes show much more plasticity than previously thought. This will likely have major consequences for therapy.

We also have further characterized a mesothelioma model based on inactivation of the Tumor suppressors Cdkn2ab, Nf2, Bap1, with and without additional loss of p53. These combinations show extreme accelerated tumor development and therefore appear particular suited for testing therapeutic interventions, especially since these represent the most frequent lesions also found in human mesothelioma. Furthermore, the mesotheliomas show a immunophenotype closely resembling that of the human counterpart indicating that the combination of cell-of-origin and the driver lesions are sufficient to give rise to this immunophenotype and that this does not require independent inflammatory stimuli as likely induced by asbestos exposure. This makes this model particularly suited to further explore new immunotherapy regimen that already have shown some promising results.

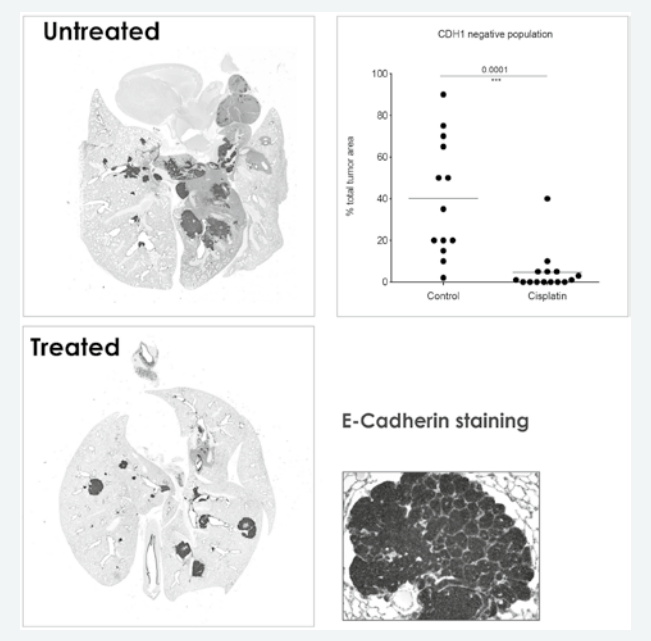

Figure 1. The CDH^{-}, Nfib^{high} population in a Rb$^{flox/flox}$;p53$^{flox/flox}$; LSL-Myc mouse model for SCLC is sensitive to cisplatin, whereas the CDH^{hi} population is resistant and largely responsible for relapse.

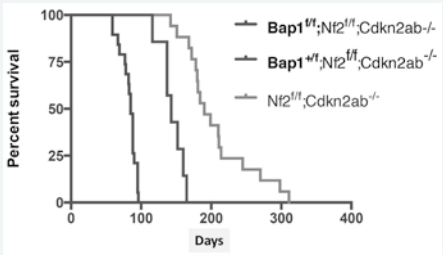

Figure 2. Loss of BAP1 causes a dramatic acceleration of tumor development in an autochthonous mouse model for mesothelioma, making it suitable for the swift testing of new intervention protocols.

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Combining targeted therapy and immunotherapy

We aim to identify mechanisms of tumor immune escape and to develop therapeutic protocols to combine cancer immunotherapy with targeted and other therapies. Tumor immune escape mechanisms include inhibitory molecules on tumor cells or on antigen presenting cells and immune regulatory cells in the tumor environment. The functional characterization of inhibitory molecules, exploration of their inhibition and the examination of possible synergy with small molecule-based targeted and other therapies may help in designing novel approaches to improve cancer immunotherapy.

Alteration of immune infiltrates upon combined targeted therapies

Targeted therapy does not only alter tumor signaling pathways, but also the tumor environment. Thus, it is crucial to simulate targeted therapies in immune-competent mouse models for cancer.
Previously, we have tested combined targeting of the MAPK and the PI3K pathways (selective BRAF, MEK, PI3K and mTOR inhibitors) in murine melanoma. We found that short-term intermittent combination of BRAF and MEK inhibition was superior to all other targeted combinations when combined with PD-1 blockade. This has led to a phase 1b trial testing several intermittent combinations in melanoma patients (IMPemBra, www.clinicaltrials.gov, NCT02625337).
Currently, we are testing further triple combinations of compounds targeting cells considered to be immune-regulatory in combination with PD-1 blockade.

Biomarker identification for personalized immunotherapy

Immunotherapies like CTLA-4 or PD-1/PD-L1 blockade have revolutionized the treatment of late stage melanoma. In addition, cellular therapies like TIL or gene-modified T cell therapies have shown clinical activity.
Analyzing patients treated neoadjuvant with CTLA-4 plus PD-1 blockade allows extensive biomarker analyses, due to the tumor surgery after the immunotherapy.
In these patients, we found that T cell and interferon-gamma RNA signatures, as well as the capability to expand in peripheral blood low frequency tumor-resident T cell clones (as measured by TCR sequencing) was associated with response to the therapy. None of the patients that had favorable signatures has relapse so far, possibly being the first step toward personalized immunotherapies.

Targeting tumor metabolism

We have previously described lactate-dehydrogenase (LDH) as the strongest prognosticator for patients' outcome, but also response, upon checkpoint inhibition. Recently, our collaborators and us could show, that LDH is not only a marker of tumor load, but also responsible for tumor mediated T cell inhibition.

This has led to a phase 3 trial aiming at LDH normalization upfront checkpoint inhibition (COWBOY trial, clinicaltrials.gov, NCT02968303). Preclinical analyses of additional approaches modulating lactate production or T cell sensitivity upon lactate are underway.

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Psychosocial oncology in clinical genetics and supportive care

This psychosocial oncology group is concentrating on survivorship and supportive care in individuals with cancer, and those at high risk because of an inherited gene mutation. The overall aim of the research is to improve the quality of life and quality of care. The study designs vary from observational (uptake and impact studies) and prospective (long-term surveillance studies) to randomized controlled trials (psychosocial intervention studies to support decision making and improve quality of life and quality of care). Examples of ongoing studies on the two main themes of this group (clinical genetics and survivorship) are described.

Clinical genetics

Whole body-MRI for carriers of a *TP53* mutation

Li-Fraumeni syndrome is a rare cancer predisposition syndrome characterized by a high lifetime risk of developing different tumors including sarcomas, breast cancer, brain tumors, leukemia, and adrenal cortical carcinomas and is associated with germline mutations in the *TP53* gene. In our LiFe-Guard study, we assess the diagnostic yield, the false-positive rate, and the burden of an annual surveillance program including whole-body magnetic resonance imaging (WB-MRI). The results of the initial whole body-MRI in 56 *TP53* mutation carriers showed 32 abnormal findings in 24 patients. Four of these abnormal findings were malignant (12.5%), the other abnormal finds turned out to be false positives. We concluded that in the initial round of our annual surveillance program malignancies are detected in approximately 7% of patients. This detection rate comes at the expense of many false-positives. Currently, we are investigating the experiences of participating in an annual surveillance program, and the psychological impact of having additional investigations for abnormal findings.

Uptake of genetic testing after being informed by a clinical geneticist

A study about family communication, funded by the KWF, was initiated in 2016. This study aims to develop, test, and implement a new way to facilitate family communication of genetic test results to relatives of counselled individuals. In a retrospective study, we are investigating the uptake of genetic testing of relatives of *BRCA1* and *BRCA2* mutation carriers at 12.5%, 25%, or 50% risk of being a carrier in the period after the introduction of the new guideline: "*Informing relatives about hereditary cancer*". Secondly, a prospective study has started, using a new active approach by clinical geneticists. In this approach at risk relatives are informed about their option of genetic testing by the clinical geneticist, without the intermediate role of the index patient (proven carrier of a *BRCA1/2* gene mutation). This study will show the extent to which an active approach may increase the uptake of genetic testing for BRCA1/2 gene mutation in at-risk relatives of tested individuals.

Survivorship and supportive care

Supporting women in making a well-informed decision about breast reconstruction: the development and evaluation of an online decision aid (TANGO-project)

In 2015, funding was received from Alpe d'HuZes/ KWF for a five-year study which aims to develop and implement an interactive, online patient decision aid (pDA) for the Dutch population of women who have to decide on breast surgery and reconstruction. Decisions about breast reconstruction are complex and largely depend on patients' personal preferences. In 2016, we developed the online pDA in partnership with ZorgKeuzeLab and together with a national multidisciplinary working group. As part of the developmental process, we performed a needs assessment among patients (n=17) and professionals (n=33) to investigate current experiences with decision-making about breast reconstruction and wishes regarding the pDA. The resulting pDA consists of six modules with information about the reconstructive options, pros and cons of the options and the most frequent complications. The pDA also includes experiences of other patients and value clarification exercises that stimulate women to weigh the options. The pDA consists of multiple illustrations and has an attractive design. The pDA results in a printable summary that patients can bring to consultation with their plastic surgeon in which a decision about breast reconstruction is made. In August 2017, we started a randomized controlled trial to evaluate the impact of the pDA on the decision-making process. Women (n=280) with breast cancer or ductal carcinoma in situ undergoing ablative surgery and eligible for an immediate breast reconstruction are invited to participate. Currently, three out of eight participating hospitals are recruiting and 17 patients have been randomized.

Male breast cancer: development of an online information portal for patients, health care professionals and researchers

This study (2016-2017) is Pink Ribbon funded, and aimed to develop and implement an online, easy accessible, central information portal for male breast cancer patients, health care professionals and researchers. First, all relevant literature and (online) information was reviewed. Expert meetings with representatives of all relevant organizations (patient federation, cancer websites, research groups) were organized. A needs-assessment with men treated for breast cancer, health care professionals, and researchers was performed. The results showed that patients (N=86) desired male patient information with more attention for sexuality, swollen breast, weight problems, cognitive problems, neuropathy, worries about future, genetics, possible causes and control of disease. Health care professionals (N=139) would like more information about genetic testing, psychosocial problems, anti-hormonal therapy and research results. Results from the literature review and expert meeting showed that there is a need for one central location with information for male breast cancer patients, professionals and researchers. As a result, an informative website www.mannenmetborstkanker.nl has been developed and was launched in October 2017, including a guide to up-to-date information, photographs and useful links.

Patient navigation

Studies have shown that patients' needs for supportive care frequently remain unidentified. The use of a Patient Navigation approach entailing the systematic identification of physical and psychosocial problems and supportive care needs, along with relevant health education, behavior activation, and matched care, is likely to address the unmet needs of cancer survivors, and in turn improve health related quality of life. In 2015-2017 such a patient-navigation intervention was developed and pilot tested in the Antoni van Leeuwenhoek. The Navigation Intervention protocol includes three consultations with a patient navigator, a specialized oncology nurse, who identifies psychosocial (e.g. distress, coping with significant others, work-related problems) and physical problems (e.g. pain, fatigue, body-weight) problems, and assesses patients' needs for supportive care. The navigator gives tailored lifestyle advice and psycho-education, uses motivational interviewing to stimulate self-management to attain patients' goals. In contrast to usual care, which focuses on medical aspects, the intervention focuses on resuming daily life activities.
Following the first positive results of the pilot-test, in 2016 a randomised controlled trial was initiated to determine the additional value of this Patient Navigation intervention to usual care. In this RCT, newly diagnosed lung cancer, melanoma and ovarian cancer patients treated at the Netherlands Cancer Institute (n=120), are invited to participate in the study. Currently, data collection of the RCT is ongoing. In total 76 patients are yet enrolled in the study.

Improving sleep quality, psychosocial functioning, and cancer related fatigue with light therapy (SPARKLE-study).

Cancer related fatigue is a frequently reported symptom in survivors of (non-) Hodgkin lymphoma (40-60%). It is defined as a distressing, persistent and subjective sense of tiredness or exhaustion related to cancer or its treatment, which is not explained by recent activity and interferes with daily functioning. A novel and promising intervention to treat this symptom is light therapy. During a 4-week light therapy intervention, patients are exposed to bright white light for 30 minutes within the first half hour after awakening. The aim of the SPARKLE-study, funded by the KWF, is to perform a multi-center RCT to investigate the efficacy of this intervention in 160 (non-)Hodgkin survivors. Moreover, the secondary aim is to explore possible working mechanisms, including changes in sleep quality, psychological variables, biological circadian rhythms, circadian activity rhythms, and/or inflammation markers that have been identified as correlates and potential causes of fatigue. The study is coordinated by the Netherlands Cancer Institute and performed in close collaboration with the BETER-consortium, a nationwide survivorship care program for lymphoma survivors. Patient accrual started in September 2017.

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Publications

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Targeting tumor radiosensitivity and heterogeneity

Radiotherapy is one of the cornerstone treatments for cancer patients in different phases of their disease. We believe that since the introduction of tumor specific targeting agents and advanced tumor imaging modalities radiotherapy strategies have not sufficiently been adapted to optimize their full potential and efficacy.
In our work, we want to use novel agents and imaging modalities to further increase the efficacy and therapeutic window of radiotherapy.
Our work field is both in the preclinical and clinical setting and therefore allows us to investigate and translate general concepts as well as tumor specific approaches. We study radiosensitization strategies preclinically that have a high potential to be introduced directly into clinical trials. Also, we study tumoral changes (in both anatomical and functional aspect) in patients with brain metastases or primary brain tumors to directly optimize logistics and treatment protocols in our clinical practice.

Optimizing local response in cancer in preclinical models

Since the introduction of radiosensitizing agents (like cisplatin), the standard clinical practice is to start radiotherapy and systemic treatment simultaneously, and also to use the same agents throughout the course of radiotherapy as long as the side-effects allow the regimen.
However, we have now shown that upfront treatment of Olaparib (a potent radiosensitizer) does not lead to a direct local regression of the tumor but sensitizes the tumor for irradiation by improving oxygenation. Following this result, we postulate that further modulation of different agents (targeting different factors involved in radioresistance) will improve the radiotherapy outcome. To investigate this novel concept, we make use of different tumor models and targeted agents. Using in vivo imaging and ex vivo assays we aim to elucidate how different targeted agents can and should be used to optimize the local response. We want to identify biomarkers to help us understand which type of agents should be combined with radiotherapy, and at which specific time during fractionated radiotherapy they should be applied.
We are collaborating with different groups (groups of Olaf van Tellingen, Jos Jonkers and Leila Akkari) to synergize our joint expertise and productivity in different preclinical models and different targeted strategies (DNA repair, cell cycle, immunotherapy).

Optimizing radiotherapy in patients with brain metastases and primary tumors

Imaging and treatment protocols for patients with brain metastases

With the introduction of novel targeted agents the survival of cancer patients has improved. This improved survival increased the incidence of patients with brain metastasis because brain

metastases do not always follow the extracranial response. High precision and dose local radiotherapy, also called stereotactic radiosurgery (SRS), is an efficient way to achieve high local control for smaller brain metastases. However, irrespective of the primary tumor all lesions are similarly treated despite large tumoral differences in radiosensitivity. Therefore, we are searching for factors that predict local failure and local toxicity. We do this in collaboration with the Gamma-Knife center in Tilburg aiming to further customize the best treatment for the individual patient.

In contrast to what always has been assumed, we observed that brain metastases can undergo significant shifts in short time intervals. We found shifts up to 7 mm and in our current practice, we do take this phenomenon into account. For our linear accelerator based SRS treatments we limit the time between treatment preparation and the actual treatment to 1-3 days. With the future introduction of the Gamma-Knife in our department we will further decrease this time interval and limit the probability of these changes.
With SRS we are able to better spare normal tissue for unwanted irradiation dose compared to "Whole Brain Radiotherapy" (WBRT). WBRT is less and less applied because of its inferior effect on local control and neurocognitive decline. However, any brain dose may have an impact on the neurocognitive functions. This side-effect might be dependent on the tumor location and how the radiotherapy is modulated. Parallel to our improved delivery techniques we are collecting functional MRI scans and neurocognitive tests in collaboration with the Radiology Department and the Schagen group. With this approach, we can interpret whether and how our treatment strategies should be adapted to optimally preserve both neurocognitive function and local control.

For larger brain metastases we often apply fractionated-SRS or postoperative-SRS, but with an impaired local control compared to SRS of smaller lesions. The field of radiobiology had assumed that the larger number of tumor cells to be eradicated by radiotherapy was the only reason contributing to this impaired local control. However, for this particular group of patients we observed large tumoral changes in more than 50% of the patients during treatment resulting in a high likelihood of suboptimal treatment (i.e. underdosing of the tumor). We are currently investigating this phenomenon in a prospective trial N17MRB with repetitive anatomical and functional MR imaging. We will obtain spatial and temporal changes that are relevant for radiotherapy outcome (e.g. cellular density and hypoxia) understanding more about optimal imaging and dose delivery strategies.

Imaging protocols for patients with primary tumors

Although radiotherapy is the mainstay (most efficient treatment) for patients with high grade gliomas, the prognosis is very poor due to local progression. Unfortunately, dose escalation studies have not proven to be very effective in improving the local control. Our group has observed larger tumor shifts during fractionated treatment for high grade glioma patients whereas new and ongoing trials are not taking these into account. We want to further investigate these anatomical and functional changes as a preparation for a dose escalation study that will irradiate the tumor in an image-guided, adapted, (individualized) and robust fashion.

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Molecular mechanisms that govern the T-cell response

Our work is inspired by the desire to improve (radio-)immuno-therapy of cancer. We focus on T cells and dendritic cells (DCs), costimulatory and coinhibitory receptors and their downstream signaling pathways. Our work is carried out in mouse models and in matching mouse and human cellular systems *in vitro*.

Optimizing CTL responses to cancer

We use therapeutic vaccination and radiotherapy in mouse model systems to delineate bottlenecks in the T cell response to cancer and to validate means to overrule these. Part of our work is concerned with DC activation. When DCs are not activated, they promote T cell tolerance, by offering ligands for T cell coinhibitory receptors. When DCs are activated, they promote T cell immunity, by offering ligands for costimulatory receptors. Pathogens activate DCs, but tumors may not. From our work, the costimulatory receptor CD27 has emerged as an important target in cancer immunotherapy. In collaboration with Aduro Biotech and MSD, we are bringing CD27 agonism to the clinic.

Therapeutic vaccination

CD4 T cells can also activate DCs. We are delineating the molecular mechanisms underlying CD4 T-cell help for the CTL response. We use two versions of a DNA vaccine that contain a human papilloma virus (HPV)-derived CD8 T-cell epitope alone or in combination with CD4 T cell epitopes. This vaccination strategy optimally reveals the impact of CD4 T cell help on CD8 T cell priming, the generation of effector and memory CTLs. We have found that CD27-CD70 costimulation is the key effector pathway of CD4 T-cell help for the CTL response. We have delineated by mRNA deep-sequencing the molecular signature of CD4 T-cell help in newly primed CTL effector cells. This work has identified numerous novel molecular mechanisms that optimize CTL function, which are highly relevant for cancer immunotherapy (figure 1). We have also proven that these mechanisms are general and apply to all CTL responses, including those against viruses. Recently, we have performed epigenetic analysis to study imprinting of CTL memory. These data are integrated with mRNA expression profiles of responding memory CTLs. In this way, we achieve a molecular understanding of how CD4 T-cell help that is delivered during priming alters the long-term fate and functionality of CTLs. In this model, we have also identified key variables in vaccine antigen formulation and delivery to DCs that dictate whether CD4 T-cell help will take place. Currently, we are focusing on the consequences of CD4 T-cell help for short term and long-term DC function.

Radio-immunotherapy

Radiotherapy is aimed at local tumor control with curative or palliative intent. In our radio-immunotherapy approach, spearheaded by Dr I. Verbrugge, local radiotherapy is combined with systemic antibody-based immunomodulation with the aim to achieve a systemic anti-tumor immune response that eliminates both the irradiated tumor and distant metastases. In

a transplantable mouse breast cancer model (AT-3), carrying a previously identified CTL epitope, combining radiotherapy with PD-1 blockade and CD137 agonism is highly efficacious in local tumor control. However, tumors implanted outside the radiotherapy field are not eliminated in this experimental setting. Mechanistic follow-up studies, including mRNA deep sequencing, revealed bottlenecks that impede systemic T cell activity against the non-irradiated tumor. By rationally adding clinically relevant interventions to the radio-immunotherapy protocol, we succeeded at improving systemic T cell responses and control of non-irradiated tumors. Follow-up work is aimed at delineating the consequences of (radiotherapy-induced) cell death modalities for the induction of systemic T cell immunity. In collaboration with biotech/pharma, we will test rational approaches that promote such immunity. Our ultimate aim is to define strategies that improve systemic T cell responses in conjunction with radiotherapy that can be implemented in clinical trials.

Generating primary DCs and related cell types from their precursors

Associate staff scientist Dr Y. Xiao has developed a research line on the homeostatic development of mouse and human DCs from hematopoietic precursors. She has defined in the mouse bone marrow a common precursor of macrophages, osteoclasts and DCs (MODP) and a downstream precursor for macrophages and osteoclasts (MOP). She has also identified the MODP in human bone marrow and cord blood and proved that it lies downstream of what was known as the granulocyte/macrophage progenitor, but should be redefined as granulocyte-, macrophage-, osteoclast and DC progenitor (GMODP) (figure 2). Y. Xiao and coworkers have developed protocols for the generation of human DC subsets from these progenitors and have proven that these subsets can crosspresent antigen and prime T cells. Having the ability to generate functional human DC subpopulations at will, we can characterize them and optimize them for T-cell priming. We also investigate the cellular origin of Langerhans cell histiocytosis, in collaboration with Dr. A. van Halteren (LUMC, Leiden). We also study osteoclast development, which is important for diagnostics and interventions in human cancers that display bone metastasis.

Understanding regulatory T cells

Regulatory T cells (Tregs) are hallmarked by the expression of the Foxp3 transcription factor that installs all their unique characteristics. Tregs are an important target in cancer immunotherapy, since they impede anti-tumor immune responses. We aim to define unique, targetable vulnerabilities of Tregs. For this purpose, we are carrying out a large project, in collaboration with the groups of Drs. D. Amsen/R. van Lier at Sanquin and C. Berkers at the University of Utrecht to delineate key differences between conventional CD4 T cells and Tregs. This work is supported by grants from ZonMW and the Institute of Chemical Immunology and involves global analyses by transcriptomics, proteomics and metabolomics. The first proteomics study is completed and has revealed that human Treg identitify is defined by adaptations in multiple signaling pathways that act downstream of the TCR, costimulatory- and cytokine receptors. We have set up an *in vitro* system, wherein we can investigate at all "omics" levels, the consequences of TNF receptor family- and CD28 signaling, as well as PD-1 signaling for conventional T cells as compared to Tregs. Our analyses have already revealed remarkable properties of thymic Tregs.

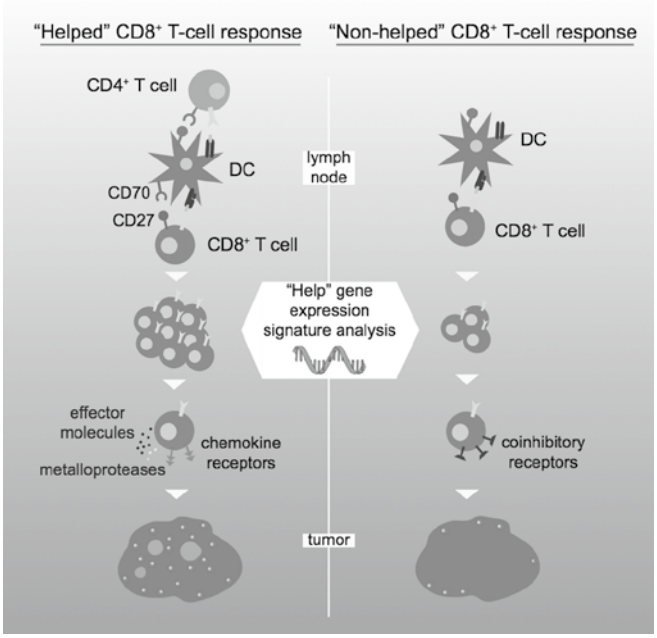

Figure 1. The approach to find the molecular programs that optimize CTL effector function as a result of CD4 T-cell help.

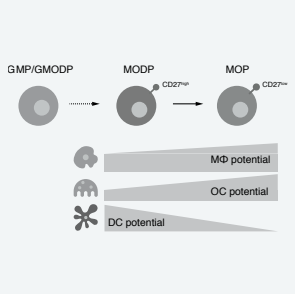

Figure 2. The development of macrophages, osteoclasts and dendritic cells from common progenitors.

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Publications

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Experimental Biomedical Genetics

Our group employs a classical genetic approach to randomly mutate the DNA of an organism and study the consequences. We use two significant improvements to apply this approach to human biology with high precision and throughput: the use of haploid human cells and the application of deep sequencing to measure the effects of millions of mutations in parallel. We apply this approach to study how genes collaborate to affect phenotypes and to identify new players in processes linked to human disease.

Regulators of Molecular Phenotypes

As key executers of biological processes, the activity and abundance of proteins is subjected to extensive regulation. We have developed an approach to directly couple genomic mutations to protein measurements within individual cells. Using this approach (figure 1), which is both sensitive and scalable, genes can be identified that regulate any molecular protein phenotype that is quantifiable in haploid human HAP1 cells. We have studied various cellular processes such as signal transduction pathways, epigenetic modifications, stress responses and previously uncharacterized posttranslational modifications. In all cases genes could be linked to the measured traits. From these studies we identify the E3 ligase subunit KCTD5 as key regulator of the AKT signaling pathway, a novel component of the cholesterol sensing pathway as well as CMTM6 as a new component of the PD1-PDL1 axis which is a successful target for cancer immunotherapy (in collaboration with the group of Ton Schumacher).

A Genetic Wiring Map for Human Cells

The ability to link genes to protein phenotypes using deep sequencing will enable us to assign a wealth of phenotypic information to genes. The genetic regulators that are linked to a molecular phenotype can be studied on their own but they can also be studied in comparison. This will point out genes that cause very narrow phenotypic effects and genes that lead to broad phenotypic consequences. Choosing a diverse set of molecular phenotypes as readouts will in the future enable us to generate a genetic wiring map for human cells (figure 2).

Genetic Interactions

When the function of one gene affects the activity of another gene this is referred to as a genetic interaction. We use genetics in haploid cells to study two types of genetic interactions: synthetic lethality, a situation where mutations in individual genes do not affect cell viability but a combination of both mutations in the same cell (or organism) leads to lethality and genetic suppression: a situation where a gene-associated phenotype gets neutralized by mutation of another gene. To study the principles of synthetic lethality in human cells we applied an approach that enables systematic synthetic lethal screens in human cells solely based on paired genetic mutations. In these studies, we observe that human genes frequently

engage in synthetic lethal interactions, that genes that are synthetic lethal with a query gene often function in the same compartment.
We use quantitative molecular phenotypes in order to identify genetic suppression mechanisms. Using this approach, we have identified a viral clearance pathway responsible for the resistance phenotype of PLA2G16-deficient cells (see below) and we have identified elevated GPCR signaling as a responsible mechanism for AKT activation in KCTD5-deficient cells.

Pathogen Portals

Our group studies viral families that cause the most-deadly human infections (Filovirus [eg. Ebola virus], Arenavirus [eg. Lujo virus], Bunyavirus [eg Hanta virus] as well as the most frequent human infections (Picornavirus [eg rhinovirus]). We use haploid genetics to gain insight into their entry tactics.
Haploid genetic screens revealed that our previous understanding of virus entry was incomplete. In the classical model receptors recognized at the cell surface mediate all steps to deliver viral cargo into the cytoplasm. This model does not apply to Ebola or Lassa viruses. Instead, entry of these pathogens requires a 'receptor switch' to an intracellular transmembrane protein, recognized deep in the endosomal compartment. For Ebola virus, this intracellular receptor is NPC1, the lysosomal cholesterol transporter and for Lassa virus the intracellular lysosome-resident protein Lamp1.

Non-enveloped Picornaviruses generate a pore into the endosomal membrane. It was thought that this was sufficient for efficient release of viral RNA into the cytoplasm. We identified PLA2G16 as a critical host factor for picornavirus infection and showed that PLA2G16 was recruited to the perforated endosomal membrane. Remarkably, loss of PLA2G16 leads to a virus-resistance phenotype that could be suppressed by ablation of another pathway that also responds to membrane damage. This pathway consists of Galectin-8 which senses membrane damage leading to subsequent digestion of the damaged endosome. This pathway had been linked before to the clearance of intracellular bacteria. Thus, infection by picornaviruses involves two competing processes triggered by viral membrane perturbation: activation of a pore-activated clearance pathway and recruitment of a phospholipase to enable genome escape.

Modification of the Cytoskeleton

Human cells contain a cytoskeleton, a dynamic structure important for cell shape and intracellular transport, composed of polymerized α- and β-tubulin heterodimers. The importance of the cytoskeleton is emphasized by the working mechanism of a widely used group of cancer medicines called taxanes that target microtubules. Extensive enzymatic modifications create different microtubules with specialized functions. Whereas enzymes for most of these modifications have been identified, the detyrosinating enzyme, which initiates the tyrosination cycle, has escaped identification for 40 years. Using a haploid screen, we identified SVBP, a peptide that regulates the abundance of Vasohibins (VASH1 and VASH2), as a regulator of detyrosination. In complex with SVBP, Vasohibins act as proteolytic enzymes to remove the c-terminal tyrosine of α-tubulin. Thus Vasohibins, factors that were previously studied as secreted molecules regulating blood vessels, constitute a long-sought missing link in the tubulin tyrosination cycle (figure 3).

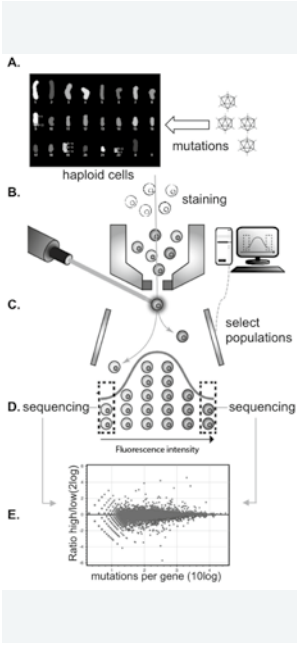

Figure 1. Regulators of Molecular Phenotypes. Mutagenized haploid cells (A) are stained (B) for an intracellular target. Cell populations with high and low levels of the molecular trait are sorted (C). Mutation frequencies in individual genes are quantified in both populations (D) yielding negative and positive regulators (E).

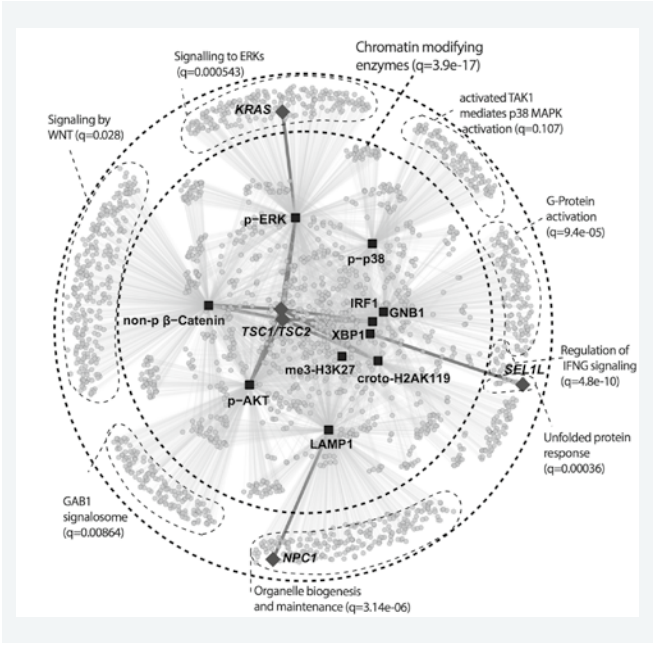

Figure 2. Genetic wiring map. Each screened protein state phenotype (black square node) is connected to genes identified as their respective significant regulators (grey nodes). Selected examples are shown (diamonds) of genes affecting either a specific query phenotype or display a broader phenotypic range.

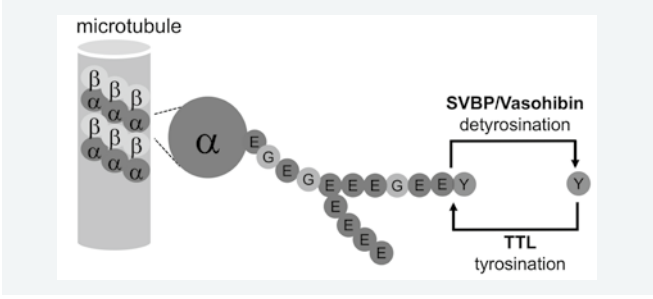

Figure 3. Posttranslational modification of a-tubulin: the detyrosination-tyrosination cycle. Synthesized a-tubulin contains a tyrosine residue which can be proteolytically removed by Vasohibins in complex with SVBP. The Tubulin Tyrosine Ligase (TTL) is subsequently able to re-tyrosinate tubulin to reset this posttranslational modification.

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Impact of the immune system on metastatic breast cancer and therapy response

Metastasis formation and unresponsiveness to conventional therapies are the challenges in cancer therapy that most urgently need solutions. We focus on the immune system and its influence on breast cancer metastasis and therapy responsiveness. Through mechanistic understanding of the crosstalk between the immune system and cancer cells, we aim to contribute to the design of novel immunomodulatory strategies to fight metastatic breast cancer and to increase the efficacy of anti-cancer therapies.

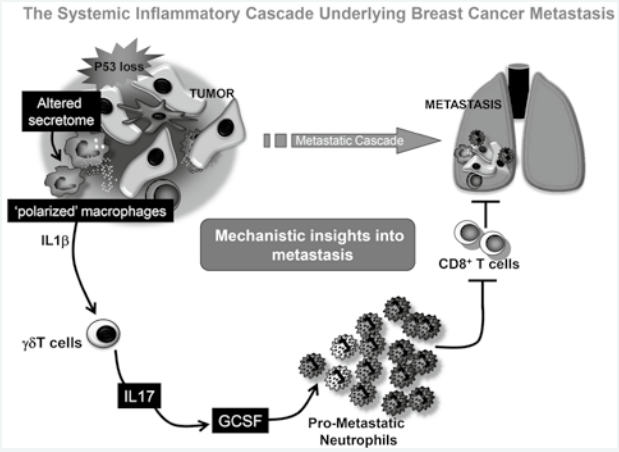
Dissecting the impact of the immune system on breast cancer metastasis

Over 90% of breast cancer deaths are due to complications as a consequence of metastasis formation. Despite its devastating effects, metastatic disease is still poorly understood and incurable. It is now well established that cells and mediators of the immune system influence metastasis formation. Historically, our immune system was thought to form an intrinsic defense mechanism against cancer and metastasis. Yet, the majority of cancer types exploits a myriad of strategies to successfully evade destruction by the immune system. In fact, mounting evidence supports the notion that cancer cells hijack the immune system for their own benefit, allowing them to escape from immune attack, survive under dire circumstances and spread to distant organs. One major focus of our lab is to dissect the impact of the immune system on breast cancer metastasis formation. Utilizing pre-clinical mouse models of spontaneous breast cancer metastasis that mimic the clinical course of metastatic disease in humans, we discovered that mammary tumors elicit a systemic inflammatory cascade to dampen anti-tumor T cells and maximize metastasis formation. This cascade is initiated by tumor microenvironment-derived CCL2 and IL1b that activate IL17-producing gamma delta T cells, leading to G-CSF-dependent systemic neutrophil expansion and polarization. In turn, these neutrophils suppress CD8+ T cells, allowing disseminated cancer cells to go unnoticed (Coffelt et al. Nature 2015). These findings provide novel mechanistic insights into the thus far poorly understood metastatic cascade. Moreover, our data indicate that targeting this novel cancer cell-initiated γδ T cell-IL17-neutrophil axis represents a new strategy to inhibit metastatic disease. Current efforts in the lab are focused on dissecting how the genetic make-up of breast tumors dictates activation of the immunosuppressive gamma delta T cell – IL17 – neutrophil axis. In collaboration with the lab of Jos Jonkers, we screened sixteen genetically engineered mouse models of spontaneous mammary cancer, which each carry different genetic drivers, for cytokine abundance in the serum and neutrophil expansion in the circulation. We found that tumors deficient in p53 have increased serum levels of IL1b, IL17 and G-CSF and a greater proportion of circulating neutrophils than p53-proficient tumors. We are currently finalizing studies aimed at dissecting how loss of p53 function dictates the γδ

T cell – IL17 – neutrophil axis. In addition, we are validating our findings in human breast cancer patients. In collaboration with medical oncologist Marleen Kok we have established an extensive immunomonitoring program in the lab to perform in-depth profiling of the immune landscape in fresh blood samples of patients with different subtypes of breast cancer. Our first analyses show a strong increase in circulating neutrophils in patients with triple negative breast cancer. A proportion of these patients also has increased IL17-producing γδ T cells in the circulation. In parallel, we are assessing the tumor- and metastasis-modulating effects of other inflammatory mediators and immune cell types. Together, these mechanistic data combined with validation studies in blood samples of breast cancer patients provide further insights into how breast cancer metastasis occurs and uncover potential new targets. The ultimate goal of these studies is to contribute to the rational design of personalized immune intervention strategies for cancer patients.

Elucidating the impact of the immune system on the efficacy of anti-cancer therapies

Chemoresistance is one of the key challenges in cancer patient care. Chemotherapeutic drugs elicit a number of changes in immune-related parameters including the composition, phenotype and function of immune cells. There is a growing realization that these changes in the immune system influence the success of chemotherapy. Using the *K14cre;Cdh1$^{F/F}$;Trp53$^{F/F}$* mouse mammary tumor model, we study the impact of the immune system on the anti-cancer efficacy of chemotherapy and immunotherapy. Our ongoing pre-clinical studies demonstrate that components of the innate immune system counteract the anti-cancer efficacy of chemotherapy. Targeting macrophages by CSF-1R blockade markedly improved the anti-cancer efficacy of cisplatin in a Type I IFN dependent manner, but not of docetaxel. We discovered that depletion of macrophages through CSF-1R blockade together with cisplatin treatment evoked a compensatory neutrophil response limiting the synergistic anti-cancer effect. These data highlight the importance for optimally matching chemotherapeutics with immunomodulatory compounds and indicate that the inherent flexibility and redundancy of the immune system lends itself to deleterious feedback mechanisms in which the function of a depleted population is reinstated by another population. The goal of our current projects is to understand the underlying mechanisms by which myeloid cells counteract the efficacy of conventional anti-cancer therapies, and to dissect the resistance pathways arising from within the immune system upon treatment with immunomodulatory therapies. In parallel, we are dissecting cancer-induced immunosuppressive mechanisms driving escape of primary breast tumors and metastases from immunotherapeutic strategies. We found that *K14cre;Cdh1$^{F/F}$;Trp53$^{F/F}$* mice with established mammary tumors do not respond to therapy with the immune checkpoint inhibitors anti-PD-1 and anti-CTLA-4 when applied as a single treatment modality; however, synergy is observed when combined with platinum-based chemotherapy and this is dependent on CD8$^+$ T cells. In line with these results, we found an increase in the number of tumor-infiltrating CD8$^+$ T cells in *K14cre;Cdh1$^{F/F}$;Trp53$^{F/F}$* mice treated with the combination therapy as compared to chemotherapy only. We are currently testing whether reprogramming of the immunosuppressive microenvironment increases success of cancer immunotherapy. Besides providing mechanistic insights, this research line has clear relevance for the clinic, and we foresee that findings from this project may contribute to the rational design of combinatorial strategies aimed at maximizing clinical success of immunotherapy for metastatic breast cancer patients.



The systemic inflammatory cascade underlying breast cancer metastasis as revealed in our studies

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Genome function and dynamics

Only 3% of our genome codes for proteins, the remaining 97% contains sequences that govern the expression of genes. The main objective of the group is to understand how non-coding sequences in the genome influence gene regulation. Gene expression is affected at a large range of scales; from single point mutations in regulatory sites to the modification of megabase sized three-dimensional structures such as chromatin loops. We aim to integrate these different regulatory scales into models for gene regulation.

Assigning function to non-coding genetic variation

Advances in sequencing technology have made personal genomes a reality. Understanding the effects of genetic variation on health and diseases will be an important aspect of personalized or precision medicine. The vast majority of genetic variation that has been associated with human traits in GWAS studies is found in non-coding DNA. Although we can predict the effect of a mutation in coding DNA with a very high amount of certainty, predicting the effect of mutations in non-coding DNA is extremely difficult. We are cataloguing functional genetic variation with a combination of multi-omics data and computational biology methods. We have generated haplotype-resolved human genomes for a number of human cell lines. By assessing the allele-specific expression data we can identify genes that are affected by cis-acting genetic variants. By combining these data with chromatin profiles (ATAC-seq, ChIPseq) and 3D genome information, we will identify the cis-acting gene regulatory variants.
In addition to whole genome haplotyping, we are performing targeted haplotyping of the cancer-risk genes BRCA1 and BRCA2 to identify genetic variants that may be associated with allele-specific expression of these genes.

Functional dissection of the three-dimensional genome

At the sub-megabase scale the genome is organized into chromatin loops, which are thought to facilitate wanted interactions and restrict unwanted interactions between promoters and enhancers, leading to correct gene expression. Chromatin loops are formed between CTCF binding sites and the ring-shaped cohesin complex. The cohesin complex is critically important for the formation and maintenance of these loops. Together with the Rowland lab we have determined the 3D genome in mutants that affect the stability of cohesin on chromatin. Importantly, when cohesin is stabilized, we see that chromatin loops become longer (figure 1). Conversely, lower levels of cohesin on chromatin leads to a shortening of chromatin loops. Disruption of chromatin loops affects hundreds of genes, presumably by disruption of correct promoter-enhancer communication.
To further dissect which proteins affect the long-distance interaction between genomic loci, we are building a catalogue of

3D genomes in mutants that affect nuclear organization. These mutants span a broad range of functions: the aforementioned proteins that affect cohesin function, proteins that affect general transcription, but also tissue-specific transcription factors. These mutants provide an ideal platform for studying the relationship between gene regulation and the 3D genome.

Software for the analysis of 3D genome data

3D genome data is complex genome-wide data that requires computational tools for analysis. We are actively developing software for statistical and visual analysis of 3D genome data. For the analysis of 3D genome where the interaction profile of a specific locus is analyzed (such as 4C, figure 2) we have developed a peak calling algorithm. This R package, called peakC, enables the robust and systematic analysis of 4C profiles. Our method has a lower false positive rate compared to competing packages.
For 3D genome data where the entire genome is analyzed (such as Hi-C, figure 2) we have developed a visual analytics tool, called GENOVA. In GENOVA we have combined a number of visual analysis methods into an R package. With GENOVA, users with relatively limited R experience can make publication quality figures of their Hi-C data and perform all manner of systematic analyses on their data.
Our software can be freely downloaded from our GitHub page: https://github.com/deWitLab.

Charting the regulatory landscape of tumor models

Organoids represent an interesting model for studying tumors and tumor development. Together with the lab of Hans Clevers and Jarno Drost (Hubrecht Institute, Utrecht) we are charting the regulatory landscape of tumor organoids and of genetic organoid models of tumor progression. We have generated ATAC-seq and RNAseq profiles to link regulatory regions to downstream transcriptional events. By charting the regulatory landscape after the ablation of critical drivers of tumor formation, we strive to identify regulatory elements that drive tumor formation.

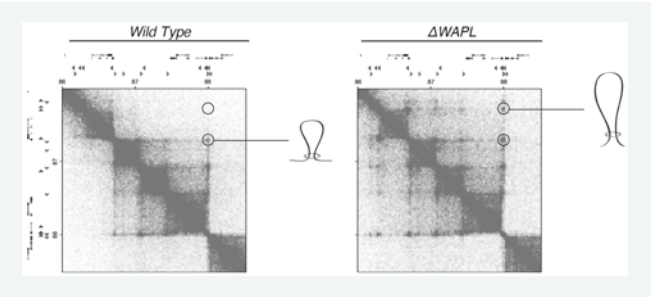

Figure 1

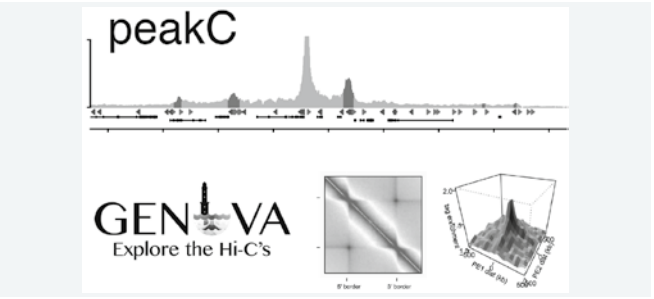

Figure 2

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Unravelling the role of RNA translation in cancer

Our main research focus is on the role that RNA translation plays in the development and progression of cancer. Dysregulation of this process is considered by many to be one of the hallmarks of cancer and has been shown to play an important role in the proliferation and survival of cancer cells, as well as other key changes in cancer, including alterations in angiogenesis, immune response and metabolism.
In our lab we study RNA translation using mouse models of cancer, and employ a range of genome-wide screening approaches. We are particularly interested in the functional and mechanistic implications of deregulation of this process.

Apc deletion in the intestine

Excluding skin cancers, colon cancer is the third most common form of cancer, and the second most common cause of cancer death. Nearly 80% of colon cancers harbor an inactivating mutation in Apc, which results in signaling through the Wnt pathway. When this gene is deleted in the mouse intestine, we see several oncogenic phenotypes, including increased proliferation and a block in differentiation. Furthermore, if we delete Apc specifically in the stem cells, we drive rapid adenoma formation.
We have shown that after Apc deletion there is an mTOR-mediated increase in RNA translation. If we block this by using inhibitors of mTOR, we can block the oncogenic phenotypes, including adenoma formation. Additionally, if mice have already developed adenomas, we can regress these lesions, showing that this increased translation is required for the maintenance of the adenomas. We showed that this is mediated via the mTORC1 – S6K – eEF2K – eEF2 pathway, driving the elongation phase of RNA translation. We have also showed that this increase in elongation rate is not a global effect, but seems to regulate specific genes.

Identifying genes regulated by RNA translation

The primary focus of the lab is to identify genes that are regulated by RNA translation, particularly the elongation phase. As we have shown that increased elongation is required by adenomas, understanding this is of utmost importance. To study this, we are making use of a ribosome profiling technique, called RiboSeq. This technology allows us to identify ribosome bound RNAs, giving us information about translational efficiency, ribosome occupancy and amino acid dependencies of the cells. By combining this with a pulse chase assay known as the Ribosome Runoff Rate assay, we can identify genes that are specifically regulated by elongation, a process known as ElongationSeq.
In order to analyze this *in vivo* we are using a mouse that expresses a tagged version of ribosomal protein in our tissue of interest (known as the RiboTag allele). This allows us to easily and efficiently isolate the ribosomes and associated mRNA from animal intestines, without having to sort the cells. By combining

these techniques, we can identify the genes that are regulated by elongation following Apc deletion in the intestine. We can then use Crispr-Cas9 technology or shRNA to pinpoint the genes that are functionally important in this context (figure 1).
One of the genes we have shown to be regulated in this manner is Cyclin D3. Unlike the highly homologous family members Cyclin D1 and Cyclin D2, Cyclin D3 is upregulated by increased elongation following Apc deletion. When we delete Cyclin D3 in human colon cancer cell lines using Crispr, we see a significant decrease in the proliferation of these cells, suggesting that it may be an interesting therapeutic target in this disease.

Mechanism of elongation control

A second focus of our lab is understanding why some genes are regulated in this way and others are not. To do this we are combining several genome-wide analyses of RNA secondary structure, tRNA availability and charging, and ElongationSeq. We aim to identify the characteristics of an mRNA that determine the rate at which it is translated. For example, the same amino acid sequence can be encoded for using different codons, resulting in different rates of production of the protein. Interestingly, Cyclin D3 (which we have shown to be elongationally controlled) uses several distinct codons compared to Cyclin D1 and Cyclin D2. We are currently switching these codons to see if this has an effect on the rate of elongation. Once we understand this, we can begin to consider designing rational therapeutic strategies to target the process.

RNA translation in intestinal stem cells

The intestinal stem cell can be found at the base of the crypt, interspersed between Paneth cells. It is known to respond to nutrient availability, and maintain the homeostasis of the organ. It is also thought to be the cell of origin for colon cancer, to maintain the cancer's growth, and to potentially mediate the response of the cancer to therapy. Interestingly, we and others have shown that these stem cells have distinct pattern of translation.
In order to study this in more depth, we are using the RiboTag allele, as described above. Using a Cre-Recombinase driven by a stem cell specific promoter, we can isolate the ribosomes specifically from this tiny population of cells and compare that to other populations present in the intestine (figure 2).
We will also combine this with analysis of the nutrient requirements of the cells to identify any amino acid limitations that may allow us to alter cell fate decisions. For example, we have shown that restriction of Lysine increases the number of stem cells, while restriction of Valine has the opposite effect. Using these complementary approaches, we will define the translation landscape of intestinal stem cells, and hope to identify amino acids and signaling pathways that will allow us to alter stem cell fate decisions.

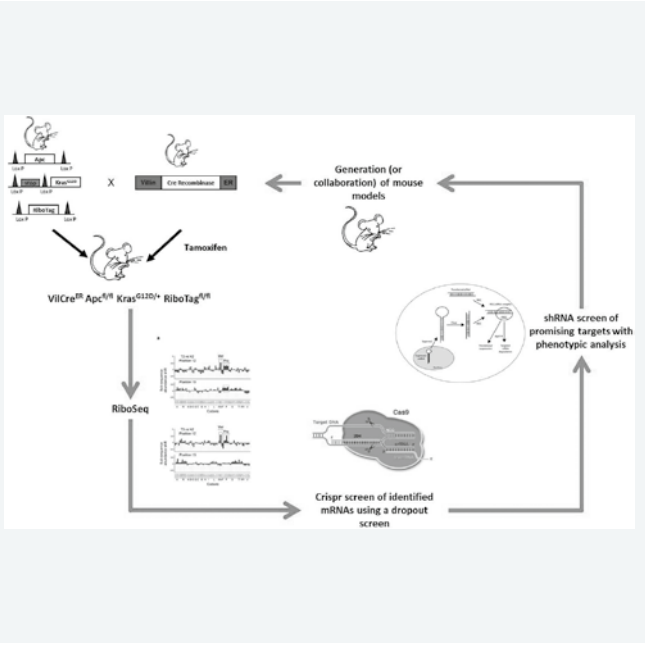

Figure 1: Outline of the experimental process for identifying and functionally analyzing genes regulated by RNA translation.

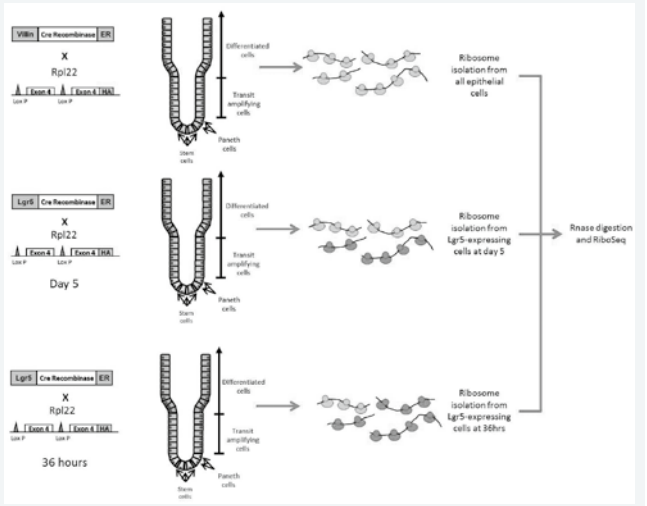

Figure 2: Cell-type specific expression of the RiboTag allele allows the isolation of ribosomes from rare cell in the intestine for comparison of stem cells to differentiated cells.

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Immunotherapy, immunomonitoring and production facility

This research line is aimed at developing novel T-cell based immunotherapies that can be applied in cancer patients. The focus is on patients with solid tumors, especially melanoma, renal cell carcinoma, and HPV-associated cancers. These immunotherapies comprise DNA based vaccines and T-cell products, including TILs and genetically modified peripheral blood T cells. GMP production of these therapeutic agents takes place in the Biotherapeutics Unit (BTU), situated in the hospital pharmacy. A second objective concerns immunomonitoring, primarily to evaluate the effects of novel immunotherapies. These studies are conducted together with the labs of Ton Schumacher, Pia Kvistborg and Christian Blank at the NKI-AVL and with national and international collaborators.

DNA vaccination for the treatment of cancer

DNA vaccination for the treatment of high-risk HPV-associated cancers. HPV infection (serotypes 16 and 18) is associated with development of squamous cell cancer of the cervix, penis, vulva, anus and oropharynx. HPV proteins E6 and E7 are foreign antigens and are required for carcinogenesis. Therefore, they are exquisite targets for immunotherapy, as already demonstrated by therapeutic vaccination in patients with vulvar lesions.
In preclinical studies, we have developed highly immunogenic and safe HPV 16 E6- and E7-containing DNA vaccines for which we have produced GMP grade vaccines. These vaccines are currently being tested in a phase I clinical trial (Prof Gemma Kenter, gynaecologic oncologist and co-workers). Patients with HPV 16-positive Vulvar Intraepithelial Neoplasia Grade III (VIN III) are vaccinated using a novel and potent intradermal DNA vaccination strategy. Immunomonitoring is being performed by us, see below.

Adoptive immunotherapy program

TIL therapy

Adoptive therapy with TIL is based on results from the NIH, Bethesda, USA and the Sheba Medical Center, Tel Aviv, Israel, showing a 50% objective response rate in heavily pretreated stage IV melanoma patients. This treatment combines the *ex vivo* culture of melanoma-reactive T cells isolated from metastases with non-myeloablative chemotherapy and high dose bolus IL-2. Our goals are: 1) to show that this treatment can be given safely at the NKI-AVL, 2) to demonstrate in a randomized controlled phase III trial that this treatment improves progression-free survival compared to standard treatment and 3) to perform a comprehensive analysis of the T-cell specificities of the melanoma-reactive TIL prior to and after adoptive transfer.
A few year ago, we have finalized a pilot study and enrolled ten patients. Five patients had an objective response (3 PRs and 2 CRs). One patient with CR is now free of disease for over 6 years and the other patient for more than 4 years. The median overall survival in this small study is 16 months. The

safety of the TIL treatment was as expected and side-effects could be attributed to the chemotherapy and high dose IL-2.
In collaboration with Sanquin and one European cancer center in Copenhagen, Denmark, we have initiated an international, randomized controlled phase III trial in stage IV melanoma patients, comparing TIL with standard of care for second line treatment. Enrollment of patients started in October 2014. Up to date 50 patients have been randomized. Materials (liquid and tumor biopsies) are being collected for translational research.

We are currently also developing TIL therapy for other malignancies, such as ovarian cancer (collaboration with gynecology), and are aiming to further improve the anti-tumor reactivity of TIL.

TCR gene therapy

In collaboration with the Schumacher lab, we have selected a highly avid TCR specific for melanocyte differentiation antigen MART-1_{26-35}. This TCR, called 1D3, has been produced by a German GMP manufacturer, by expression in a retroviral vector (MP-71). The construct prevents mispairing with endogenous TCR chains to prevent unwarranted cross-reactivities of transduced T cells. Clinical grade culturing and transduction of peripheral T cells with the 1D3-MP-71 retrovirus has been validated step-by-step in our GMP facility. Cells are cultured in the presence of IL-7 and IL-15 to keep them in a less differentiated state.

A phase I/II clinical study was started in melanoma patients in 2012. The first patient had lethal multi-organ failure, probably induced by a cytokine release syndrome. The study was immediately halted and was reopened in 2013 as a dose escalation study. A second patient was treated with 100-fold fewer TCR gene transduced T cells. In 2014, two more patients were enrolled. The treatment was without complications except a skin rash, which was biopsied. Pathology showed infiltration of activated CD8+ T cells in the epidermis and loss of MART-1 expressing melanocytes. In 2015 two patients were treated with 5 times higher T cell dose (2.5 x 10^8 transduced T cells). For the first time apart from skin toxicity, now grade 3, also other toxicities were seen, including a cytokine release syndrome, indicating the potency of this treatment. This patient developed a partial response to the treatment. The study was opened for metastatic uveal melanomas as well. In 2016 another metastatic cutaneous melanoma patient was treated, now with 1x10^8 transduced T cells. Apart from a grade 2 skin rash and grade 1 uveitis this patient did well. In 2017, we have treated 5 more patients in this last cohort. Side effects were manageable and some transient tumor control was observed. The main take-home message of this study is that with the developed production protocol, only very low cell numbers (compared to other clinical studies) are already resulting in high on-target reactivity.

New developments

Together with the Emile Voest lab and an external partner, we are working on strategies to extract tumor reactive cells from the blood as novel treatment option.
In addition, we have entered an exciting collaboration with NEON therapeutics (Cambridge, MA), in which we develop new T cell therapies directed against patient specific neo-antigens.

Tumor grafting and resistance to targeted agents

In collaboration with Prof Daniël Peeper, we have developed a mouse model to study drug resistance of human melanomas, such as to the BRAF inhibitor vemurafenib, dabrafenib or the combination of a BRAF and MEK inhibitor. Biopsies or resected melanoma metastasis tissue are subcutaneously grafted in immunodeficient (NSG) mice. The tumor take in these animals is highly successful and hence these animals can subsequently be treated with targeted drugs to study resistance. Tumor tissues from these animals are subsequently subjected genomic, transcriptomic and proteomic analysis. This work is performed under supervision of Prof Peeper.

Immunomonitoring of patients treated with immunotherapy

We aim to map the effect of immunotherapies by dissecting cancer-specific T-cell responses in peripheral blood and tumor tissues of cancer patients. The results can be correlated with clinical outcome to improve our understanding of the mechanisms underlying the anti-tumor effects of the therapies.

For the DNA vaccination trial, vaccine induced E6 and E7 directed T cell responses are detected directly *ex vivo* in blood to monitor the immunogenicity of these therapeutic vaccines.
For the first TIL study, T cells directed against mutated self-antigens are detected in both infusion products and blood samples. We showed that neo-antigen specific T cells could be detected in TIL infusion products in three out of three responding patients. In most cases, these neo-antigen reactivities significantly increased in the peripheral compartment and were detectable for up to 3 years after cell infusion.
For the MART-1 TCR study the level of gene-modified cells is monitored in the blood. In all patients, these cells can be found in the blood for at least a month and in some cases even up to six months.

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Biostatistics

The group investigates statistical techniques for modelling the association between radiation exposure and the risk of cancer and cardiovascular disease and develops efficient designs and analytic methods for studies of predictive biomarkers to improve personalized medicine. Moreover, the group provides statistical expertise and training to investigators from the hospital and the research laboratories on topics from basic to clinical and epidemiological research.

Novel statistical methods for efficient identification of biomarkers for personalized cancer treatment

We started this year to characterize statistical methods for the evaluation of predictive markers in observational clinical studies or trials with archived specimens. Specifically, we evaluate various study designs (cases and non-cases, case-only, hybrid approaches) including additive and multiplicative models with regard to required sample size and statistical power, using data on BRCA1-like breast cancer and substantial benefit of high-dose alkylating chemotherapy, carboplatin, and capecitabine added to standard adjuvant chemotherapy. We will also simulate data in order to compare the results of various approaches with the truth. Providing powerful statistical methods will maximize the chance that truly predictive markers are identified and promoted for confirmatory evaluation in randomized clinical trials.

Exposure to ionizing radiation from pediatric computerized tomography scans and subsequent cancer risk

Computed tomography (CT) delivers substantially higher radiation doses than most other diagnostic imaging techniques, e.g., X-ray. Its use has increased dramatically since 1980.
We collected data on 162,886 patients who received 258,297 pediatric CT scans during 1979-2014 in one of 42 participating Dutch hospitals. After extrapolation, the estimated annual number of pediatric CT scans in the Netherlands increased from 7,731 in 1990 to 26,023 in 2012. More than 70% of all scans were of the head. During the last decade, substantial increases of more than 5% per year were observed in general hospitals with less than 500 beds and among children of 10-18 years of age (Meulepas et al, Eur Radiol 2017).

We linked our cohort with the Netherlands Cancer Registry and the Dutch Childhood Oncology Group (DCOG) to determine cancer incidence. Evaluation of radiation-related risks of leukemia and brain tumors is currently underway. These data have been contributed to the EPI-CT consortium for a pooled analysis of several European studies, directed by the group and including over one million children.

To assess the feasibility of a CT study among adults, who receive many more CT scans than children and have higher cancer

incidence, we quantified potential indication bias using electronic records from 75,968 adult patients who received 212,487 CT scans at Columbia University Medical Center in the period 1994-2014 (mean follow-up, 7.6 years). Our data suggest that in studies of adults who underwent CT scans, indication bias is unlikely important for colorectal and female breast cancer but may be a concern for lung cancer (Meulepas et al. 2017).

Statistical assessment of cancer risks from therapeutic radiation exposure incorporating the spatial distribution of radiation dose in the target organ

Incorporation of dose distributions is currently not standard in epidemiologic studies of radiotherapy-related second cancer risk. For example, in a pooled analysis of three international case-control studies of stomach cancer following Hodgkin lymphoma, testicular cancer, and cervical cancer, we used radiation dose to the tumor location and found that risk increased with increasing radiation dose ($p<0.001$, Gilbert et al, Radiat Res 2017). The excess OR (EOR) per Gy increased with time since exposure (p-trend=0.004) with an EOR/Gy of 0.38 (95% CI 0.12-1.04) for stomach cancer occurring ≥20 years after exposure corresponding to ORs of 4.8 and 10.5 at radiation doses to the stomach of 10 and 25 Gy, respectively. Of 111 stomach cancers occurring ≥20 years following radiotherapy, 63.8 (57%) could be attributed to radiotherapy. These findings highlight the need for direct evaluation of the health effects of high dose fractionated radiotherapy rather than relying on data on persons exposed at low and moderate acute doses.

It is expected that using data on the distribution of radiation dose in the target organ yields more efficient and less biased estimates of the dose-response relationship as well as better risk predictions for clinical use. In a project which started this year, we use two case-control studies, on breast cancer among Hodgkin lymphoma survivors (174 cases, 466 controls) and on meningioma among childhood cancer survivors (150 cases, 1,450 controls) with estimates of dose distributions to the breasts and the brain, respectively. Based on these data and simulations, we will evaluate the operational characteristics of statistical approaches using summary measures of dose concentration such as the percentage organ volume receiving a dose above a certain level or the Gini index, and approaches including the entire spatial dose distribution (case-control matched-location, case-location, and case-control-all-location methods). We will predict absolute lifetime risks for a second tumor among 200 recently treated patients based on their contemporary radiotherapy treatment plan, with smaller fields and lower target doses, and evaluate how predicted risks vary across methods.

Incorporation of dose distributions can overcome the perceived intrinsic problem of late effects research, i.e., the translation of risk estimates from patients treated decades ago with high-dose, high-volume exposures to current patients receiving contemporary radiotherapy involving lower doses and different dose distributions, by using radiation exposure metrics suitable for translation across treatment scenarios.

Biostatistics

Statistical collaboration in projects of other groups included pre-clinical studies on biological mechanisms, evaluations of determinants of disease occurrence as well as clinical studies of prognosis and clinical trials for treatment comparisons.

In order to improve the design and statistical analysis of animal experiments at the NKI, we identified state-of-the-art statistical methodology for each group of experiments. An example is the analysis of longitudinal measurements of tumor size using linear mixed models. Our aim is to provide knowledge to researchers which enables them to design and analyze their experiments (online hand book, online tools, courses/workshops) and to offer tailored statistical support when needed.

The group offered statistical training, including a one-week course on Basic Medical Statistics and several half-day workshops on specific methodologic challenges such as sample size calculation, interaction analysis, missing data.

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Programmed & non-Programmed mutagenesis

Lymphocytes and their precursors are licensed to transiently activate specific mutation pathways that enable efficient remodeling of antigen-receptor genes. To generate the enormous diversity of clonotypic antigen receptors, specific DNA lesions are generated and resolved in an error-prone fashion at defined stages of lymphocyte development. These lymphocyte specific characteristics provide ideal model systems to study not only the role of DNA damage response (DDR) and DNA damage tolerance (DDT) pathways in resolving specific DNA lesions and shaping the immunoglobulin (Ig) repertoire but also in maintaining genome stability and tissue homeostasis.

Our research activities are focused on two subjects:

(i) DNA damage tolerance (DDT) in physiology and precision cancer medicine

(ii) Genetic and epigenetic regulation of lymphocyte development and differentiation

DNA damage tolerance in hematopoietic stem and progenitor cells in mice

DDT enables bypassing of DNA lesions during replication, thereby preventing fork stalling, replication stress, and secondary DNA damage related to fork stalling. The role of DDT to tissue homeostasis and ageing remain to be defined. Four modes of DDT have been documented: translesion synthesis (TLS), template switching (TS), fork reversal (FR) and repriming. While TLS is facilitated by monoubiquitinated PCNA-Ub at lysine K164, K63 linked polyubiquitin moieties at K164 facilitate TS and FR. To investigate the role of DDT in maintaining hematopoietic stem cells (HSCs) and progenitors, we used *PcnaK164R/K164R* mutant mice as a unique DDT-defective mouse model. Failure to tolerate endogenous DNA damage resulted in accelerated aging of HSCs, which was characterized by progressive changes in the cellularity of several early hematopoietic progenitor subsets (see figure). In line with this notion, exogenous DNA damage inducing agents augmented the phenotype. In addition, bone marrow reconstitution assays revealed a strong cell intrinsic defect and competitive disadvantage of DDT deficient HSCs. Our findings highlight the importance of an intact DDT system in preserving HSC function and preventing premature aging of HSCs.

Precision cancer therapy: Profiting from tumor specific defects in the DDT system

The strategy where a defective DDR status of a tumor dictates the intervention mode, holds great promises in treating this group of cancer patients. DDT is an activity within the DDR network that enables replication to continue in presence of a damaged template and constitutes an essential step in the repair of DNA interstrand crosslinks. In this way DDT minimizes replication stress inflicted by a wide range of endogenous and exogenous agents, DNA structures, providing an essential

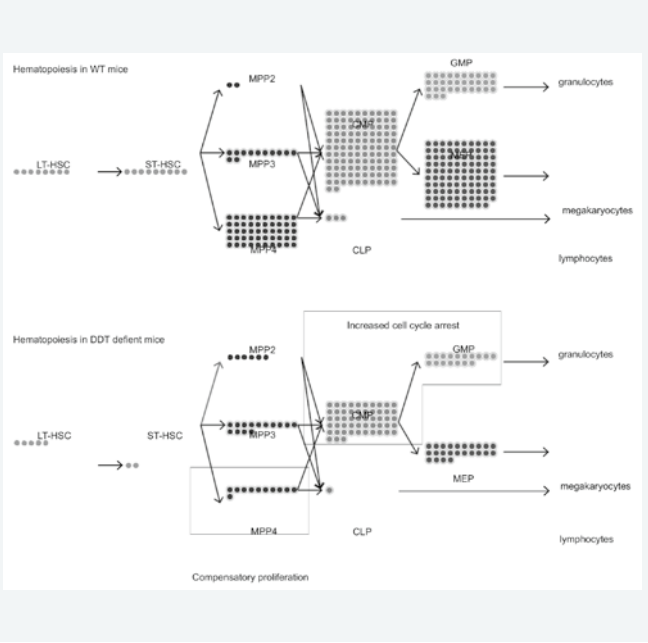
intermediate step in the repair of DNA interstrand crosslinks (ICLs). In this way, DDT provides a critical first line defense against alkylating and platinating chemotherapeutics. Effective DDT strongly depends on damage-induced, site-specific PCNA-ubiquitination at Lysine (K) 164 by the E2/E3 complex (RAD6/18). To determine the potential benefit for tumor-specific DDT defects, we followed a genetic approach by establishing unique sets of DDT-proficient PcnaK164 and -defective *PcnaK164R* lymphoma and breast cancer cell lines. In the absence of exogenous DNA damage, *PcnaK164R* tumors grew comparably to their *PcnaK164* controls *in vitro* and expanded aggressively and similarly *in vivo*. However, compared to their DDT-proficient controls DDT-defective lymphomas and breast cancers were hypersensitive to the chemotherapeutic drug cisplatin (CsPt), both *in vitro* and *in vivo*. Tumor growth was strongly hampered and the overall survival of tumor bearing mice greatly improved in the DDT defective condition. These insights imply a unique opportunity for precision cancer medicine with DNA damaging agents, that profit from tumor-specific DDT defects. These defects open new therapeutic possibilities for intervention with DNA damaging chemotherapeutics and optimize Next-Generation-Sequencing (NGS)-based precision cancer-diagnostics, -therapeutics, and -prognostics.

Not just a tale of the protein: The Immunoglobulin Heavy 'Chain' Checkpoint

V(D)J recombination assembles antigen receptor variable region of Immunoglobulin (Ig) in B lymphocytes. Productive assembly of one allele signals to stop further rearrangement, a process known as allelic exclusion. How B-cell progenitors control V to DJ rearrangement at the molecular level to establish the critical "one B-cell - one antibody" rule appears only incompletely understood. Our recent findings indicate that a progenitor B-cell is capable of sensing and distinguishing a productive from a non-productive rearrangement on the basis of differential mRNA stability. We wondered whether the Igμ Heavy chain (μH) mRNA, apart from being translated, plays a role in B-cell development. To approach this goal, we dissected stable μH RNA transcription and accumulation from translation. In fact, stable μH mRNA incapable of being translated into IgM protein impaired recombination at Igh locus. We now provide evidence that this non-translatable μH mRNA, promotes early B-cell development. This was revealed by increased expression of Pre-B cell transcriptome signature, transcriptional induction of differentiation markers, activation of Ig light chain V genes and initiation of Igh locus de-contraction. Our studies argue for a critical regulatory non-coding function of coding μH mRNA in coordinating immunoglobulin rearrangements and ensuring B-cells mono-specificity as well as in driving further B-cell development.

DOT1L: A key epigenetic regulator in T-lymphocyte development and differentiation

This joint-project is executed in close collaboration with dr. Fred van Leeuwen in the Division of Gene Regulation. Differentiation is tightly associated with epigenetic changes, which to a large extent are based on posttranslational histone modifications resulting in specific alterations of the chromatin structure. The dynamic changes of the epigenetic landscape associated with T cell development and differentiation are no exception to this rule. DOT1L is a unique, conserved epigenetic writer that selectively methylates histone H3K79. As ablation of *DOT1L* is embryonic lethal, we use T-lineage specific *DOT1L* ablation and inhibition to study the impact of altered H3K79 methylation dynamics in the well-defined pathways of T cell development and differentiation. Molecular, cellular, and functional analysis of CD8+ T cells revealed premature differentiation. Our results identified H3K79 methylation as a key barrier towards terminal T cell differentiation. Ongoing studies address the functional potential of T cells lacking DOT1L as well as the mechanism by which the absence of H3K79 methylation drives T cell differentiation.



Model: Effect of DDT deficiency on HSC and early progenitors.
Steady state hematopoiesis in wild type (WT) mice is indicated. In DDT deficient *PcnaK164R/K164R* mice, the replication stress induced differentiation of long-term (LT) and short-term (ST) hematopoietic stem cells (HSC) towards myeloid/erythroid associated multipotent progenitors 2 (MPP2) is indicated by red arrow. Furthermore, compensatory proliferation for lymphoid-primed MPP4 is specified, as well as cell cycle arrest in common myeloid progenitors (CMP) and granulocyte-macrophage progenitors (GMP)subsets. Arrows indicate direction of differentiation. Blue dots indicate Lineage-, Sca-1+, cKit+(LSK) subsets and green Lineage-, cKit+, Sca-1- (LKS-). Each dot represents 500 nucleated cells per femur.

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Telomere and genome integrity

To maintain genome integrity cells need to repair DNA lesions efficiently and in an error-free manner by engaging the right DNA repair pathway at the right moment and place. In addition, DNA repair activities need to be prevented from acting inappropriately at the natural ends of our chromosomes. The latter is taken care of by telomeres, specialized nucleoprotein structures that shield natural chromosome ends from the DNA damage response machinery and DNA repair activities. However, upon defects in telomeric proteins or progressive shortening of telomeric DNA repeats as a consequence of ongoing cell division, telomere protection is lost. Natural chromosome ends are then recognized and processed as if they were broken DNA. This inappropriate 'DNA repair' at telomeres, as well as any inappropriate or faulty processing of DNA lesions, can result in loss of genome integrity, including complex and unbalanced chromosome rearrangements. This can result in premature aging and promote the development of cancer. While tight control of DNA repair pathways is critical in maintaining genome integrity and in preventing or treating pathology, the processes underlying this are not well understood. As a consequence, important knowledge is lacking about the causes underlying cancer development and about the consequences of DNA-damaging anti-cancer therapies. We therefore aim to reveal the mechanisms underlying the choice between different modes of DNA repair of a DNA double-stranded break (DSB), or underlying the processing of uncapped telomeres by repair pathways.

Mechanisms of DNA repair control at telomeres and DNA DSBs

The main mechanisms by which cells repair DSBs are non-homologous end-joining (NHEJ) and homology-directed repair (HDR). These operate mutually exclusive and are activated by 53BP1 and BRCA1, respectively. The appropriate choice for engaging these repair pathways is critical for genome stability and is believed to be regulated at the level of DNA end-resection. End-resection strongly inhibits NHEJ while committing to HDR, and is under control of 53BP1 and its interaction partners RIF1 and PTIP. Recently, through a functional genetic screen aiming at factors contributing to genomic instability upon telomere uncapping, we identified MAD2L2, a.k.a. REV7 or MAD2B, as a critical regulator of DNA repair. We found that MAD2L2 promotes NHEJ by inhibiting 5' end-resection downstream of 53BP1 and RIF1. It does so both at telomeres and at DSBs in multiple settings, including upon irradiation and during immunoglobulin class switch recombination (CSR). This newly discovered role of MAD2L2 in DNA repair suggests that aberrant MAD2L2 expression could have pathological consequences by compromising genome integrity due to inappropriate DNA repair pathway activity at telomeres or DNA lesions. Indeed, bi-allelic inactivation of MAD2L2 was recently reported to cause Fanconi Anemia, a genetic disease associated with an impaired response to DNA damage, although it is not yet established

which functions of MAD2L2 are most critical here. Furthermore, our finding that MAD2L2 is essential for CSR identifies MAD2L2 as a potential disease-susceptibility gene for human primary immunodeficiency. Over the last year we followed up on these discoveries and further investigated the mechanisms underlying control of DNA repair pathway activity.

In order to better understand how the 53BP1, RIF1 and MAD2L2 proteins act in DNA repair pathway choice we undertook different approaches aiming at identifying protein interactions with MAD2L2 relevant for its role as an inhibitor of DNA end-resection or aiming to address how MAD2L2 is recruited to DNA DSBs. This work revealed that MAD2L2 is recruited to DSBs in chromatin dimethylated on lysine 20 of histone 4 (H4K20me2) by forming a protein complex with 53BP1, which binds H4K20me2, and RIF1. We identified both previously reported protein interactions with MAD2L2 and several new protein interactions that are currently being investigated for their contribution to DNA repair control. In addition, we found that MAD2L2, similar to 53BP1 and RIF1, suppresses DSB accumulation of BRCA1 in S/G2, suggesting that MAD2L2 could be a limiting factor in DNA repair pathway choice (figure 1).

DNA repair pathway choice in S-phase

An important fundamental question is how DNA repair pathway choice decisions are made as cells progress through the cell cycle, especially through S-phase. In S-phase, the replication of the genome represents a particularly interesting challenge to the DNA repair machinery. In S-phase, NHEJ (activated by 53BP1) and HDR (activated by BRCA1) are both functional and non-replicated and replicated DNA regions co-exist, with the risk of aberrant HDR activity at DSBs in non-replicated DNA or the risk of replication intermediates being processed by NHEJ and leading to chromosomal fusions. As such, repair of DSBs in pre-replicative chromatin requires the NHEJ pathway and suppression of resection to avoid loss of genetic information, while repair of DSBs in replicated regions is preferably done by the HDR pathway, as an intact template for error-free repair is present. The question that we therefore addressed is how the DNA repair pathway choice machinery is able to distinguish pre-replicative chromatin from post-replicative chromatin and activate the correct repair pathway according to the replication status of the DNA. We found that the replication status of the DNA locally ensures the engagement of the correct DNA repair pathway, through epigenetics. 53BP1 and BRCA1 compete to occupy DSBs and the accumulation of 53BP1 at DSBs depends on binding of 53BP1 to both histone H2A ubiquitinated on lysine 15 (H2AK15ub) and histone H4 dimethylated on lysine 20 (H4K20me2). While H2AK15ub is induced upon DNA damage, the levels of H4K20me2 fluctuate during the cell cycle, with 90% of the genome containing H4K20me2 in G1, a 50% drop in H4K20me2 in S-phase, and re-establishment of H4K20me2 levels at the end of G2. We found that the number of 53BP1 foci correlates with H4K20me2 levels over the cell cycle. In non-replicated DNA, saturating levels of H4K20me2, lead to robust 53BP1-RIF1-MAD2L2 recruitment at DSBs, with consequent exclusion of BRCA1. Conversely, replication-associated 2-fold dilution of H4K20me2, due to incorporation of non-methylated H4K20me0, promotes the release of the 53BP1-RIF1-MAD2L2 complex and favours the access of BRCA1. Premature restoration of H4K20me2 in S-phase due to ectopic expression of the histone methyltransferase SETD8, that is normally degraded before entry into S-phase, causes prematurely increased accumulation of 53BP1 and reduced accumulation of BRCA1 to DNA lesions (figures 2 and 3). Thus, the differential H4K20 methylation status between pre-replicative and post-replicative DNA represents an intrinsic mechanism that locally ensures appropriate recruitment of the 53BP1-RIF1-MAD2L2 complex at DSBs to engage the correct DNA repair pathway.

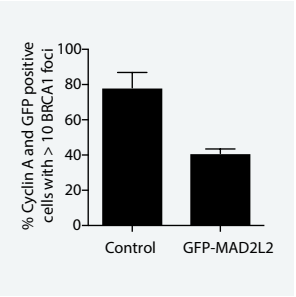

Figure 1. Quantification of U2OS cells in S/G2 phase (Cyclin A positive) with more than 10 foci in which BRCA1 accumulates at DNA DSBs at 1 hour after irradiation. Overexpression of MAD2L2 suppresses the accumulation of BRCA1 to DNA DSBs.

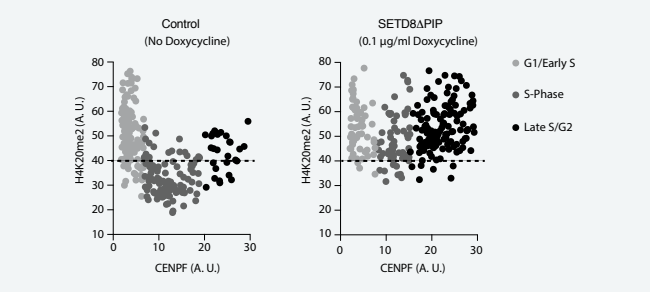

Figure 2. Quantification of H4K20me2 levels and CENPF (for cell cycle staging) by immunofluorescence detection in cells containing doxycycline-inducible SETD8 that is resistant to PCNA-mediated degradation: SETD8DPIP. In control cells only expressing endogenous SETD8, that is degraded before entry into S-phase, the levels of H4K20me2 fluctuate during the cell cycle with a clear drop in S-phase and a restoration in G2 when SETD8 becomes re-expressed (see left panel). In cells induced to express SETD8 resistant to PCNA-mediated degradation, H4K20me2 levels stay high in S-phase (right panel).

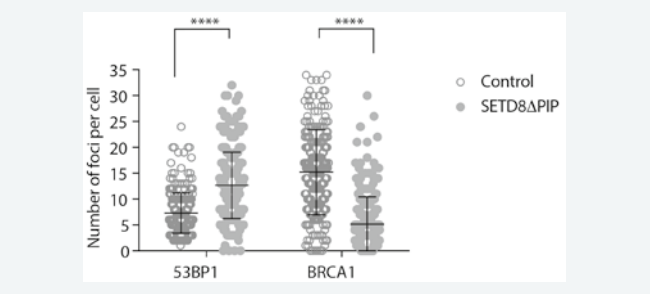

Figure 3. Quantification of 53BP1 and BRCA1 foci in irradiated S-phase U2OS cells with and without expression of SETD8 that is resistant to PCNA-mediated degradation. SETD8 expression in S-phase, causing H4K20me2 to remain high (see Figure 2), leads to increased accumulation of 53BP1 to DSBs in S-phase, at the cost of BRCA1 accumulation.

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Publications

Leyton-Puig D, Isogai T, Argenzio E, van den Broek B, Klarenbeek J, Janssen H, et al. Flat clathrin lattices are dynamic actin-controlled hubs for clathrin-mediated endocytosis and signalling of specific receptors. Nature communications. 2017;8:16068

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Biophysics of cell signaling

We use advanced microscopy and spectroscopy techniques to study cell signaling events and cytoskeletal dynamics with high spatial and temporal resolution. Our expertise is predominantly in advanced functional imaging and Super Resolution microscopy. Functional imaging techniques aim to provide information about the function of molecules, rather than just static images of their position within the cell. The most common techniques are Fluorescence Resonance Energy Transfer (FRET), Fluorescence Lifetime Imaging (FLIM), Fluorescence Cross Correlation Spectroscopy (FCCS) and opto-chemistry/opto-genetics. We also develop FRET hard- and software and biosensors for various intracellular messengers, and we develop and apply 'super-resolution' light microscopy. These techniques are used in research projects in our group as well as in collaborations within and outside our institute.

High-content screening

Over the last years, we have developed hard- and software to be able to perform microscopy screens at very high resolution: so-called high-content screens. We have continued our screen of 300 candidate genes that have been selected for playing a possible role in determining the dynamics of the intermediate filament network. Large series of high-quality time-lapse recordings of HaCaT cells expressing YFP-tagged keratin-14 were obtained. After initial quality control, a number of morphometric and dynamic parameters were extracted by automated image analysis, using software routines developed in our group. These include parameters such as number, length and thickness of individual filaments, reticulate interactions, average speed of motion and directionality (optic flow; see figure 1). We also developed a routine capable of detecting the peculiar continuous inward movement of tangential keratin fibers in these cells. The most interesting candidates are currently being investigated in further detail in collaboration with Dr. R. Windoffer at Aachen University. In addition, several screens aimed at characterizing DNA damage complexes were carried out, most often in collaboration with members from the Medema lab.

Functional imaging

This year saw the start of a 3-year NWO-TTW technical project to follow up on our single-image FLIM technique. FLIM records the fluorescence lifetime of a fluorophore, i.e. the average time that a fluorophore remains in the excited state following excitation. This intrinsically quantitative technique is used to detect the physicochemical properties of the molecular environment of the dye (e.g., pH, ionic strength, radical stress, oxygen levels and more) and it presents the most robust manner to determine FRET efficiency. The conventional FLIM detection approach, Frequency Domain analysis, suffers from drawbacks in that it is slow, requires several (typically 12) individual fluorescent images to be taken in rapid succession, and it tends to produce artifacts when the preparation changes during acquisition (as is the case

for living cells). Using a newly developed CCD camera that allows direct on-chip demodulation, we developed a new paradigm, single-image FLIM (siFLIM) to speed up detection up to 30 times. siFLIM causes less photodamage to the cells and less bleaching of the dye. In collaboration with industrial partners, an improved version of the chip and camera have been manufactured, and we have guided its embedding in a user-friendly and flexible software environment. siFLIM is used in our lab for studies into the heterogeneity of signal transduction pathways, in particular, to understand cellular factors that affect the kinetics of signaling of the second messenger cAMP. cAMP is a ubiquitous messenger that affects cell division, differentiation and migration, and it is known to affect efficacy of certain cancer treatments.

Marrying functional imaging with high-content screening

Functional imaging approaches such as FRET have traditionally been hard to automate because the FRET signals are often small, image acquisition analysis was very slow and cell-to-cell variability has been significant. This precluded using FRET for screening applications. Two important improvements have changed that. On the one hand, our longtime experience in constructing FRET sensors has enabled us to devise a generation of sensors that exhibit very robust FRET changes of up to 50%. On the other hand, our developments in setting up high-speed FLIM detection to read out FRET have boosted both speed and accuracy. In addition to the development of wide-field siFLIM, we have also collaborated with Leica Mannheim to set up extremely fast confocal FLIM detection methods. With these changes, we are now able to reliably detect even small changes in e.g. cytosolic metabolite concentrations and protein activity. We have set up screens to identify gene products involved in receptor desensitization by reading out signals in the *Galpha-q* and *Galpha-s* pathways. These screens employ dynamic recording of metabolite concentrations following perturbations

Super resolution imaging

We have been instrumental in devising key improvements in preparation and post-acquisition analysis of super-resolution (SR) microscopy (over the past few years, preparation techniques and acquisition for GSDIM were much refined and problems related to the extreme sensitivity of the technique, including nanometer-scale drift and chromatic aberration, were solved in our lab). Since then, our attention is shifting towards application of the GSDIM (Ground-State Depletion IMaging) method to biological research questions in our lab. Collaborations with several groups within and outside the NKI have led to publications on topics varying from invadopodia, intermediate filaments and microtubules to receptor distribution and clustering at the cell surface. Last year we have focused on SR imaging of chromosome organization. Post-doc Leila Nahidi has been appointed in a collaboration with Dr. Jop Kind (Hubrecht Institute, Utrecht) who employs SR microscopy to understand association of chromosome domains with the nuclear lamina, and we have collaborated with Dr. Benjamin Rowland to study chromosome folding and the role of condensin proteins therein (see figure 2). It has become apparent that SR images also demand novel quantitative analysis algorithms, because conventional analysis methods like quantification of co-localization no longer suffice. Several of our analysis software routines have been shared with labs worldwide.

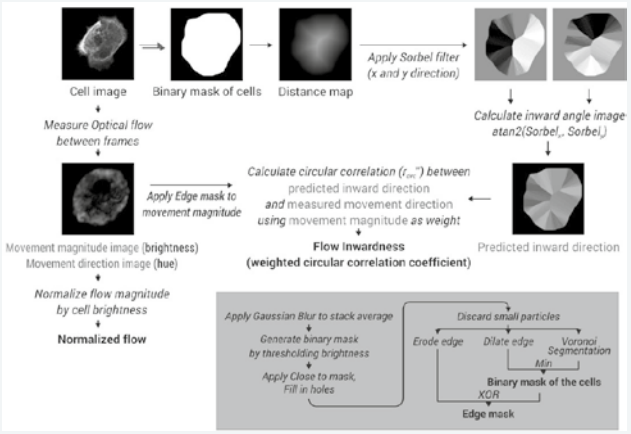

Figure 1: Automated image analysis of keratin filament movements in HaCaT cells. Image made by Andriy Volkov.

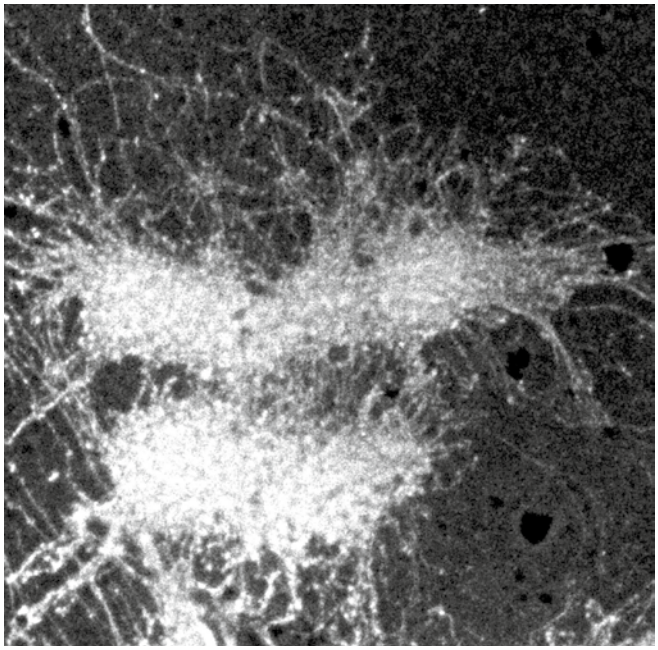

Figure 2: DNA loops extending from a single chromosome studied by GS-DIM. Image prepared by Julia Eppink.

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Publications

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Mouse models of breast cancer

My group studies human breast cancer development and progression, as well as therapy response and resistance, in genetically engineered mouse models (GEMMs) and patient-derived tumor xenograft (PDX) models. To this end, we have developed mouse models for BRCA1/2-associated breast cancer and invasive lobular carcinoma (ILC). We are using these models to (1) investigate genotype-phenotype relations and identify novel breast cancer driver genes; (2) study the role of stromal fibroblasts in mammary tumorigenesis; (3) develop prophylactic therapies for prevention of breast tumors in *BRCA1*-mutation carriers; (4) study mechanisms of acquired resistance to targeted therapeutics such as PARP inhibitors and FGFR inhibitors.

Non-germline GEMMs of breast cancer

Large-scale sequencing studies have yielded large collections of candidate drivers. Validation of these drivers requires novel approaches for high-throughput *in vivo* perturbation of gene function. To this end, we have developed non-germline GEMMs of human breast cancer that permit rapid introduction of putative drivers by intraductal injection of lentiviruses encoding candidate oncogenes or sgRNA-encoding lentiviruses for CRISPR/Cas9-mediated disruption of candidate tumor suppressors. We have successfully used these models for *in vivo* validation of drivers in BRCA1-associated breast cancer and ILC.

Driver genes in BRCA1-associated breast cancer

We have used our GEMMs of BRCA1-associated breast cancer to identify candidate driver genes in recurrent DNA copy number aberrations (CNAs). Cross-species comparison of CNAs in human and mouse BRCA1-deficient mammary tumors, combined with iterative *in vivo* validation of candidate drivers, identified loss of RB and amplification of MYC and MCL1 as drivers of BRCA1-associated breast cancer. Moreover, MCL1 inhibition potentiated the *in vivo* efficacy of the PARP inhibitor (PARPi) olaparib, underscoring the therapeutic potential of this combination for treatment of BRCA1-associated cancer patients with poor response to PARPi monotherapy.

Driver genes in ILC

ILC accounts for 10-15% of all breast cancers and shows frequent inactivation of E-cadherin. To identify cancer drivers that collaborate with E-cadherin loss in ILC development, we have performed Sleeping Beauty (SB) transposon mutagenesis screens in mammary-specific E-cadherin knockout mice. We identified recurrent and mutually exclusive SB insertions in *Ppp1r12a/b, Trp53bp2* and *Myh9*, which are implicated in regulating actomyosin contractility. *PPP1R12B, TP53BP2* and *MYH9* are frequently mutated in human breast tumors, suggesting that this novel oncogenic pathway may also be relevant for human cancer development. In addition, we observed truncating mutations in *Fgfr2* leading to FGFR2

activation in more than 50% of all tumors. *In vitro* and *in vivo* analysis of various FGFR2 mutants enabled us to identify the C-terminal interaction partners that mitigate the oncogenicity of FGFR2.

Therapy resistance in BRCA-deficient breast cancer

BRCA1/2-deficient cancers are defective in homologous recombination repair and therefore hypersensitive to DNA-damaging agents, including platinum drugs and PARP inhibitors (PARPi). However, these treatments do not result in tumor eradication and eventually resistance develops. To study mechanisms of PARPi resistance, we combined functional genetic screens in BRCA1/2-deficient cells with multi-omics analysis of PARPi-resistant tumors from our GEMMs and PDX models of BRCA-deficient breast cancer. These studies have yielded multiple PARPi resistance mechanisms in BRCA1-deficient tumors, including (epi)genetic reactivation of BRCA1, upregulation of the P-glycoprotein drug efflux pump, and loss of factors that block DNA end resection (53BP1, REV7, and members of the CST complex and the newly identified Shieldin complex). PARPi resistance in BRCA2-deficient tumors was found to be driven by loss of the poly(ADP-ribose) glycohydrolase PARG.

To study the effects of specific *BRCA1* mutations on tumorigenesis and therapy response, we have generated mouse mutants mimicking defined *BRCA1* founder mutations (*185delAG*, *5382insC* and *C61G*) and introduced these alleles into our BRCA1 mammary tumor model. All three mutants fail to suppress mammary tumor formation, but show different activities following treatment of tumors with platinum drugs or PARP inhibitors. Whereas BRCA1-null and BRCA1-5382insC tumors never develop resistance to cisplatin, the BRCA1-185delA and BRCA1-C61G tumors readily become resistant due to expression of a RING-deficient BRCA1 protein, demonstrating that BRCA1 RING function is required for tumor suppression but dispensable for therapy resistance.

Therapy resistance in ILC

We used SB transposon mutagenesis to screen for genes conferring *in vivo* resistance to FGFR inhibitors in ILC. To this end, we performed orthotopic transplantations with SB-induced tumors with *Fgfr2* overexpression and treated the tumor-bearing mice with the FGFR inhibitor AZD4547. All tumors regressed completely but eventually acquired resistance to AZD4547. SB transposon tagging combined with RNA sequencing-based analyses of the AZD4547-resistant tumors identified several known and novel resistance mechanisms to FGFR inhibition, including mutations in FGFR2, overexpression of MET, inactivation of RASA1 and activation of the drug-efflux pump ABCG2. Notably, ABCG2 and RASA1 were only identified from *de novo* transposon insertions acquired during AZD4547 treatment, demonstrating that insertional mutagenesis in mice is a useful tool for identifying therapy resistance mechanisms.

Role of CAFs in ILC

Since human and mouse ILCs show strong stromal infiltration, we are also studying the role of cancer-associated fibroblasts (CAFs) in ILC development and progression. Specifically, we are investigating (i) the mechanisms underlying fibroblast recruitment, (ii) how fibroblasts promote ILC development and progression, and (iii) whether genetic ablation of CAFs will attenuate tumor development or inhibit growth of established tumors.

In vitro and in vivo models of DCIS

Ductal Carcinoma In Situ (DCIS) was virtually unknown before the advent of breast screening, yet now accounts for 25% of all 'breast neoplasms' detected. This increased detection rate has resulted in overtreatment since many DCIS lesions will not progress into invasive breast cancer. Better insight into the biology of DCIS is required to distinguish indolent lesions from potentially hazardous ones. To this end, we are generating genetically engineered and patient-derived *in vitro* organoid models and *in vivo* mouse models of DCIS. These approaches will enable the identification of DCIS driver genes and yield models to study disease progression and response to targeted therapeutics.

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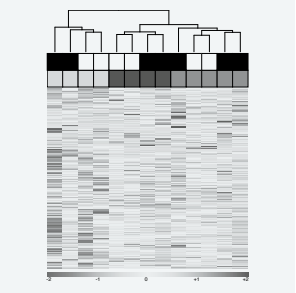
The aim of our research is to dissect the tumor-specific T cell response

It is clear that immunotherapy can be highly effective in human cancer, in particular for melanoma and lung cancer. The evidence for a role of T cells as an 'active component' in cancer immunotherapy comes both from trials exploring the adoptive transfer of *ex vivo* expanded tumor-infiltrating lymphocytes (TIL therapy) and from trials exploring treatment with antibodies that target inhibitory receptors on T cells such as CTLA-4 and PD-1.
Importantly, in spite of the recent major successes of immunotherapy, only part of the treated patients responds to therapy and many patients relapse after initial responsiveness. It is likely that in some cases such resistance is caused by tumor cell-intrinsic properties (e.g. loss of MHC expression or lack of antigens). However, differences in the level of T cell (dys) functionality between patients (and malignancies) is likely to form an important factor.
Knowledge on T cell functionality will be of importance for three reasons. First, on the basis of such knowledge, rational decisions for (combination) therapies can be made to expand the success of immunotherapies. Second, it is expected to allow the identification of biomarkers to select patients that are most likely to benefit from therapy. Third, a better understanding of the long-term effects of anti-cancer therapy on T cell function will help us understand the potential role of T cell exhaustion in therapy resistance.

T cell functionality and antigen-specificity

A main research line in our group is to understand if there is a fundamental difference between T cells specific for e.g., self-antigens and tumor-specific antigens. Multiple factors can play a role in such potential differences including the T cell receptor (TCR) repertoire available for recognition of a given antigen. For most self-antigens, the high-affine repertoire is expected to be deleted during thymic selection whereas for antigens such as neo-antigens central tolerance is not expected.
In addition to investigating if there is a fundamental difference between T cells specific for different classes of antigens, we have a high interest in understanding how these T cell populations respond to immunotherapies such as the checkpoint targeting therapies. If we can understand if a given T cell state and/or T cells specific for certain types of antigens are more likely to become reactivated by checkpoint targeting therapies we can use such knowledge to design novel treatment strategies.
To address this question, we are identifying antigen-specific T cell responses towards shared self-antigens, neo-antigens and viral antigens so that we can isolate the cells and obtain transcriptome profiles. We are investigating the tumor specific T cell response across multiple malignancies including melanoma, lung cancer, mesothelioma, head & neck carcinoma, bladder cancer and ovarian cancer.
We have for example analyzed three T cell populations from a

melanoma patient treated with anti-PD-1 therapy. Strikingly, we have observed that the largest amount of variation is not introduced by the immunotherapy but rather based on the antigen specificity of the T cell populations (Figure 1). Based on these data we have made functional associations by identifying pathways differentially regulated between the different antigen-specific T cell populations. For example, pathways associated with proliferation and activation are down-regulated in MART-1-specific T cells together with CD28 signaling, while apoptosis pathways are up-regulated, in comparison to CMV-specific T cells. These data are the first demonstration of such differences in the human setting, and strongly indicate both feasibility of obtaining gene expression profiles from low T cell numbers, and that there is much knowledge to be gained from this line of work.



Hierarchical clustering of T cell transcriptome data obtained for three T cell reactivities before and on anti-PD-1 therapy. The heat map shows the 250 genes which account for the largest amount of variation within the data set. Tumor-, Self-antigen- and virus-specific T cells are labeled medium gray, Light gray and dark gray, respectively. White boxes indicate pre-therapy time point and black post-therapy.

Not all neo-antigens are created equally

We now have ample evidence for tumor-specific T cells responding to the antigenic fragments that arise as a consequence of DNA damage. These neo-antigens are conceptually highly attractive as they have the potential to be as foreign to the immune system as e.g., viral antigens as no central tolerance is expected.

To dissect the properties of T cell recognized neo-antigens we have previously screened for neo-antigen specific T cells in material from 12 melanoma patients (work done within the group of Ton Schumacher). Interestingly, we see a major variability in the strength of neo-antigen specific T cell responses, we see a range in magnitude between 0.002 and 23% of MHC multimer$^+$ CD8$^+$ of total CD8$^+$. Strikingly, this observation of heterogeneity in response magnitude is strongly correlating to predicted binding affinity to MHC when we look at the neo-antigen specific T cells across patients (p=0.0004). An unequal contribution of T cells to the combined protective immune response towards a disease is well characterized for the viral infections, and this phenomenon is termed immunodominance. Our data provide a first evidence of a similar hierarchy within neo-antigens in human cancer and we are now working on understanding how this hierarchy arises.

This work will greatly enhance our understanding of the fundamentals of anti-tumor immunity. Obtaining this knowledge will be of key importance for designing immunotherapeutic strategies by: 1) Providing a method for selecting which neo-antigens to target and; 2) Identifying potential targets to abrogate hierarchy formations and induce epitope spreading to avoid therapy resistance through loss of antigen.

Experimental methodology

To carry out our research, we are exploiting and expanding on a technological platform for T cell immunomonitoring developed within this institute; peptide MHC multimer combinatorial coding. We have previously been able to assess T cell reactivities towards ~50 epitopes in parallel. With new development within both hardware and new fluorescent dyes, we are now able to assess >120 T cell reactivities in parallel and we are aiming at reaching ~2000 within the next year. This development is allowing us to carry out T cell reactivity screens in highly limited patient material such as tumor biopsy material.

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Transcription dynamics

Genetically identical cells can display considerable gene expression differences. A fascinating example is cellular differentiation during development, where individual cells change their transcriptional program in a deterministic way, by integrating signals from intra- and extracellular pathways, transcription factors and epigenetic regulators. However, even cells with the same differentiation state and in the same environment show considerable heterogeneity in gene expression. This non-deterministic variation is the result of the stochastic nature of the transcription process itself, arising from the random collision of molecules. Single-cell studies have shown that even at steady state, concentrations of individual RNAs and proteins randomly fluctuate from one moment to the next. This stochastic heterogeneity can influence essential cell-fate decisions, and can also contribute to heterogeneity in tumours. We use cutting-edge single-molecule imaging approaches to visualize transcription fluctuations in living cells, in order to understand the mechanisms and regulation of transcription dynamics in eukaryotic cells.

Imaging transcription in living cells

To quantify transcription dynamics in living cells, we use the MS2 and PP7 RNA labeling system, which is based on the immediate association of the fluorescently tagged MS2/PP7 coat proteins to stem loop repeat sequences that are introduced into the gene of interest. When transcribed, binding of the coat protein to the stem loops in the RNA concentrates the fluorescence, resulting in a bright spot on a background of freely diffusing coat protein (see figure). After quantifying the fluorescent intensity of the transcription site, we can extract kinetic information from the traces about the underlying regulatory mechanisms of transcription in single cells.

Understanding the mechanisms of transcriptional bursting

Previous studies on transcription dynamics have shown that genes are often not transcribed in a continuous fashion, but show transcriptional bursting, with periods of gene activity followed by periods of inactivity. Transcriptional bursting is a conserved property that occurs from bacteria to yeast to human cells. During bursting, gene promoters switch between different states of activity. The rate of switching from the inactive to the active state (the burst frequency), the duration of the burst, and the number of polymerases that initiate (burst size) influence not only the mean expression level of a gene, but also its 'noisiness' or variability. However, the origin and regulators of bursting remain largely unknown.

Using our single-molecule RNA labeling technique, we have previously directly visualized and measured transcriptional bursts at the galactose responsive gene *GAL10* in budding yeast (see figure). We are now applying this imaging assay to understand how different levels of regulation control bursting.

Transcription factors binding dynamics controls burst size

Transcription factors activate gene transcription, but how they relate to transcriptional bursting is unknown. We used our single-molecule imaging assay to show that the binding dynamics of a transcription factor controls bursting by determining how many polymerases initiate during a burst. Our assay was combined with a novel technology called single-molecule tracking, which allows for direct *in vivo* measurements of the binding kinetics of single transcription factor molecules to DNA in living cells. As complementary approach, single-molecule *in vitro* measurements were performed to measure the binding kinetics of the transcription factor to nucleosomal DNA, in collaboration with Micheal Poirier of Ohio State University. Collectively, our data support a model where multiple polymerases can initiate during a burst as long as the transcription factor is bound to DNA and a burst ends when the transcription factor dissociates from the DNA. We are currently investigating how different regulatory factors can influence the binding dynamics of transcription factors.

The effect of chromatin on transcriptional bursting

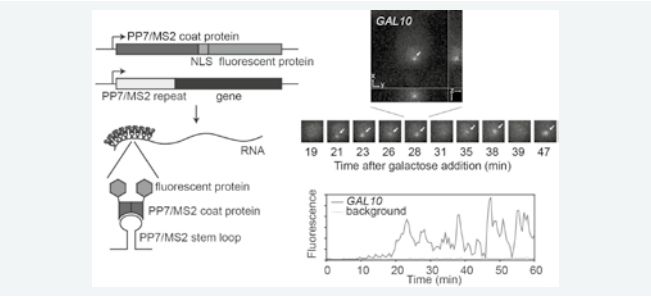
Nucleosome positioning or binding in the promoter region of genes can affect the accessibility of transcriptional regulators to DNA binding sites, which may regulate bursting. We are testing this hypothesis by removing nucleosomes from the promoter to identify which bursting properties are affected. In addition, we are setting up assays to conditionally change the nucleosome promoter structure, by dynamically depleting nucleosome remodeling complexes from the nucleus. Measurements of bursting before and after depletion will reveal how nucleosomes affects bursting patterns. To correlate bursting changes with chromatin changes, we are collaborating with John van Noort's lab in Leiden University, to develop a technique to measure the nucleosome composition on single gene templates isolated from cells. Together these experiments will reveal how chromatin structure determines transcriptional bursting.

Imaging divergent genes to determine effect of supercoiling on bursting

In bacteria, bursting was proposed to arise from build-up of supercoiling during transcription. Supercoiling inhibits transcriptional initiation and elongation and has to be released by topoisomerases before transcription can resume. However, it is unknown if supercoiling contributes to bursting in eukaryotes. If supercoiling is important for bursting, divergent genes are predicted to show higher transcription and correlated bursting, because negative supercoiling in the promoter caused by transcription would favour polymerase initiation of the neighbouring gene. We are currently setting up an imaging assay to monitor correlations in bursting of two divergent genes. Next, we will perturb topoisomerases that relieve supercoiling and determine how this affects the correlation in bursting of the divergent gene pair.

Role of non-coding transcription on transcriptional bursting in human cells

To connect the mechanistic insight from yeast to human disease relevance, we also study the regulation of transcriptional bursting in human cell lines, using the expression of the cytokine IL6 as a model gene. Cytokines are often only expressed in part of a cell population, illustrating the importance of single-cell approaches to understand their gene expression regulation. We will address how non-coding RNA transcription influences transcriptional bursting of IL6. These non-coding RNAs include ncRNAs produced at distal enhancer regions (eRNAs) and ncRNAs produced from the antisense strand (antisense RNAs) of IL6. Using simultaneous dual-color imaging of coding and non-coding transcription, we aim to understand the spatiotemporal regulation and function of ncRNA transcription. For example, we will address how sense and antisense transcription are coordinated, and whether simultaneous transcription can be a source of R-loops or DNA damage.



We use the PP7/MS2 RNA labeling system to visualize transcriptional bursting. Example images of *GAL10* transcription in yeast cells after stimulation with galactose show transcriptional bursting at the transcription site (arrows). The quantification of the fluorescent intensity at the transcription site is shown below.

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Molecular dissection of cancer by differential drug sensitivity

In the clinic, we mainly use anticancer drugs based on outcomes of clinical trials that have been carried out in the general breast and ovarian cancer population, whereas little is known about the molecular mechanisms underlying differential drug sensitivity. The focus of our research line is to unravel these molecular mechanisms in order to develop tests that may guide treatment decisions in the clinic and ultimately improve survival. For this purpose, we use several genome-wide approaches and molecular techniques, in order to dissect the mechanisms that divide clinically well-defined cohorts of breast and ovarian cancer patients into resistant and sensitive to a particular drug. We have a close collaboration with the group of Jos Jonkers, who uses genetically engineered mouse models for breast cancer, and derived clonal cell lines, to study differential chemosensitivity in a controlled fashion. In addition, we collaborate with the group of Wilbert Zwart, particularly focusing on molecular mechanisms underlying endocrine therapy resistance. A second research line focuses on the impact of prognostic molecular classifiers on adjuvant systemic treatment advice in breast cancer.

Development of a predictive test for tamoxifen resistance in breast cancer

In earlier work, we translated preclinical evidence into clinical evidence that an activated phosphatidyl-inositol-3-kinase (PI3K) pathway can cause endocrine therapy resistance (Beelen et al, Breast Cancer Res, 2014). However, none of the single activated proteins in the PI3K pathway could be measured robust enough to implement it as an endocrine resistance marker in daily clinical practice. Therefore, we examined whether we could develop a classification rule using information on seven PI3kinase pathway proteins. This appeared indeed possible, and led to a clear separation of postmenopausal, hormone-receptor positive, HER2-negative patients benefiting or not from adjuvant tamoxifen (p-interaction < 0.01). The next step is to confirm the reproducibility and robustness of this classification rule in another randomized clinical trial with long-term follow-up, such as the STO-3 trial, or the NSABP B-14 trial.

Molecular mechanisms underlying sensitivity to high dose alkylating agents

The inability of breast cancer cells deficient in homologous recombination (HR), such as *BRCA1/-2*-mutated cells, to repair DNA double strand breaks (DSBs) appears to offer a target for DSB-inducing therapies, such as platinum agents, intensified alkylating therapy, and poly(ADP)ribose polymerase inhibitors. Our institute previously described characteristic DNA copy number aberrations (CNAs) of *BRCA1*- and *BRCA2*-mutated breast cancers. We called these profiles BRCA-like profiles that can be derived from any platform assessing DNA copy number aberrations. The BRCA1-like classifier, a genomic scar, will be evaluated as a selection biomarker for niraparib benefit in

metastatic breast cancer patients (ABC trial, NCT02826512). In parallel a functional test (RAD51 foci formation) will be evaluated in the same ABC trial, in collaboration with Erasmus Medical Center, Rotterdam.

Using a similar approach as for breast cancer, ovarian cancer specific BRCA1-like and BRCA2-like profiles have been derived from characteristic DNA CNAs of gBRCAm ovarian cancers (figure 1). In collaboration with the German AGO study group and the University of Cologne, we performed panel sequencing, BRCA1-methylation and low-coverage whole genome sequencing to classify 308 ovarian cancer samples as BRCA1-or 2-like (AGO-TR1 cohort study (NCT02222883). A high number of ovarian cancer cases display a BRCA-like profile. Mutations (germline/somatic) in BRCA1/2, RAD51C as well as BRCA1-promoter methylation strongly associate with a BRCA-like profile explaining 150 of 220 cases. Future studies are needed to investigate, if the classifiers identify patients who benefit from HR-deficiency directed approaches beyond the BRCA mutation status.

Netherlands Breast Cancer Project

In collaboration with the Netherlands Cancer Registry (NKR) and UMCU we have initiated a project to find answers for clinical and translational research questions that will never be answered anymore through prospective clinical trials. For this, we make use of the NKR, where data of over 150,000 breast cancer patients has been stored with clinical follow-up. The ultimate aim is to combine clinical with molecular data of tumor material that has been traced back through the Dutch nationwide surgical pathology registry.

Recently we addressed the clinically unresolved question whether perimenopausal, hormone-receptor positive, HER2-negative breast cancer patients derive differential benefit from adjuvant tamoxifen versus an aromatase inhibitor (AI). We studied 2,293 patients with this breast cancer subtype diagnosed between 2005-2007 in the Netherlands. Women diagnosed 45<age≤50 years showed superior recurrence-free survival and overall survival when treated with AIs rather than with tamoxifen (figure 2). These results are consistent with results from randomized literature for premenopausal and postmenopausal women. Using population-based cohorts like NBCP may provide a reliable source of information to answer research questions for which no randomized data are available, as demonstrated here for women diagnosed between 45 and 50 years of age, used as a proxy for perimenopausal status.

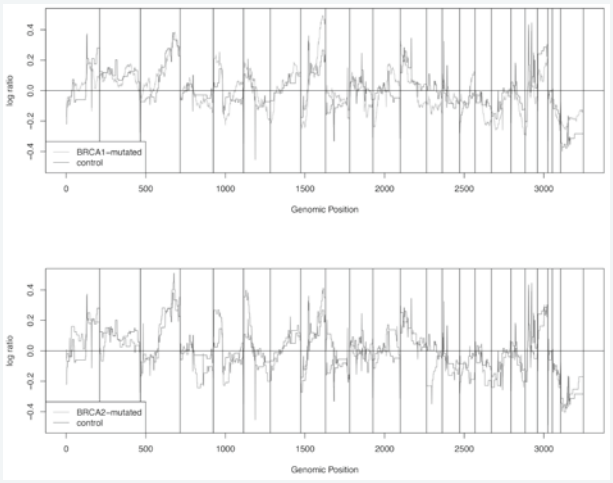

Figure 1. Average copy number aberration profiles of BRCA1- and BRCA2-mutated ovarian cancer. A) Average copy number aberration profile of 48 BRCA1-mutated ovarian cancers and 13 control ovarian cancers. On the x-axis the chromosomal position and on the y-axis the average log2 ratio of tumor DNA over normal DNA. B) Average copy number aberration profile of 10 BRCA2-mutated ovarian cancers and 13 control ovarian cancers. On the x-axis the chromosomal position and on the y-axis the average log2 ratio of tumor DNA over normal DNA.

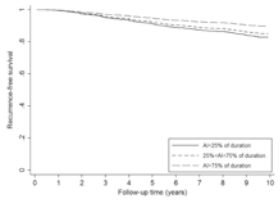

Figure 2: Adjusted Kaplan-Meier estimation of recurrence-free survival (RFS) for all 2,293 estrogen receptor-positive breast cancer patients aged between 45-50 years at diagnosis, according to AI treatment duration defined as the percentage of total endocrine treatment duration (AI+TAM) that was spent on AI treatment. 5 year RFS rates = 91% vs 92% vs 95% for AI <25%, 25<AI<75% and AI>75% respectively. The analyses were adjusted for age at diagnosis, trastuzumab use, grade, number of positive lymph nodes, pT-stage, progesterone receptor status, HER2 status and ovarian ablation.

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Cell cycle checkpoints and chromosome segregation

The research in the Medema group aims to gain a better understanding of the cellular response to classic anti-cancer drugs that damage the DNA or perturb mitotic spindle assembly. His group uses the knowledge that is generated to define and experimentally test new anti-cancer strategies.

The cellular response to DNA damaging insults

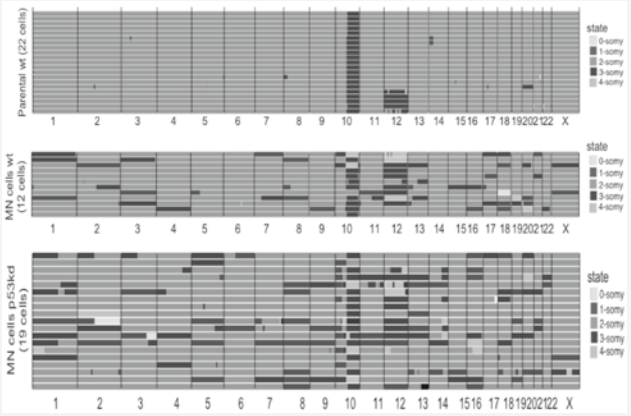
The group is interested to know how DNA damage causes cells to arrest, and how recovery from that arrest is controlled. DNA damaging agents cause a variety of lesions of which DNA double strand breaks (DSBs) are the most genotoxic. Unbiased approaches aimed at investigating the relationship between the number of DSBs and outcome of the response have been challenging due to the random nature in which damage is induced with classical DNA damaging agents. We have now established a cellular system that permits us to regulate Cas9 activity in a highly temporal fashion and use this to efficiently introduce DSBs at defined sites in the genome. To validate our system, we have monitored DNA break formation, checkpoint activation, DNA repair, recovery and cell survival. This allows us to estimate the number of DSBs needed to enforce a G2 checkpoint and diminish proliferative capacity. In depth analysis of DNA repair kinetics revealed unequal rates of repair and concomitant differential repair pathway choices at different locations. We are currently using this system to map differential sensitivity to repair pathway inhibitors, dependent on the dominant repair pathway used at a given site.
In a parallel line of investigation, we have demonstrated that the G2 checkpoint has to be silenced within a few hours after break formation to allow for recovery. Checkpoint reversal is critically dependent on rapid silencing of ATR signalling, suggesting that a delay in HR-mediated repair is what drives cells into a permanent cell cycle arrest. Indeed, we could show that slower processing of double strand breaks and high levels of resected DNA increases the duration of ATR-dependent signalling, allowing p21 to rise to levels at which it drives cell cycle exit.

Chromosome segregation

The other aim of the lab is to unravel the mechanisms underlying bipolar spindle assembly and proper chromosome segregation, with the intention to enable us to exploit chromosome segregation errors as a means to selectively target the fitness of cancer cells. Taxol belongs to a class of microtubule targeting agents that suppresses microtubule dynamics and interferes with the functioning of the mitotic spindle, thereby effectively blocking cell cycle progression of rapidly proliferating tumor cells. Despite its antitumor activity, drug resistance remains a common obstacle in improving its overall clinical efficacy. Previous studies have shown that the expression of a specific β-tubulin isotype, βIII-tubulin/TUBB3, is dysregulated in drug-refractory tumors. However, whether enhanced TUBB3 expression is directly involved in promoting taxol resistance

remains a subject of debate. We have used several approaches to assess the functional relation of TUBB3 overexpression and taxol resistance. We demonstrated that solely enhancing TUBB3 expression results in a very minor decrease in the sensitivity to taxol. This was further substantiated by selective depletion of TUBB3 in a series of breast cancer cell lines expressing high levels of TUBB3. We find that TUBB3 depletion had a minimal effect on the sensitivity to taxol in one of these cell lines, but had no effect in all of the others. Based on these findings we propose that TUBB3 overexpression can only marginally affect the sensitivity to taxol in cultured cell lines.

We are also investigating how (tumor) cells can deal with the detrimental effects of chromosome segregation errors. The presence of an abnormal karyotype has been shown to be profoundly detrimental at the cellular and organismal level, but is an overt hallmark of cancer. Aneuploidy can lead to p53 activation and hereby prevents proliferation, but the exact trigger for p53 activation has remained controversial. To study this, we have induced aneuploidy in untransformed human cells to explore how cells deal with different segregation errors. We have shown that p53 is activated only in a subset of the cells with an altered chromosome content. Also, we showed that at least a subset of whole chromosome aneuploidies can be propagated in p53-proficient cells, indicating that aneuploidy does not always lead to activation of p53. Importantly, we find that propagation of structural aneuploidies (gain or loss of part of a chromosome) induced by segregation errors is limited to p53-deficient cells.



Induced aneuploidy using Mps1i/CENP-Ei combinatory treatment.
A) Top panel: Genome-wide chromosome copy number profile of RPE-1 wt cells (top panel) as determined by single cell sequencing using the AneuFinder pipeline. Each row represents a single cell with chromosomes plotted as columns. Different colours are used to depict copy number state. Clustering is done on the similarity of copy number profiles. Middle panel: Genome-wide copy number profile of micronucleated RPE-1 wt cells after overnight treatment with the combination of CENP-E inhibitor (50nM) and Mps1 inhibitor (480nM) as determined by single cell sequencing. Bottom panel: Same as middle panel but then for RPE-1 p53kd cells.

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Translational Gastrointestinal Oncology

Disease phenotype, including clinical outcome, is driven by underlying biological mechanisms. Translating disease biology into new diagnostic applications holds great promise for improving outcome for patients. We characterize gastrointestinal pre-malignant and malignant lesions at DNA, RNA, and protein level by tumor profiling using -omics techniques, in order to stratify patient groups and arrive at individually tailored therapies, as well as for biomarker development to improve colorectal cancer screening. Disease biology is studied using pre-clinical model systems such as organoid cultures. Clinical validation is performed by making use of large series of patient sample collections derived from screening programs and multi-center clinical trials. To facilitate the logistics that are needed for these validation studies we are involved in several (inter)national research infrastructure programs.

Early detection of colorectal cancer

Patients can be cured from colorectal cancer (CRC) when the tumor is detected and removed at an early stage. CRC as a disease lends itself perfectly for screening since it has a high prevalence, and it has a well-defined precursor lesion (adenoma) with a long dwell time. Current immunochemical fecal occult blood test (FIT) based screening can reduce CRC mortality, but still approximately 30% of carcinomas and 70% of pre-malignant lesions remain undetected. The main objectives of this research line are unraveling the biology of adenoma to carcinoma progression, and identification and clinical validation of new biomarker based tests.

Biology of adenoma to carcinoma progression

By genomic analysis of tumor development, we identified AURKA and TPX2 as major candidates driving 20q gain-associated colorectal adenoma-to-carcinoma progression. We have established organoid cultures derived from adenomas and carcinomas, which we are using to study the biology of AURKA and TPX2 in tumor progression. We also performed a (phospho) proteomics analysis in a series of more than 100 adenoma and CRC samples, which shows differences in kinase activities between adenomas and carcinomas.

Identification and clinical validation of new biomarker based CRC screening tests

Based on several tumor profiling studies of adenomas and carcinomas we identified candidate biomarkers for early detection, including promoter hypermethylation markers, miRNAs and proteins. These biomarkers were subsequently validated in large collections of clinically well-characterized tumor and stool samples. We established marker panels consisting of four complementary proteins that outperform hemoglobin as a single marker for the detection of CRC. We are currently developing antibody-based assays for further

biomarker validation, which will be tested in a prospective screening trial in the SU2C MEDOCC project.

Biomarker tests for post-polypectomy surveillance

Colonoscopy is currently being used for surveillance after removal of lesions detected during (e.g.) the screening program. This translates into a colonoscopy capacity problem, as surveillance alone consumes more than 25% of all capacity. Within the MOCCAS (MOlecular stool testing for Colorectal CAncer Surveillance) study we are evaluating the performance of molecular markers as possible surveillance tools. We are collecting up to 4000 stool samples from individuals under surveillance for molecular testing, and will perform modeling analysis to design the best surveillance scenarios.

Patient stratification

Cancer is a heterogeneous disease caused by genomic alterations that affect tumor biology and clinical behavior. By DNA-, RNA-, and protein-profiling of tumor tissue it becomes feasible to stratify patients according to their molecular tumor profile, and to optimize treatment for individual patients. Next to tissue samples, also the minute amounts of tumor material in liquid biopsies (i.e. blood samples), which can be obtained more easily than tissue biopsies, are amenable to these assays.

Tumor profiling

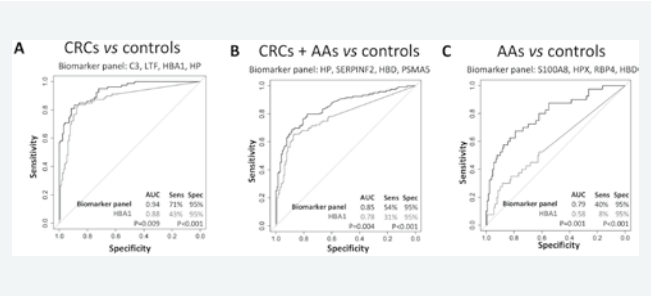
Somatic DNA alterations comprise non-synonymous point mutations, somatic DNA copy number aberrations (SCNA) and structural variants (SVs). Knowledge about the prevalence of SVs in CRC is limited, and the impact of genomic aberrations on patient outcome is poorly understood. We developed an algorithm, GeneBreak, to detect genomic regions that are recurrently affected by chromosomal breakpoints. Our studies revealed hundreds of genes that may be affected by SVs in CRC. In collaboration with dr. S. Abeln (VU, Amsterdam), we now apply machine learning approaches on large public datasets to investigate what genomic regions with recurrent chromosomal breakpoints have highest biological impact.

Circulating tumor DNA biomarkers

Cancer-specific mutations in cell-free circulating tumor DNA (ctDNA) is a promising biomarker for minimal residual disease, with realistic potential to be applied in clinical setting. Technically, the methodology to reliably detect ctDNA mutations in a panel of genes by targeted error correction sequencing was developed by our collaborator prof. V.E. Velculescu (Johns Hopkins Kimmel Cancer Center, Baltimore, USA). Clinically, this technology will be applied within the SU2C MEDOCC project to investigate prognostic value of ctDNA to detect stage II CRC patients at risk of recurrence. The logistics have been established for collecting blood samples in a multi-center nation-wide setting for several large series of clinically well-defined CRC patients. In coming years, these liquid biopsy collections will be used to investigate added value of ctDNA biomarkers to better determine who to treat, how to treat, and when to treat CRC patients.

Translational research infrastructure

The paradigm in personalized medicine is that a better understanding of disease genotype-phenotype will enable disease prevention or improvement of treatment outcomes. To improve translation 'from bench to bedside', current clinical practices need to be changed. This can only be done when research of excellent quality is performed, and operations, logistics and data stewardship of studies have been optimized: data must be FAIR (Findable, Accessible, Interoperable and Reusable). Nationally, Dutch initiatives like BBMRI-NL, ELIXIR-NL, TraIT and EATRIS-NL are converging into one initiative focused on personalized medicine&health research: the Health Research-Infrastructure initiative (Health-RI).
Health-RI offers services for sustainable management of research data, e.g. an online digital research environment (www.ctmm-trait.nl/trait-tools) with various applications for clinical, imaging, biobank and experimental data. There are two data-integration platforms, tranSMART and cBioPortal, that enable researchers to integrate pseudonymized patient data with experimental, imaging and biobank data.
To work towards FAIR data, we are currently filling tranSMART with data from multiple TGO studies. We use the biobank Molgenis catalogue procedures to annotate our biobank of tissue, feces and blood samples; enabling easy data retrieval and sample ordering.
Initiatives in Health-RI are closely linked to (inter)national knowledge and data management initiatives such as IMI eTRIKS, the tranSMART Foundation, OpenPHACTS, BioMedBridges, IKNL, ELIXIR, AACR GENIE and CCE. Health-RI is endorsed by more than 70 national organizations including KWF, patient advocacy groups and others. Moreover, Health-RI has been recognized by authorities in several ways: it is on the KNAW agenda for large scale research facilities, recommended by the Dutch National Health Council, listed in the Dutch National Science agenda and associated science investment agenda, and partner of the ministries of Health, Welfare and Sport, and Economic Affairs.



ROC curves of best-performing colorectal cancer (CRC) biomarker panels in comparison to hemoglobin (HBA1) alone, discriminating between CRC and control (figure A); between CRC plus advanced adenomas (AA) and control (figure B); and between AA and control (figure C). (*Bosch et al. Annal of Internal Medicine 2017)*

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Lipid growth factor signaling

Our group has a long-standing interest in the production and signaling properties of the lipid mediator lysophosphatidic acid (LPA) and its role in tumor progression. LPA signals through specific G protein-coupled receptors to stimulate the proliferation, migration, survival and other functions of numerous cell types. LPA is produced by a secreted lysophospholipase D, named autotaxin (ATX), once identified as an autocrine motility factor for melanoma cells. ATX-LPA signaling is vital for embryonic development and, when hyperactive, promotes fibrosis, tumor growth, invasion and metastasis. In addition, LPA has been implicated in T cell migration in lymph nodes and the tumor microenvironment. Thus, the ATX-LPA receptor signaling axis is an attractive target for therapy.

A more recent line of research focuses on membrane-integral glycerophosphodiester phosphodiesterases (GDEs), notably GDE2 and GDE3. These intriguing ecto-enzymes function as glycosylphosphatidylinositol (GPI)-specific phospholipases that activate signaling pathways through cleavage of GPI-anchored proteins at the plasma membrane, resulting in altered cell behavior and suppression of the malignant phenotype.

Autotaxin-LPA receptor signaling

This line of research concerns ATX-LPA signaling pathways relevant to cancer, in close collaboration with the groups Anastassis Perrakis (Division of Biochemistry) and Kees Jalink (Divison of Cell Biology). We explore signaling properties, structure-function relationships and pharmacologic inhibition of ATX. One area of renewed interest is the regulatory role of ATX/LPA in immune cell function with possible implications for immunotherapy. LPA stimulates the invasion of T-lymphoma cells and enhances the motility of naïve T-cells in lymph nodes and hence may act as an immunomodulator. We have begun to establish how ATX-LPA signaling affects the migratory behavior and transcriptome of tumor-infiltrating lymphocytes derived from melanoma patients (collaboration with the groups of Ton Schumacher and John Haanen, Division of Immunology). Collectively, these studies should lead to new ways of interfering with undue ATX-LPA signaling in cancer cells and their microenvironment.

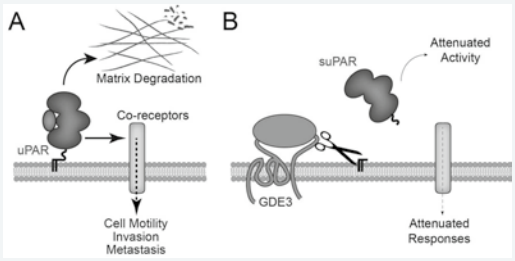
GPI-specific phospholipases as signal transducers

The cell surface of virtually all cell types habors numerous GPI-anchored proteins with diverse biological functions. GPI-anchoring is a complex post-translational modification that anchors select proteins in the outer leaflet of the plasma membrane. Yet, the physiological significance of GPI-anchoring has long remained a mystery. Collaborating with numerous colleagues, we and others recently discovered that GDE2 and GDE3 function as GPI-specific phospholipases that cleave GPI-anchored proteins at the plasma membrane and thereby activate signaling pathways leading to altered cell behaviour.

For example, GDE2 can cleave and shed a GPI-anchored Notch regulator as well as glypican-6, a heparan sulfate proteoglycan that may serve as a ligand for an as-yet-unidentified transmembrane receptor. As a result, GDE2 promotes neuronal differentiation, suppresses neurite retraction and modulates the expression of multiple differentiation-associated genes. Strikingly, GDE2 expression is strongly associated with favorable outcome in neuroblastoma, a childhood cancer characterized by impaired neuronal differentiation and in urgent need of new therapies. Furthermore, GDE2 was found to regulate pancreas differentiation in zebrafish (collaboration Anna-Pavlina Haramis, Leiden University). Further insights into GDE2 signaling and structure-function relationships may suggest new therapeutic possibilities for overcoming the differentiation-inhibited state of neuroblastoma cells and, possibly, pancreas dysfunction.

More recently, we found that GDE3 (but not GDE2) cleaves the GPI-anchored urokinase receptor (uPAR) in a phospholipase C (PLC)-like manner, leading to loss of uPAR function. uPAR promotes tissue remodeling, cell adhesion, migration and invasion through protease recruitment, vitronectin binding and interactions with integrins and other receptors. High GDE3 expression in breast cancer cells depletes endogenous uPAR from the plasma membrane resulting in a less transformed phenotype, it slows tumor growth in a mouse xenograft model and correlates prolonged survival in breast patients. These findings establish GDE3 as the first mammalian GPI-PLC and as a negative regulator of the uPAR signaling network (see figure). In a broader context, our studies highlight selective GPI-anchor hydrolysis as a cell-intrinsic mechanism to suppress malignant cell behavior.

While many questions remain to be addressed in this emerging field of research, the finding that membrane-integral phospholipases such as GDE2 and GDE3 cleave GPI-anchored proteins to modulate signaling pathways and cell behavior sheds new light on the biological function of the once mysterious GPI anchors.



Scheme showing how GDE3 suppresses uPAR function.
(A) GPI-anchored uPAR normally promotes tissue remodeling through matrix degradation and interacts with coreceptors as indicated. (B) GDE3 is a membrane-integral phospholipase C that liberates uPAR from its GPI anchor leading to loss uPAR function.

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Functional genomics for cancer and immune cell therapy

Introduction

The Peeper laboratory develops and uses function-based genomic approaches to better understand the mechanistic principles of cancer progression, and to identify novel therapeutic targets for achieving more durable clinical responses for cancer patients. We have two main strategies. First, we are increasing our understanding of how cancer cells function and particularly how they rewire their signaling networks. This allows for the identification of specific and pharmacologically tractable cancer vulnerabilities. Second, we are manipulating both tumor and immune cells to increase the impact of immunotherapy. Our objective is to contribute to the development of combinatorial therapies, which simultaneously eliminate the patients' tumor cells and harness their immune cells.

Function-based oncogenomics

We have developed genetic functional perturbation screens, for several cancer types, including melanoma and lung and breast cancer. Hits are identified in cancer-relevant models both *in vitro* and *in vivo*. This allows us to annotate individual genes and pathways to particular cancer cell functions, in a highly effective, unbiased and high-throughput manner. Candidate genes are prioritized by bioinformaticians in our laboratory and subsequently validated. Often, our computational approaches yield additional insight into the signaling pathways affected by the screen hits. Eventually, validated targets are characterized in-depth in a clinically relevant context. The outcome of these strategies is the identification of druggable pathways as well as predictive biomarkers.

Developing systems to integrate targeted and immunotherapy

Notwithstanding remarkable clinical advances, it is clear that large groups of patients will not durably benefit from immunotherapy, mostly because of resistance. Therefore, in collaboration with the group of Ton Schumacher at NKI, we have built *in vitro* and *in vivo* systems to study tumor cell - T cell interactions. We use these systems to perform function-based screens to develop combinatorial targeted and immunotherapy regimens to achieve more durable clinical responses. Similar matched epitope/TCR systems have now been set up for lung cancer, also to use large-scale genetic perturbations for the identification of predictive biomarkers and new therapeutic targets.

A preclinical platform for human melanoma

The therapeutic landscape of melanoma is improving rapidly. Targeted inhibitors show promising results, but drug resistance often limits durable clinical responses. There is a need for in *vivo* systems allowing for mechanistic drug resistance studies and (combinatorial) treatment optimization. Therefore, we

established, in collaboration with our clinical colleagues John Haanen, Christian Blank and Ton Schumacher, a large collection of PDX, derived from $BRAF^{V600E}$, $NRAS^{Q61}$, or $BRAF^{WT}/NRAS^{WT}$ melanoma metastases prior to treatment with BRAF inhibitor and after resistance had occurred. We have demonstrated the utility of this platform both for discovery of resistance mechanisms and preclinical validation of potential new treatments. We have recently derived a few dozen low-passage cell lines that we are currently characterizing, also in the context of immuno-oncology.

Melanoma progression

Previously, in collaboration with Wolter Mooi (VUmc), we discovered that melanocytic nevi (moles) undergo oncogene-induced senescence (OIS) *in vivo*. Now, we found, in collaboration with the group of Bas van Steensel, that numerous phenotypic changes occur during OIS, both in the cytoplasm and in the nucleus. These include the activation of autophagy, a catabolic process operating in the cytoplasm and downregulation of lamin B1, a component of the nuclear lamina. We discovered that cells entering OIS downregulate lamin B1, lamin A, and several other nuclear envelope (NE) proteins, resulting in an altered NE morphology and contributing to cell cycle exit. Our results revealed a previously unknown connection between autophagy and the disruption of NE integrity during OIS.

Using cancer drug addiction for developing alternating therapy

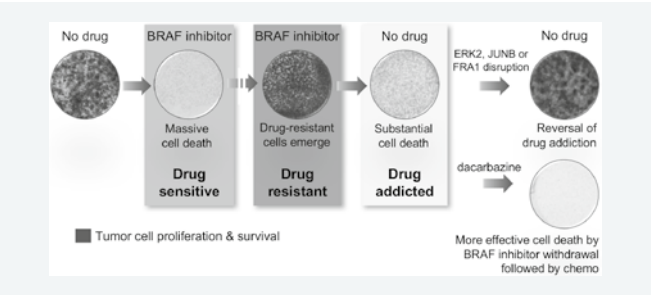
We discovered that cancers can get addicted to the very drugs that serve to eliminate them. With a CRISPR–Cas9 knockout screen, we uncovered a signalling pathway comprising ERK2 and JUNB/FRA1 transcription factors, disruption of which allowed addicted tumour cells to survive on treatment discontinuation. In patients with melanoma that had progressed during treatment with a BRAF inhibitor, treatment cessation was followed by increased expression of the receptor tyrosine kinase AXL, which is associated with a phenotype switch. Drug discontinuation synergized with the melanoma chemotherapeutic agent dacarbazine by further suppressing MITF and its prosurvival target BCL-2 and by inducing DNA damage in cancer cells. These results uncover a pathway that underpins drug addiction in cancer cells, which may help to guide the use of alternating therapeutic strategies for enhanced clinical responses in drug-resistant cancers.

Breast cancer metastasis: mechanism and drug target identification.

We have previously discovered a novel critical mediator of breast cancer metastasis, the Fra-1 transcription factor. Fra-1 depletion reduced metastatic potential by >3 orders of magnitude. Function-based mining of the prognostic Fra-1 signature revealed several additional factors amenable to targeted inhibition. Our data uncover a core genetic and prognostic network driving human breast cancer. We propose that pharmacological inhibition of components within this network, such as PAICS, may be used in conjunction with the Fra-1 prognostic classifier towards personalized management of poor prognosis breast cancer. For PAICS, we have collaborated with MRC Technology (London) to develop a drug screening program; inhibitors have been generated and is currently being evaluated by pharma. Our recent observations suggest that the Fra-1 prognostic classifier harbors several breast cancer-driving factors amenable to targeted inhibition.

Clinical translation

The objectives outlined above illustrate that a central goal of our laboratory is to translate our findings to the benefit of the patient, taking advantage of our comprehensive cancer institute. To maximize these efforts, Daniel Peeper and Christian Blank (a clinician researcher/medical oncologist) have engaged in a partnership to complement their respective basic and clinical expertise. This warrants not only the clinical relevance of our research questions, but also facilitates translation of our laboratory findings (therapeutic targets, prognostic and predictive biomarkers) to the clinic, particularly by initiating trials.



Using cancer drug addiction for developing alternating therapy
Initially, BRAF mutant melanoma cells are highly susceptible to pharmacologic BRAF inhibition and will massively undergo cell death. Nonetheless, eventually resistant clones often emerge, causing relapse of the disease. Remarkably, such resistant tumor cells can also become addicted to the very drugs that serve to eliminate them: when BRAF inhibition is discontinued, substantial cell death is observed. This study demonstrates that this addiction relies on the activity of the ERK2, JUNB and FRA1 genes, disruption of which breaks drug addiction. As a proof-of-concept clinical possibility, we show that cell death resulting from drug withdrawal is strongly enhanced if it is immediately followed by a secondary treatment with dacarbazine (chemotherapy).

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Structural biology

Our research aims to provide molecular insight to macro-molecular interactions, understanding how these regulate specific biological activities in space and in time. Many proteins have a specific biochemical activity that needs to be brought to a specific place in the cell. Typically, additional regulatory domains form interactions with other proteins, DNA, polysaccharides, or lipids, and bring the activity in the correct spatiotemporal context. Understanding these interactions can offer additional options for developing drugs that could inhibit the function of these proteins for therapeutic intervention, hopefully in a more subtle and specific manner.

In parallel to studying specific biological questions in the above context, we maintain an active interest in improving the methods that help us to understand these questions. Specifically, we have a long-standing interest in providing new concepts, algorithms, and software for building optimal macromolecular models based on crystallographic data.

Structural studies of Autotaxin

ATX (or ENPP2) is the lysoPLD producing the signaling phospholipid lysophosphatidic acid (LPA) from lysophosphatidylcholine (LPC); LPA and ATX have been shown by numerous studies to be involved in cancer metastasis and other pathogenic situations, such as chronic inflammation. We had found that ATX binds bile salts in a tunnel near the active site, which act as partial non-competitive allosteric inhibitors, attenuating LPA receptor activation, and may have clinical implications e.g. in the treatment of pruritus. Motivated by the discovery of this new class of allosteric inhibitors of ATX, together with Craig Jamieson at Glasgow, we performed a structure-guided evolution campaign, fusing fragments of known inhibitors to the bile salt scaffold, obtaining a lead compound that has a 6 nM affinity to ATX.

The finding of this allosteric site prompted a more detailed evaluation of the kinetics of the enzymatic activity of ATX, taking into account binding to the allosteric site. We have generated kinetic data and analysed with a global modelling approach that reveals a product activation mechanism, whereas hydrolysis of various LPC species is activated by various LPAs. These data could be of relevance to the lipidomic profiles that results upon ATX inhibition with various classes of inhibitors, some of which are in clinical trials.

Structural studies of proteins involved in mitotic progression

The Spindle Assembly Checkpoint (SAC) is a protein network that ensures that the cell does not proceed with separating the sister chromatids in mitosis before all chromosomes have been aligned and attached to the spindle machinery. We previously showed that a module in the N-terminus of Mps1, the NTE-

TPR, is important for localization of Mps1 to the kinetochores. Previously, we showed that the NTE-TPR interacts with the HEC1 protein of the NDC80 complex in the outer kinetochores directly. Importantly, the strength of the interaction is enhanced upon phosphorylation of the NTE. Furthermore, we showed that microtubules compete with Mps1 for this NDC80 interaction. This established for the first time a physical interaction of the SAC and the microtubule-binding end of kinetochores, suggesting a mechanism through which the inhibitory effect of the SAC is alleviated when microtubules occupy all kinetochore sites and exclude Mps1.

Using biophysical approach, including (paramagnetic) NMR, fluorescent polarisation and microscale thermophoresis assays, we have now shown the interaction of the TPR domain with the NTE. We have also characterised the interaction of the TPR with a C-terminal extension (CTE) and the so-called Middle Region (MR) that is also crucial for interaction with Ndc80c. Collectively, we have made progress understanding how exactly the Mps1 modules interact with the outer kinetochore complexes, modulating microtubule attachment.

We also continue our studies of the interaction of the Mps1 kinase with inhibitors. We studied mutations in the catalytic domain of Mps1 that give rise to inhibitor resistance, but retain catalytic activity and do not display cross-resistance to other Mps1 inhibitors, namely the interactions of C604Y and C604W, which raise resistance to two closely related compounds, NMS-P715 and its derivative Cpd-5. We showed that estimates of the IC50 and the binding affinity (*KD*) indicate that, in both mutants, Cpd-5 should be better tolerated than the closely related NMS-P715, and determined the crystal structure of the Mps1 kinase mutants bound to Cpd-5 and NMS-P715 and compared the binding modes (figure 1). This analysis enforced the notion that inhibitors targeting Mps1 drug-resistant mutations can emerge as a feasible intervention strategy based on existing scaffolds, if the clinical need arises.

Structural studies of J-base binding proteins

The JBP1 protein binds to DNA that contains base J (β-D-glucosyl-hydroxymethyluracil) and is also a thymidine hydroxylase. Almost twenty years following the discovery of base J, Piet Borst and colleagues found a function of base J in non-telomeric regions, being responsible for terminating transcription.

We have previously shown that JBP1 recognizes J-containing DNA through a single aspartate residue in a small DNA Binding Domain (DBD), with ten thousand-fold preference over normal DNA and demonstrated that full-length JBP1 binding to DNA takes place in two distinct steps. Small Angle X-ray scattering (SAXS) studies allowed us to define the low-resolution shape of the J-DNA complex with JBP1 helps explain the mechanism of J-base inheritance, suggesting a two-step mechanism whereas J-base binding triggers a conformational change that brings DNA in position for hydroxylation.

Methods for X-ray crystallography

PDB-REDO is a project we lead together with Robbie Joosten, a senior post-doc and Vidi fellow embedded in my group. We strive to make better crystallographic structure models in two ways: improving models already in Protein Data Bank (PDB) and making these available through the PDB_REDO data bank; and providing a web-server that allows practicing crystallographers to take full advantage of the PDB_REDO procedure without having to install complicated software.

PDB_REDO is a decision-making system that makes rational decisions for the best crystallographic model optimization protocols. This year we proceeded using structural homology as a tool to create better structures, especially at low resolution. We deployed a high performance computing project, utilising more than 60-years of CPU time in less than a week, succeeding to re-refine all PDB structures taking into account the evolutionary relationships between them into account (Figure 2).

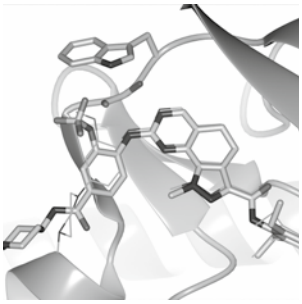

Figure 1. Comparison of the binding modes of NMS-P715 and Cpd-5 to Mps1 kinase domain mutant C604W.

Figure 2. An example network of the transfer of evolutionary information within PDB structures.

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Therapy escape of cancer

We are studying drug resistance mechanisms in "spontaneous" mammary tumors arising in genetically engineered mice. In particular, we are using mammary tumors with conditional defects of the *Brca1, Brca2,* and *p53* genes. In these models we are focusing on (1) mechanisms of secondary drug resistance, (2) the characterization of drug tolerant tumor cells, and (3) the identification of markers that are useful to predict therapy response. These projects are carried out in close collaboration with the group of Jos Jonkers and with Piet Borst.
Using our mouse models, we have also started to investigate the escape from local radiotherapy control (4). For this project we are collaborating with the NKI-AVL radiotherapist Gerben Borst.

Mechanisms of secondary drug resistance

Error-free repair of DNA double-strand breaks (DSB) is achieved by homologous recombination (HR), and BRCA1 and BRCA2 are important factors for this repair pathway. In the absence of BRCA1/2-mediated HR, administration of PARP inhibitors induces synthetic lethality of tumor cells of patients with breast or ovarian cancers. Despite the benefit of this tailored therapy, drug resistance can occur by HR restoration. Little is known about BRCA1-independent restoration of HR, however. In particular, the mechanisms underlying the decision to initiate resection are unclear. Here, our loss-of-function CRISPR/Cas9 screens yielded an interesting hit: depletion of *Ctc1* causes PARPi resistance in BRCA1-deficient cells (figure 1). This suggests that CTC1 plays a critical role in the PARPi-induced DNA damage response. The function is likely CST complex-dependent, as the knockout of the CST complex members *Stn1* or *Ten1* also induces PARPi resistance. Mechanistically, our data show that depletion of *Ctc1* enhances end-resection of DSBs and restores RAD51 loading upon IR in BRCA1-deficient cells, while not affecting the localization of 53BP1 or RIF1 to sites of DSBs. Moreover, depletion of *Ctc1* suppressed c-NHEJ mediated telomere fusions in mouse embryonic fibroblasts. These data demonstrate that depletion of *Ctc1* suppresses the synthetic lethal interaction between BRCA1 deficiency and PARP inhibition, suggesting that CTC1 plays a more global role in DNA repair than previously anticipated.

In contrast to BRCA1-mutated tumors, HR is not restored at all in the BRCA2-deficient PARPi-resistant tumors in our model. Intriguingly, when we performed loss-of-function screens for PARPi resistance in BRCA2-deficient cells, we found that the loss of poly(ADP-ribose) glycohydrolase (PARG), which depolymerizes PAR, causes PARPi resistance. Loss of PARG could also be confirmed in several PARPi-resistant mouse mammary tumors by next generation sequencing. PARG depletion restores PAR formation, rescues controlled fork progression and promotes the recruitment of downstream DNA repair factors. However, the gain of PARPi resistance comes at a cost, as PARG inactivation results in increased radiosensitivity, a new

vulnerability that can be exploited therapeutically. Moreover, PARG-negative clones are pre-existing in a subset of human triple-negative breast cancers, underscoring the potential relevance of PARG in clinical PARPi resistance.

In 2017 we also made progress in employing new technologies that are useful to study drug resistance mechanisms *in vivo*. In collaboration with Norman Sachs (group of Hans Clevers, Hubrecht Institute, Utrecht), we established the generation of 3D cancer organoids from our mammary tumor models. We can now introduce genetic modifications using the CRISPR/Cas9 technology in these organoid cultures. The transplantation of these organoids allows a rapid *in vivo* validation of drug resistance mechanisms, and to identify new treatment vulnerabilities. We think that this technology paves the way for larger genomic *in vivo* screens to identify mechanisms of drug resistance under more realistic treatment conditions.

Drug tolerance

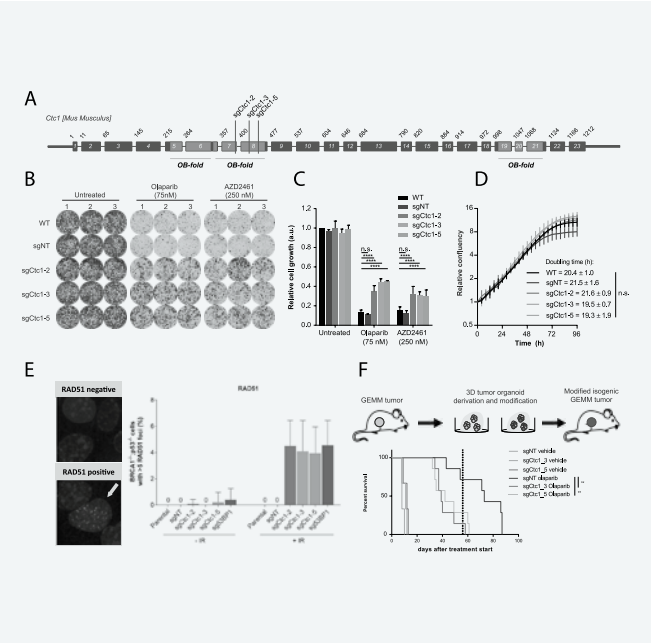
Despite their high sensitivity to platinum drugs, we have found that mammary tumors arising in our mouse model for BRCA1-deficient breast cancer are usually not eradicated, not even by a frequent dosing schedule. We found that the resistance of "remnants" is not due to specific biochemical defense mechanisms of putative tumor-initiating cells, but due to the ability of a sub-fraction of the cells to stall in their cell cycle progression until the drug is gone and the DNA damage has been repaired. After treatment of tumors with cisplatin, most tumor cells initially became giant multi-nuclear cells; relapse comes, however, from cells avoiding entry into S phase. Slowly cycling cells are present within the drug-naïve tumor population and are enriched in tumor remnants. High dose platinum therapy was not tolerated in mice, but we found that nimustine eradicates all tumors. Complete eradication is dose-dependent and lowering the nimustine dose by 50% results in relapse of all tumors. In contrast to platinum drugs, nimustine reduces the number of G0-like cells, which appears to cause disease relapse in our model.

Identification of markers to predict therapy response

In collaboration with Thijn Brummelkamp, we are also employing haploid screens in HAP1 cells to identify new synthetic lethal interactions that may explain sensitivity to microtubule-destabilizing agents. Using the vinca alkaloid vinorelbine, we identified a novel synthetic lethal interaction with the E3 ubiquitin ligase FBXW7. Surprisingly, no synthetic lethal effect was observed when FBXW7-mutated cells were treated with the microtubule-stabilizing taxane docetaxel. The tumor suppressor FBXW7 is a known regulator of the mitotic checkpoint and is frequently mutated in human cancers. Consistent with its role in regulating the mitotic checkpoint, FBXW7-mutated cells accumulated in the G2/M cell cycle stage upon vinorelbine treatment and eventually died. Based on our current data we hypothesize that patients with FBXW7-mutated tumors may benefit more from vinca alkaloid-based microtubule-targeting drugs than from taxanes.

Escape from local radiotherapy control

More than 50% of cancer patients undergo irradiation as part of their treatment. Despite the frequent benefit of this treatment, local tumor recurrence is a major clinical handicap and accompanied by poor prognosis. To address this, we have started irradiating our genetically engineered mouse mammary tumors with clinically relevant doses using a high precision cone beam micro-irradiator. Despite their high sensitivity, BRCA1-deficient carcinomas were not easily eradicated, and eventually relapsed. Although most recurrent tumors responded again to radiation treatment, the response durations were shortened and some recurrent tumors could no longer be controlled. As an alternative way to escape local radiotherapy, we observed the occurrence of metastasis. Hence, basic mechanisms underlying the escape from local radiotherapy control can now be studied in this model.



Loss of *Ctc1* causes PARPi resistance in BRCA1/p53-deficient mouse mammary tumors.
A: Overview of *Ctc1* and gRNA-targeting locations.
B-D: The BRCA1/p53-deficient cell line KB1P-G3 was transfected with pX330puro vectors in which *Ctc1*- or non-targeting (NT) sgRNAs were cloned. The cells were then analyzed using clonogenic assays (B) and quantified (C) for their response to the two different PARP inhibitors olaparib and AZD2461. The difference between *sgCtc1*- and *sgNT*-transfected cells cannot be explained by a difference in proliferation rate (D).
E: Measurement of RAD51 foci formation of the indicated cells in the presence (+) or absence (-) of irradiation (IR, 2h post 10Gy).
F: *In vivo* validation of PARP inhibitor resistance using BRCA1/p53-deficient mammary tumor organoids transduced with *sgCtc1* constructs as intermediate step. Modified organoids were transplanted into the mammary fat pad of animals and stratified into groups that were either treated with vehicle (n=3) or with 100mg olaparib per kg i.p. daily for 56 consecutive days (dashed line, n=7). Differences in survival were analyzed using the log-rank test (**P<0.01).

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Publications

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Chromosome biology

Human chromosomes are centimetres in length, but are organized such that they fit into a cell of micrometre-scale dimensions. Within this confined setting, chromosomes allow for tightly controlled cellular processes such as mitosis and transcription. These processes are made possible by two conserved protein complexes known as cohesin and condensin. Both cohesin and condensin are so-called SMC complexes that by entrapping DNA inside their ring-shaped lumens can structure chromosomes. Research in our lab centres on the mode of action of cohesin and condensin. How do these complexes entrap and release DNA? How does condensin drive mitotic chromosome condensation? And how does cohesin contribute to the formation of the often megabase-sized loops that shape interphase chromosomes? These are the kind of questions that drive our research. We are addressing such questions using a multi-disciplinary approach that covers genetics, genomics, biochemistry and imaging.

Chromosome organization by cohesin

The cohesin complex by default has a dynamic mode of DNA binding that involves a continuous cycle of DNA entrapment and release. Entrapment to a large degree is dependent on the cohesin loader complex consisting of SCC2 and SCC4 (also known as NIPBL and MAU2 respectively). Release in turn requires the cohesin release factor WAPL. We recently found that WAPL-mediated cohesin release involves the action of specifically one of cohesin's two ATPase sites (Elbatsh et al., Mol Cell, 2016 and Beckouët et al., Mol Cell, 2016). The acetylation of a subset of cohesin rings proximal to this ATPase site protects these rings against WAPL. This allows cohesin to stably hold together the sister chromatids from DNA replication until anaphase onset.

This year, we discovered that WAPL-mediated cohesin release plays a major role in 3D genome organization. Cohesin is important for the looping together of CTCF sites. These sites can be megabases apart along a chromosome. The model has been proposed that cohesin might facilitate this looping by capturing a tiny loop inside its lumen, and that this loop is then processively enlarged by the sliding of cohesin down the base of the loop. We now provide vital experimental evidence that this model may be correct. We find that the duration with which cohesin embraces DNA determines the degree to which loops can be enlarged. We suggest that the genome is constantly forming, losing, and re-forming loops in a cohesin-dependent manner, and that WAPL-mediated cohesin turnover thereby ensures that the 3D genome is kept dynamic (figure 1).

What drives the enlargement of cohesin-dependent loops in unknown. We find that this loop enlargement is dependent on the SCC2/SCC4 complex, and that the key function of this complex lies in the C-terminal part of SCC2. The N-terminus of SCC2

contains the binding site for SCC4, which appears to be solely required to stabilize SCC2. In contrast to what was previously thought, SCC4 plays only a minor role in sister chromatid cohesion. It rather plays a key role in loop elongation. How SCC2 affects loop enlargement remains unknown. SCC2 promotes cohesin's ATPase activity. This raises the interesting possibility that cohesin's ATPase activity in fact drives loop enlargement.

Within the nucleus, the genome is divided into active and inactive compartments. We find that cohesin counteracts this compartmentalization. Stabilizing cohesin on DNA by WAPL depletion results in less pronounced compartmentalization, whereas reduction of cohesin levels on DNA by SCC4 deficiency rather results in more pronounced compartmentalization. Our data indicates that nuclear organization is dictated by at least two distinct forces. One force would then be cohesin-mediated loop formation, and the other is compartmentalization. Cohesin-dependent loop formation counteracts this latter force, and could for example serve to relocate a genomic locus from one compartment to another to control gene expression.

Mitotic chromosome condensation by condensin

Mitotic chromosome condensation is dependent on the condensin complex. Like cohesin, condensin can entrap DNA inside its ring-shaped lumen. Condensin has two SMC subunits that form a composite ATPase with two pseudo-symmetric catalytic sites. Unexpectedly, we find that specifically one ATPase site drives condensation, while the other rather acts as a brake. Mutation of this brake site generates hyperactive condensin that compacts DNA faster than wild type, both in vitro and in vivo. Condensin's ATPase apparently controls condensation in a dual manner. We find that this mechanism in fact is conserved from yeast to humans. Asymmetric ATPases with distinct driver and brake sites are likely to reflect a universal principle for SMC complexes that enables these ancient molecular machines to intricately control chromosome architecture.

Metazoans have two condensin complexes, I and II. We find that specifically condensin II is important for sister chromatid decatenation and the formation of a straight chromosomal axis. Condensin II is nuclear, but condensin I can only access chromatin upon the nuclear envelope breakdown (NEBD). We also find that the former complex forms long loops, and that the latter forms shorter loops. Considering these findings, and the timing at which the two complexes contact DNA, our data would support the model that condensin II initiates condensation by forming long loops, and that upon NEBD, condensin I makes small loops within these larger loops (figure 2). We propose that the formation of such loops within loops is required for the formation of a straight chromosomal axis.

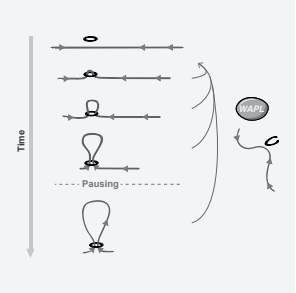

Figure 1: Model depicting the role of cohesin and WAPL in loop formation. DNA is depicted as a line, cohesin as a ring, and CTCF sites as triangles. WAPL opens up cohesin rings, and hereby keeps the 3D genome dynamic.

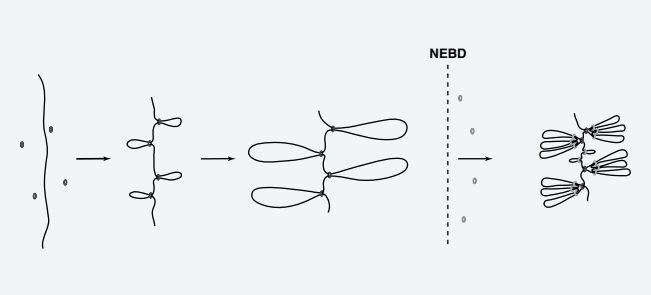

Figure 2: Model depicting the specific roles of condensin I and condensin II in mitotic chromosome condensation. Condensin II (dark grey rings) initiates condensation by forming long loops. Condensin I (light grey rings) contacts DNA upon nuclear envelope breakdown (NEBD), and forms shorter loops within the long condensin II loops.

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Publications

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Cognitive function in cancer patients

The projects constituting our lines of research center around the investigation of the incidence, pattern, course, cause, and risk of cognitive impairment associated with cancer and its treatments, and at the development of strategies to diminish cognitive impairment.

High levels of inflammatory markers in breast cancer survivors 20 years after cessation of chemotherapy are associated with impaired cognitive performance

Increased inflammation is an important candidate mechanism underlying cancer- and cancer treatment-related cognitive impairment. Inflammatory markers are often dysregulated in patients receiving chemotherapy. Less is known about the inflammation status in cancer survivors and its effect on long-term cognitive performance. To target this knowledge gap, we investigated the levels of different inflammatory markers in breast cancer survivors more than 20 years after cessation of chemotherapy and explored the relationship of these markers to cognitive functioning.

166 chemotherapy-exposed breast cancer survivors were compared with 1,444 women from a population-based sample who were not diagnosed with cancer (aged 50-80 years). Inflammation status was assessed by neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII). Participants underwent a cognitive test battery, from which the g-factor was derived assessing general cognitive function. We examined the association between cancer, inflammatory markers, and g-factor using linear regression models.

Breast cancer survivors had higher inflammatory markers compared to controls (mean difference for log NLR =0.29;95% confidence interval (CI) 0.22;0.35, log PLR=0.17;95%CI 0.11;0.22, log SII=0.30;95%CI 0.22;0.38. G-factor was lower in cases compared to controls (mean difference=-0.12;95%CI -0.27;0.03). In cases, higher levels of inflammatory markers were associated with decline in g-factor (per standard deviation (SD) increase of NLR=-0.14;95%CI -0.28;0.00, PLR=-0.13;95%CI -0.26;0.01, SII=-0.15;95%CI -0.29;-0.02). The interaction between cancer status and inflammatory markers showed an additional decline in g-factor per SD increase in inflammatory markers in cancer survivors (β-coefficient for the interaction for NLR=-0.14;95%CI -0.28;-0.01, PLR=-0.17, 95%CI -0.29;-0.05, SII=-0.16; 95%CI -0.30;-0.03).

Breast cancer survivors have more than 20 years post-chemotherapy increased inflammatory markers compared to controls. Increased levels of inflammatory markers were associated with poorer cognitive performance. This association was more pronounced in breast cancer survivors than in controls, suggesting a role for inflammation in long-term cognitive impairment in cancer survivors.

Mild cognitive impairment and dementia show contrasting associations with risk of cancer

Multiple studies have shown a decreased risk of cancer in patients with dementia. Various biological mechanisms have been proposed for this link, but methodological bias has not been satisfactorily ruled out. Mild cognitive impairment (MCI) represents an earlier clinical manifestation of the disease process underlying dementia. We investigated the relation between MCI and cancer and contrasted that with the association between dementia and cancer.
13,207 persons from the Rotterdam Study were followed between 1990 and 2013 for the onset of dementia and cancer. Between 2002 and 2005, a subset of 5,181 persons underwent extensive cognitive testing for MCI and subsequently were followed up for cancer until 2013. We used Cox proportional hazard models to determine the association between dementia and cancer and MCI and cancer. We repeated analyses lagged by two and five years to minimize potential effects of reverse causality.
In total 1,404 patients were diagnosed with dementia, and 2,316 developed cancer (63 among dementia cases). Dementia was associated with a decreased risk of cancer (hazard ratio (HR) 0.53; 95% CI 0.41-0.68). 513 persons were diagnosed with MCI and during follow-up 670 persons developed cancer (81 among MCI cases). In contrast to individuals with dementia, those with MCI tended to have an increased risk of cancer (HR 1.25; 95% CI 0.99-1.58). Using a lag interval of two and five years did not affect the difference between dementia and MCI with respect to cancer risk.
We found that persons with MCI might be at an increased risk of cancer, whereas those with dementia have a decreased risk. These findings call into question a biological explanation for the inverse link between dementia and cancer, instead suggesting methodological bias. Research efforts need to be redirected towards understanding shared mechanisms.

Improved processing of diffusion tensor imaging data increases sensitivity to detect brain white matter changes in breast cancer patients

The aim of this project was to assess side-effects of chemotherapy on brain white matter integrity in breast cancer patients as a neural correlate of cognitive problems.
We implemented an enhanced approach for processing brain magnetic resonance imaging (MRI) diffusion tensor imaging (DTI) data in a longitudinal setting. We used an improved registration algorithm and omitted white matter 'skeletonization' within the widely used tract-based spatial statistics (TBSS) framework.
Twenty-six breast cancer patients scheduled to receive adjuvant chemotherapy with or without endocrine treatment (Ch+), 23 breast cancer patients who did not require chemotherapy or endocrine treatment (Ch-), and 30 age-matched healthy controls (HC) received a T1-weighted scan and a DTI scan at two time points. Baseline data for Ch+ was collected after surgery but before receiving chemotherapy (t0). A follow-up session took place 6 months after chemotherapy and at matched intervals for Ch- and HC (t1). After eddy current correction and diffusion tensor model fitting, a T1-weighted group-wise template was built to warp the fractional anisotropy (FA) maps. We used the ANTs Symmetric Normalization (SyN) registration algorithm.
Ch+ showed a significant decrease in mean FA from t0 to t1 compared to the HC group. Voxel-wise between group analysis showed that both Ch+ and Ch- had significant decreases in FA compared to the HC group, with Ch+ showing more affected voxels than Ch- (5203 vs 230).
These findings suggest a decrease of brain white matter integrity in breast cancer patients, with an added effect of chemotherapy treatment. The improved processing pipeline within the TBSS framework increases sensitivity to detect brain white matter changes in breast cancer patients and demonstrates the feasibility of using this pipeline for DTI data in this population.

Ongoing initiatives include

- A multicenter neuropsychological and brain MRI studies in small cell lung cancer patients after prophylactic cranial irradiation: the effect of hippocampal avoidance, together with University Hospitals Leuven/ KU Leuven.
- Risk factors for cognitive problems in breast cancer patients: the role of brain white matter, together with the Academic Medical Center.
- Trajectories of cognitive decline in survivors of non-CNS cancers: from pre-cancer diagnosis to late life after cancer, together with the Erasmus MC.
- An online testing approach to assess cognitive problems, together with the University of Amsterdam and the VU University.
- The influence of informing patients about the association between cognitive problems and chemotherapy on cognitive problems, together with the Radboud University.
- Implementation of routine neuropsychological assessment and advanced MRI in brain tumor patients.
- Effect of physical exercise on cognitive functioning after chemotherapy, together with Julius Center.
- Internet based Work-related cognitive Rehabilitation for Cancer survivors: a randomised controlled trial

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Publications

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Pharmacodynamics of anticancer drugs

Research is focused on clinical pharmacology of novel anticancer drugs, first in man studies, translational research and development and validation of assays to monitor immune oncology drug development.

Biomarker studies

We study the sensitivity and specificity of circulating tumor cells and cytology in cerebrospinal fluid of patients clinically suspected of leptomeningeal metastases. The target inclusion of 100 patients in the epithelial solid tumor cohort has been reached. Preliminary analysis reveals that the FACS based quantification is much more sensitive than the current gold standard cytology. The study in patients with melanoma is ongoing.

Development and validation of pharmacokinetic/ pharmacodynamics assays.

We developed and validated a pharmacokinetic ELISA assay for the determination of nivolumab and pembrolizumab concentrations in serum and cerebrospinal fluid from patients. The assay is highly sensitive with a limit of quantification for both therapeutic antibodies of 1 ng/ml. All validation parameters were within FDA guidelines for analytical assay validation. Recently IRB clearance for testing of the clinical applicability of the assay was received.

Pharmacodynamic assay for determination of PD-1 receptor occupancy

We develop a pharmacodynamic assay for quantification of the occupancy and number of immunotherapeutic antibodies bound to their PD-1 receptor target on different subsets of T-cells. The assay can be used for monitoring the efficacy of anti-PD1 immunotherapy. With this assay, the receptor occupancy of CD4 T cells, CD8 T cells, CD19 B cells, dendritic cells, NK cells and macrophages can be determined.

Circulating Endothelial Cells

Circulating endothelial cells (CECs) are a potential biomarker of angiogenesis. CECs increase in numbers after vessel injury. Higher CECs numbers are reported in cancer patients. Most methods for CECs detection and enumeration rely on flow cytometry (FCM), however, there is no agreement on CECs phenotype and the detection method to be used. This leads to uncertainty about the clinical applicability and variation between studies on CEC numbers reported. The aim of this study was to develop a selective and accurate method for CECs enumeration in peripheral blood by enrichment followed by FCM in healthy volunteers (HV) and cancer patients.
Samples were enriched using CD34 microbeads, stained with nuclear dye and anti-CD14, CD15, CD45, CD34 and CD146 antibodies. Putative CECs were examined for Weibel-Palade bodies (WPBs) using anti von Willebrand factor (vWF) antibody

and fluorescence microscopy. Linear range of detection (R^2), recovery and precision (CV%) were defined in three experiments by spiking a known number (range 12-12800 CECs/4ml) of surrogate endothelial cells in peripheral blood. Sample storage was determined at -80˚C for up to 2 months.
Sorted CECs showed vWF in the WPBs. The relationship between spiked and detected surrogate cells was R^2=1.0, recovery 94.0-101.4%, and CV% 1.0-18.4%. Recovery ± standard deviation (within-run day 1-3) were respectively 102.5% ±8.2, 97.8% ±4.6, 99.1% ±7.7, and after 2 months 94.3% ±15.3. The median CECs/ml in patients was 24.1 versus 14.4 in HVs.
We were able to develop a method that is selective, sensitive, and reliable (figure 1). This FCM method allows for investigation of CECs as a biomarker in clinical research.

Circulating tumor DNA in cancer patients: development of a clinical diagnostic tests and establishment of a biobank
In collaboration with VUmc, we established a database with circulating tumor DNA samples that are measured in thrombocytes and clinical information of patients with sarcoma to search for RNA-profiles that could be used in the development of a diagnostic test to distinguish cancer patients from healthy individuals and to locate the primary tumor.

Clinical pharmacology studies

Focus is on immune oncology studies with novel drugs as single agent of in combination. In the phase I/II dose escalation and cohort expansion study for safety, tolerability, and efficacy of anti-GITR monoclonal antibody (BMS-986156) administered alone and in combination with Nivolumab (anti PD-1) in advanced solid tumors the dose escalation is finished and a RP2D has been determined. The expansion part is almost finished with the combination therapy in non-small cell lung cancer, cervical cancer, bladder cancer, squamous cell carcinoma of head and neck, ovarian cancer and hepatocellular cancer.
In the phase I/II study of anti-CD73 (BMS-986179) administered in combination with Nivolumab in subjects with advanced solid tumors we initiated the escalation cohort with the combination therapy with a safety lead-in of anti-CD73. Preliminary results encourage further investigation.
In the phase 1/2a Study of BMS-986178 Administered Alone and in Combination with Nivolumab or Ipilimumab in Advanced Solid Tumors the dose escalation is finished and the RP2D is determined. The potential dual function of OX40 agonism in increasing the Teff response while decreasing Treg inhibition supports further evaluation of the synergy of the combination with nivolumab and or ipilimumab.
The monocenter 3+3 dose escalation phase I trial with olaparib (PARP-inhibitor) BID plus carboplatin followed by olaparib monotherapy (REVIVAL trial) has been finished. Twenty-four patients have been included in this trial. The study shows promising anti-tumor activity with a manageable safety profile.
In the phase II pharmacological study Wee-1 inhibitor AZD-1775 is combined with carboplatin in patients with p53 mutated epithelial ovarian cancer that show early relapse (<3 months) or progression during standard first line treatment with carboplatin – paclitaxel combination therapy. Re-exposing patients with early relapse to carboplatin in combination with Wee1 AZD-1775 has shown promising anti-tumor effect by us. Therefore, an additional safety and preliminary activity cohort was opened.
In a phase I study with weekly AZD-1775 with carboplatin we determine the MTD in patients with p53 solid tumors. The hypothesis of this study is that with dose-dense administration of AZD1775 and carboplatin, in a more frequent but lower dose schedule, efficacy increases with a manageable toxicity profile. The study protocol of this study is under review.
In a phase I study with the antibody-drug conjugate ADYS985 we evaluate the safety, pharmacokinetics and efficacy in patients with locally advanced or metastatic solid tumors. To date six patients have been included.
Other investigated novel drugs include aOX40, aCD40, CEA-TCB, and FAP-IL2v. These drugs are combined with other immunotherapeutic drugs such as vanucizumab (aVEGF/ANG-2), pembrolizumab (aPD-1), utomilumab (a4-1BB) and atezolizumab (aPD-L1) in phase IB studies. The phase I/IB studies have reached the maximal tolerated dose/optimal biological dose for FAP-IL2v, aOX40, CEA-TCB, and aCD40 and will now continue in expansion cohorts.

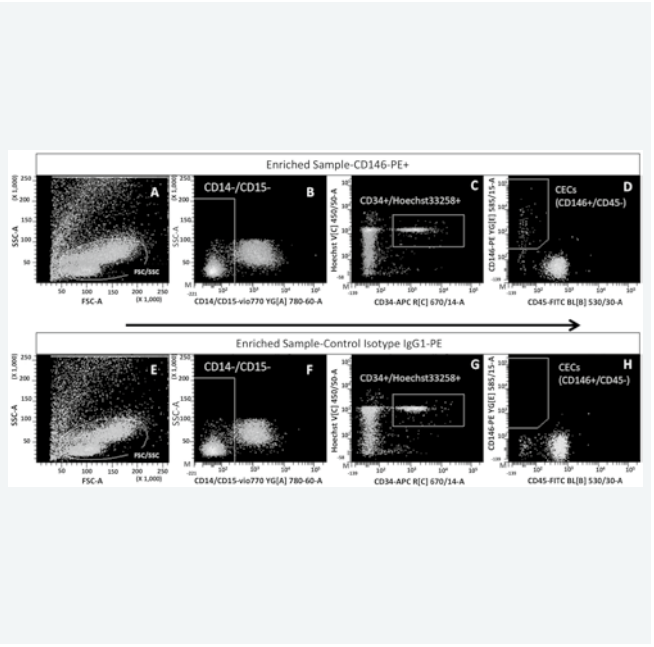

Figure 1. Five-color flow cytometry analysis of CECs. CECs were analyzed using FACS Diva software and sequential gating strategy. The black arrow depicts the gating direction. Doublets were excluded (FSC-A versus FSC-H, plot not shown) prior to gate A. A) Gate A selects for mononuclear cells, and excludes debris and platelets, B) Gate B (dump channel) is derived from gate A and excludes possible contamination by monocytes, macrophages and neutrophils, C) Gate C is derived from gate B and shows the gate with $CD34^+$-nucleated Hoechst33258+ population, D) Gate D is derived from gate C and selects nucleated, $CD45^-CD34^+CD146^+$ circulating endothelial cells. Panels E-H represent an enriched control sample stained with an isotype IgG1-PE. Abbreviations: FACS-fluorescence-activated cell sorting, FSC-A – forward scatter area, FSC-H – forward scatter height, SSC-A – side scatter area.

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Genes and proteins involved in anticancer drug resistance and pharmacokinetics

Our research focuses on genes and proteins that cause drug resistance or drug susceptibility in tumors, or influence the pharmacological and toxicological behavior of anticancer and other drugs and toxins, including carcinogens. Of special interest in this respect are multispecific drug efflux and uptake transporters, as well as multispecific drug-metabolizing enzymes. Insight into these systems may: i) improve chemotherapy and more generally pharmacotherapy approaches for cancer and other diseases; ii) increase insights into factors determining susceptibility to toxins and carcinogens, and; iii) allow elucidation of physiological functions. To study the physiological, pharmacological and toxicological roles of the proteins involved, and their interactions, we generate and analyze knockout or transgenic mice lacking or overexpressing the relevant genes. Below we describe a few recent studies that illustrate our approach.

Breast cancer resistance protein (BCRP/ABCG2) and P-glycoprotein (P-gp/ABCB1) transport afatinib and restrict its oral availability and brain accumulation

Afatinib is a rationally designed drug that acts as a highly selective, irreversible inhibitor of EGFR and (HER)-2. It is orally administered for the treatment of patients with EGFR mutation-positive types of metastatic non-small cell lung cancer (NSCLC). We investigated whether afatinib is a substrate for the multidrug efflux transporters ABCB1 and ABCG2 and whether these transporters influence oral availability and brain and other tissue accumulation of afatinib. We used *in vitro* transport assays to assess human (h)ABCB1-, hABCG2- or murine (m)Abcg2-mediated transport of afatinib. To study the single and combined roles of Abcg2 and Abcb1a/1b in oral afatinib disposition, we used appropriate knockout mouse strains. Afatinib was transported well by hABCB1, hABCG2 and mAbcg2 *in vitro*. Upon oral administration of afatinib, *Abcg2*$^{-/-}$, *Abcb1a/1b*$^{-/-}$ and *Abcb1a/1b*$^{-/-}$;*Abcg2*$^{-/-}$ mice displayed a 4.2-, 2.4- and 7-fold increased afatinib plasma AUC_{0-24} compared with wild-type mice. Abcg2-deficient strains also displayed decreased afatinib plasma clearance. At 2 h, relative brain accumulation of afatinib was not significantly altered in the single knockout strains, but 24-fold increased in the combination *Abcb1a/1b*$^{-/-}$;*Abcg2*$^{-/-}$ mice compared to wild-type mice. Abcg2 and Abcb1a/1b thus restrict both oral availability and brain accumulation of afatinib. Inhibition of these transporters may therefore be of clinical importance for patients with brain (micro-)metastases positioned behind an intact blood-brain barrier.

Ochratoxin A transport by the human breast cancer resistance protein (BCRP), multidrug resistance protein 2 (MRP2), and organic anion-transporting polypeptides 1A2, 1B1 and 2B1

Ochratoxin A (OTA) is a fungal secondary metabolite that can contaminate various foods. OTA has several toxic effects like

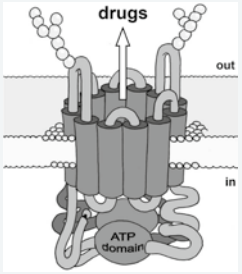
nephrotoxicity, hepatotoxicity, and neurotoxicity in different animal species, but its mechanisms of toxicity are still unclear. How OTA accumulates in kidney, liver, and brain is as yet unknown, but transmembrane transport proteins are likely involved. We studied transport of OTA in vitro, using polarized MDCKII cells transduced with cDNAs of the efflux transporters mouse (m)Bcrp, human (h)BCRP, mMrp2, or hMRP2, and HEK293 cells overexpressing cDNAs of the human uptake transporters OATP1A2, OATP1B1, OATP1B3, or OATP2B1 at pH 7.4 and 6.4. MDCKII-mBcrp cells were more resistant to OTA toxicity than MDCKII parental and hBCRP-transduced cells. Transepithelial transport experiments showed some apically directed transport by MDCKII-mBcrp cells at pH 7.4, whereas both mBcrp and hBCRP clearly transported OTA at pH 6.4. There was modest transport of OTA by mMrp2 and hMRP2 only at pH 6.4. OATP1A2 and OATP2B1 mediated uptake of OTA both at pH 7.4 and 6.4, but OATP1B1 only at pH 7.4. There was no detectable transport of OTA by OATP1B3. Our data indicate that human BCRP and MRP2 can mediate elimination of OTA from cells, thus reducing OTA toxicity. On the other hand, human OATP1A2, OATP1B1, and OATP2B1 can mediate cellular uptake of OTA, which could aggravate OTA toxicity.

Brain accumulation of ponatinib and its active metabolite N-desmethyl ponatinib is limited by P-glycoprotein (P-GP/ABCB1) and breast cancer resistance protein (BCRP/ABCG2)

The targeted drug ponatinib is an oral BCR-ABL1 inhibitor for treatment of advanced leukemic diseases that carry the Philadelphia chromosome, specifically containing the T315I mutation yielding resistance to previously approved BCR-ABL1 inhibitors. Using *in vitro* transport assays and knockout mouse models, we investigated whether the multidrug efflux transporters ABCB1 and ABCG2 transport ponatinib and whether they, or the drug-metabolizing enzyme CYP3A, affect the oral availability and brain accumulation of ponatinib and its active *N*-desmethyl metabolite (DMP). *In vitro*, mouse Abcg2 and human ABCB1 modestly transported ponatinib. In mice, both Abcb1 and Abcg2 markedly restricted brain accumulation of ponatinib and DMP, but not ponatinib oral availability. Abcg2 deficiency increased DMP plasma levels ~3-fold. Cyp3a deficiency increased the ponatinib plasma AUC 1.4-fold. Our results suggest that pharmacological inhibition of ABCG2 and ABCB1 during ponatinib therapy might benefit patients with brain (micro-)metastases positioned behind an intact blood-brain barrier, or with substantial expression of these transporters in the malignant cells. CYP3A inhibitors might increase ponatinib oral availability, enhancing efficacy but possibly also toxicity of this drug.

Other findings and outlook

Our findings illustrate the wide impact of the multispecific detoxifying systems that we study on the in vivo behavior of many anticancer and other drugs, as well as dietary toxins and carcinogens. The insights and mouse models that we generate can be used to improve the development and application of new anticancer and other drugs, to optimize drug administration regimens, and to better predict risks of variable activities in the different detoxifying systems during chemotherapy, pharmacotherapy and exposure to environmental toxins and carcinogens.



Putative structure of a prototypic ABC drug transporter.

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Publications

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Theme: molecular breast cancer epidemiology

Our work spans the themes of personalized prevention and precision medicine. We strive to make better use of hereditary genetic information, and other risk factor information, in the early detection and prevention of breast cancer and breast cancer recurrence. To investigate genetic variants, we use both candidate approaches for e.g. *BRCA1*, *BRCA2*, and *CHEK2*, and agnostic approaches for variants in other genes through Genome Wide Association Studies (GWAS). Studies include interactions between germline variants, tumor characteristics, breast cancer treatment, and lifestyle factors on development of breast cancer subtypes, breast cancer prognosis, incidence of second tumors, and cause-specific mortality. We aim to translate and implement our findings in risk prediction tools and guidelines to facilitate shared decision-making by patients and physicians so that adequate strategies can be chosen for prevention, treatment, and follow-up.

Our group is based in the Division of Molecular Pathology, and we work closely together with the Division of Psychosocial Research and Epidemiology, several clinical departments, the Core Facility Molecular Pathology and Biobanking (CFMPB), and with a large number of national and international research groups.

Genome-wide association studies to find novel genetic variants

To conduct studies into breast cancer, we set up several national cohorts, and are involved in a number of international consortia, in total comprising over 300,000 women with and without breast cancer. Our group curates the Breast Cancer Association Consortium database for tumor characteristics and clinical information; numbers of breast cancer patients included increase every year. From 96 studies with >198,000 patients in 2016 to 102 studies with >206,000 patients, of which ~149,000 with genetic information obtained by running GWAS chips on DNA from blood, this year.

Prevention and early detection of breast cancer

We found, together with 550 researchers within the Breast Cancer Association Consortium studying DNA of over 275,000 women, 65 novel genetic variants to be associated with breast cancer. Moreover, we found 7 other novel variants to be associated with estrogen receptor negative breast cancer, a type of breast cancer which does not respond to hormone therapies. Along with the genetic variants that were already known, the total number is now almost 180. Our next step now will be to start the implementation of these findings into clinical practice.

Not only genetic factors, but also other diseases or shared underlying lifestyle factors are involved in the risk profile for breast cancer. It is known that women with diabetes have a 20 per cent increased risk of developing breast cancer; and

higher chance of death after breast cancer diagnosis compared to women without diabetes. The underlying causes of these associations are not known. In the context of the CARING EU project, we studied possible links between diabetes and insulin treatment on one side and breast cancer development on the other side. We found some indications that diabetes is involved in the development of hormone receptor negative breast cancer in premenopausal women. However, we concluded that insulin analogue treatment itself does not increase the risk of breast cancer overall.

Prediction and prevention of breast cancer subtypes, breast cancer recurrence and second cancers

We have two large projects ongoing in which we will try to develop better tools for prediction of breast cancer risk and prognosis. Firstly, our group is leading a large EU Horizon 2020 grant, entitled Breast CAncer STratification (B-CAST). In this project, we are aiming to study the etiology of the development of specific breast cancer subtypes, with subsequent prognosis. We will also classify 10,000 breast tumors using a DNA mutation sequence panel and 20,000 tumors using immunohistochemical markers to support the tumor subtype classification in the project. Secondly, in collaboration with the Erasmus MC, we are also elucidating the risk factors for a second breast cancer, and developing prediction models and an online decision aid for the risk of contralateral breast cancer.

One of our key findings from one of our national breast cancer studies this year was that "*BRCA1/2*-mutation carriers diagnosed with breast cancer before age 50 are prone to a worse survival, which is partly explained by differences in tumor characteristics, treatment response, and second ovarian cancers". These analyses were done using a cohort of 6,478 invasive breast cancer patients diagnosed in 10 Dutch hospitals between 1970 and 2003. *BRCA1/2* testing of most-prevalent mutations, done using DNA isolated from formalin-fixed, paraffin-embedded non-tumor tissue, identified 3.2% *BRCA1*- and 1.2% *BRCA2*-mutation carriers. Survival estimates using Cox regression and competing risk models showed that *BRCA1*-mutation carriers had a worse overall survival independent of clinico-pathological/treatment characteristics, compared to non-carriers (adjusted-HR=1.20; 95%CI:0.97-1.47), though only statistically significant in the first 5 years of follow-up (adjusted-HR=1.40; 95%CI:1.07-1.84). A large part of this residual worse survival was explained by incidence of ovarian cancers. The most pronounced worse survival for *BRCA1*- mutation carriers was seen in the non-chemotherapy treated patients (adjusted-HR=1.54; 95%CI:1.08-2.19). Power for *BRCA2*-mutation carriers was limited; only after 5-years follow-up overall survival was worse compared to non-carriers (adjusted-HR=1.47; 95%CI:1.00-2.17)."

We also used this national breast cancer cohort for validating PREDICT, an online prognostication tool already used extensively in clinical practice, in young breast cancer patients. The key finding was that, although imprecise at the extremes, PREDICT's estimates of 10-year all-cause mortality seem reasonably sound for breast cancer patients <50 years, and PREDICT can be used to *supplement* clinical judgement and doctor–patient communication, when advising young patients about adjuvant systemic therapy.

Ethical, Legal and Social issues in biobanking and research

Precision medicine promises to bring powerful new ways of improving treatment and health care, tailored to individual patients. At the same time, this leads to a variety of different ethical, legal and societal issues (ELSI). How, for instance, can privacy be protected under new data protection regulations when data sharing is the norm in science? What about patients' rights and informed consent? Our research focuses on practical solutions for improvement of patient information, consent procedures, and return of results. We are setting up an ELSI service desk for precision medicine and next generation sequencing. This national Servicedesk aims to help practitioners of research to address ELSI issues by offering accessible advice, better opportunities for mutual learning and coordination, and an overview of areas for improvement.

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Dissecting and manipulating antigen-specific t-cell immunity

The aim of our research is straightforward 1). To design novel technologies to examine and modify immune responses 2). To subsequently use these technologies to unravel and manipulate the molecular processes that underlie T cell-based immune recognition of human cancer.

Dissecting T cell recognition in human cancer

There is now widespread evidence for the clinical value of T cell-based immunotherapies for a number of human cancers. In prior work we have aimed to dissect which antigens on tumor cells are key to such immunotherapy-induced cancer regression. The main observation from this work has been that recognition of tumor-specific neo-antigens that arise as a consequence of DNA damage forms a major ingredient of the clinical activity of the current cancer immunotherapies in tumors such as lung cancer and melanoma. In other words, the DNA damage that on the one hand leads to tumor outgrowth can also provide an opportunity for T cell-mediated tumor control.

To also understand the role of neo-antigens and other tumor antigens in cancers with lower mutational burdens, we have taken two approaches. First, we have recently completed a large-scale bio-informatics effort in which we have benchmarked the size of the 'neo-antigen space' in diverse human tumors relative to that of human pathogens that are under T cell control. Data obtained suggest that a sufficient neo-antigen repertoire may only be present in a subset of human cancers. In parallel work, we have carried out an unbiased wet-lab analysis of the tumor reactivity of the intratumoral TCR repertoire. In many tumor types, infiltration by T cells is interpreted as a sign of immune recognition, and there is a growing effort to 'rescue' the presumably exhausted T cells at such tumor sites. However, such efforts really only make sense if the intratumoral TCR repertoire carried by these cells is intrinsically tumor-reactive. To address this issue, we have analyzed whether the intratumoral TCR repertoire in ovarian cancer and colorectal cancer – two tumor types for which T cell infiltrates form a positive prognostic marker – is commonly tumor reactive. Data obtained indicate that only a small and variable fraction of the intratumoral TCR repertoire shows autologous tumor reactivity in these tumor types. These data emphasize the need for the development of technology that can distinguish (exhausted) tumor-reactive T cells from mere bystanders in a clinical setting. Towards this goal, we have started to dissect the tumor recognition potential of defined T cell subpopulations in both melanoma (figure 1) and non-small cell lung cancer. Intriguingly, in both tumor types, ability to recognize autologous tumor appears restricted to a well-defined subset of T cells, and data in NSCLC suggest that quantification of this defined T cell subset may have substantial predictive value in patients treated with PD-1 blocking antibodies. With the role of tumor-specific T cells now well-established, we are also collaborating with clinician scientists Marleen Kok, Christian

Blank, and John Haanen to devise clinical strategies to boost such T cell responses. A particularly exciting result in these studies has been the demonstration that the immune-stimulating activity of T cell checkpoint therapy is more profound when given as neo-adjuvant than as adjuvant therapy.

Regulation of T cell activity in cancer

While recognition of tumor antigens is clearly an essential condition for T cell-mediated tumor control, it is apparent that the outcome of immune – tumor cell interaction is likewise dependent on a series of other parameters. To provide more information on the regulation of immune checkpoints in cancer cells, we have carried out a set of haploid genetic screens in collaboration with the Brummelkamp lab. Using this approach, we first identified CMTM6 and CMTM4 as regulators of the PD-L1 protein in diverse tumor types. CMTM6 and 4 interact with the PD-L1 protein and regulate the stability of the PD-L1 protein at the cell surface. Based on the data obtained, these proteins should be considered potential novel targets for immunotherapeutic intervention. In ongoing work, we are evaluating whether these CMTM family members also interact with ligands for other T cell co-receptors. In parallel we have initiated genetic screens for regulators of other immune checkpoints.

Dissecting the basic concepts of immunity

In addition to the above studies that aim to describe and enhance human tumor-specific T cell responses, we continue our effort to dissect T cell-based immune responses within model systems, both to increase our fundamental understanding of this process, and as a breeding ground for novel technologies. To highlight a few of the results obtained, we have demonstrated that the generation of effector and memory T cells does not measurably occur as a consequence of asymmetric cell division of naïve T cells following their first antigen encounter. Furthermore, we have demonstrated that T cell control of tumors includes a component of 'bystander killing', perhaps explaining the relatively infrequent occurrence of acquired resistance as compared to what is seen upon targeted therapy. We have also developed technology to measure the migration of T cells in skin explant models. Data obtained indicate that – much like we previously documented for their brethren in the mouse – skin-resident CD8 memory T cells constitutively patrol the local environment of our skin. Finally, we have developed a system to measure the number of divisions (T) cells have undergone (figure 2), and are now using this approach to determine whether memory T cells differ from effector T cells with respect to their replicative history.

Figure 1. Single cell sequencing of human melanomas. Data depict phenotypic state of intratumoral T cells of an individual patient (black), plotted over a background of diverse T cell states observed in a cohort of melanoma patients.

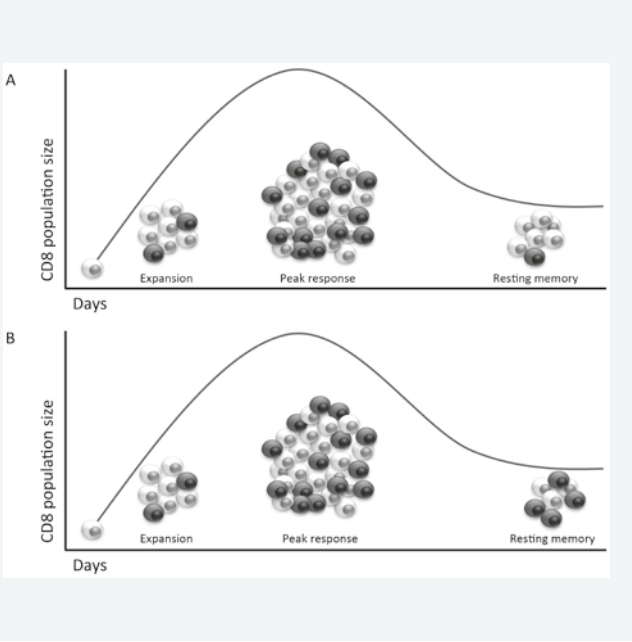

Figure 2. Measuring replicative history of immune cells. Expected frequency of tagged T cells (dark grey) throughput T cell differentiation is depicted in a setting in which memory T cells are (A) or are not (B) derived from T cells that have undergone limited proliferative bursts.

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Structural biology

Development of cancer is generally due to errors that occur in cellular pathways. Understanding the mechanisms of underlying processes will help to determine where the errors occur and how they can be treated. We study proteins using a combination of biochemical and biophysical methods, including X-ray crystallography and cryo-EM (electron microscopy) to provide three-dimensional structures. This leads to insights in molecular mechanisms that we validate in cells. In addition our structures provide targets for drug design studies. In this work we focus primarily on proteins involved in ubiquitin conjugation, particularly in stress response and DNA repair pathways and DNA mismatch repair.

DNA mismatch repair

DNA mismatch repair plays a crucial role in maintaining genome stability. Defects in the mismatch repair proteins in humans predispose to Lynch syndrome (or hereditary non-polyposis colorectal cancer) and are associated with a variety of sporadic cancers. DNA mismatch repair is initiated by recognition of a mismatch or an unpaired base by MutS (in Escherichia coli) or its MSH homologs (in humans). Initial recognition of the mismatch is followed by an ATP-dependent conformational change of MutS into a sliding clamp state that can be recognized specifically by the next protein in the mismatch repair cascade, MutL (or its homologs). Intriguingly, both MutS and MutL are critical for correct repair and germline mutations in the human homologs of either of these proteins lead cancer predisposition. The conformational states are important to transmit information from mismatch binding into repair. In recent years we have collaborated with the lab of Peter Friedhoff to make use of his single cysteine variants of MutS and MutL. These are valuable tools for structural studies, since they allow trapping of a relevant state for crystallography and cryo-EM. We have also used these states for validation of our structures by labelling of selective single-cysteine variants that change in FRET signal upon a conformational change (Friedhoff et al, 2017).
Now we are using cryo-electron microscopy in collaboration with the laboratory of Meindert Lamers to study this complex. Previously we have solved a crystal structure of a cross linked MutS/MutL^{LN40}, revealing the large conformational changes associated with sliding clamp formation. We have been able to generate a series of cryo-EM reconstitutions of this complex on blocked DNA. This has resulted in a set of different structures that reveal how the DNA runs through the MutS/MutL complex, but also show how the clamp domain can kink onto DNA. We are also pursuing other states in the initiation of DNA mismatch repair

Ubiquitin conjugation

Ubiquitin conjugation in cells provides critical signals that change the fate of the target protein. It is important almost all cellular processes, including DNA repair, apoptosis, cell cycle, chromatin regulation and endocytosis. Since these processes

are necessary for cellular integrity, deregulation of ubiquitin-dependent processes often leads to cancer. We focus on mechanisms of ubiquitin conjugation to aid the process of drug design critical pathways in ubiquitin conjugation.

The process of conjugation by ubiquitin-(like) proteins involves covalent linking of one or more 76-amino-acid ubiquitins to a target protein by an E1/E2/E3 cascade of enzymes. Correct ubiquitination requires the complex spatial arrangement of ubiquitin, E2, E3 proteins and the target simultaneously in a precise but flexible manner. We are particularly interested in the factors that determine the rate, the specificity and the selectivity of the E2/E3 dependent reaction, especially in DNA-dependent processes.

Ubiquitin conjugation is an important signal in cellular pathways, changing the fate of a target protein, by degradation, relocalization or complex formation. These signals are balanced by deubiquitinating enzymes (DUBs), which antagonize ubiquitination of specific protein substrates. Because ubiquitination pathways are critically important, DUB activity is often carefully controlled.

One topic that we are interested is the regulation of DUBs by their target. Here we focus in particular on USP7. USP7 (or HAUSP) is one of the most abundant deubiquitinating enzymes (DUBs). It is regulated by complex formation with regulatory proteins and targets, where it is found in a large number of relatively stable complexes with different possible functions. Surprisingly, many of the partners are E3 ligases. These complexes make up potential cellular 'switches', using their (de) ubiquitination ability to switch pathways on or off upon cellular signals (reviewed in Kim & Sixma, JMB 2017).

Full activity of USP7 requires that its C-terminal ubiquitin-like domains fold back onto the catalytic domain, to allow remodeling of the active site to a catalytically competent state by the very C-terminal peptide. This regulatory mode can be modulated by complex formation with other proteins. We have used NMR and biochemical methods to address the order of events in USP7 regulation (Kim et al, in preparation)

Many of our projects are in the context of the DNA damage response. DNA double strand breaks need to be repaired in an organized fashion to preserve genomic integrity. In the organization of faithful repair, histone ubiquitination plays a crucial role. We study how site-specific histone ubiquitination is achieved on a molecular level and how different multi-protein complexes work together to integrate different histone ubiquitination states (reviewed in: Uckelmann & Sixma 2017).

There are three different E3 ligases that modify H2A, RNF168, RING1b and BRCA1/BARD, each on their own specific set of lysines. Recently we designed a fluorescent polarization assay (figure 2) to screen a number of DUBs for site-selectivity on H2A and discovered that USP48 has a preference for deubiquitination of the K125/127/129 sites, modified by BRCA1.

So far no specific deubiquitinating enzymes (DUBs) are known to antagonize this function. Detailed biochemical analysis shows that an auxiliary ubiquitin, an additional ubiquitin that itself does not get cleaved, modulates USP48 activity, which has possible implications for its regulation in vivo. In collaboration with the group of Jo Morris in Birmingham we could show that USP48 promotes genome stability by antagonizing BRCA1 E3 ligase function (Uckelmann, Densham et al, *in press*).

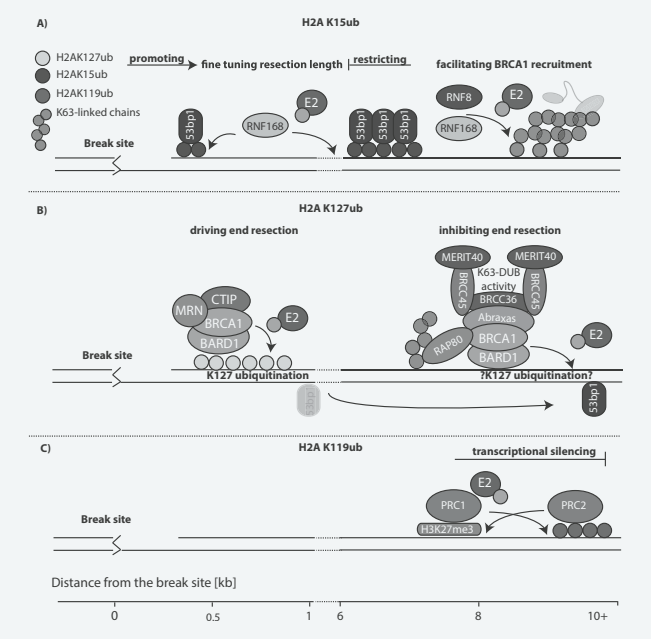

Figure 1. Model of site-specific ubiquitination in the DNA damage response. (A) RNF168 induced H2AK15ub regulates end resection through regulation of relative abundance of 53BP1. Low levels of 53BP1 promote end resection and high levels of 53BP1 inhibit end resection. K63-linked chains recruit the BRCA1-A complex distant from the break site (B) BRCA1 induced H2AK127ub (and/or H2AK129ub) drives end resection close to the break site, the BRCA1-A complex distant from the break inhibits resection. (C) PRC1 and PRC2 establish a H2AK119ub dependent transcription barrier distant from the break site (Figure and legend from Uckelmann & Sixma, 2017).

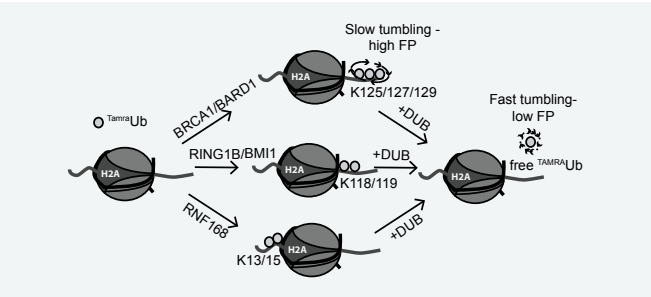

Figure 2. Fluorescent polarization assay to test for DUB activity. Different E3 ligases each modify H2A in the nucleosome at a selected site. By in vitro labelling with a ^{TAMRA}ubiquitin, we can compare activity by different DUBs on each of these sites.

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Adaptive radiation therapy

Geometrical uncertainties such as setup error, posture change, organ motion, deformations and treatment response limit the precision and accuracy of radiation therapy (RT). Consequently, the actually delivered dose typically deviates from the planned dose. To minimize the deleterious effects of geometrical uncertainties, adaptive radiation therapy (ART) aims to characterize the patient's specific variation through an image feedback loop and adapt the patients' treatment plan accordingly. Adaptive radiation therapy research therefore includes 1) improving in room imaging, 2) patient variability characterization, 3) treatment plan modification and 4) outcome modeling.

In Room Imaging

Cone beam computed tomography (CBCT) has been widely adopted in clinical practice for image-guided RT. Soft tissue contrast and Hounsfield units, however, are impaired to the presence of scattered radiation. The purpose of this work was to compare the performance of anti-scatter grids (ASG) with different selectivity (light (5.6), medium (9), and high (11)) with\without iterative and uniform scatter corrections. To that end, the scatter PSF was modeled as a sum of two bivariate Gaussians. The PSF parameters were estimated from a series of transmission measurements through polystyrene slabs of varying thickness with lead partial beam-blocker. Image quality was quantified by the contrast-to-noise ratio (CNR) in various phantoms. CNR improvements ranged between 3.9 and 3.1 for heavy to no grid combined with the iterative software correction for a head-and-neck phantom and 1.5-1.1 for a pelvis phantom. Average absolute Hounsfield differences between planning CT and CBCTs of a virtual human phantom was 59±48HU and 63±59HU with scans reconstructed with the iterative correction and higher selectivity grids. Patient scans revealed similar performace. In conclusion, the best scatter mitigation strategy was found to be a combination of a grid with selectivity larger than 9, combined with iterative scatter estimation. None of the investigated grids required increasing the imaging dose.

Four dimensional (4D) CBCT uses a constant gantry speed and imaging frequency that are independent of the patient's breathing rate. RMG-4DCBCT, on the other hand, optimally computes a patient specific gantry trajectory to eliminate streaking artefacts and projection clustering that is inherent in 4DCBCT imaging. The aim of this study was to realize RMG-4DCBCT for the first time on a linear accelerator. To that end, a real-time feedback loop was developed on a microcontroller to modulate the gantry speed and projection acquisition in response to respiratory signal. Image quality was assessed using the contrast to noise ratio (CNR) and edge response width (ERW). On average, the imaging time and image dose were reduced by 37% and 70% respectively. CNR ranged from 6.5 to 9.7 depending on the number of programmed projections

per phase, indicating that RMG-4DCBCT allows consistent and controllable CNR. In comparison, the CNR for conventional 4DCBCT drops from 20.4 to 6.2 as the breathing rate increases from 2 s to 8 s.

Variability Characterization

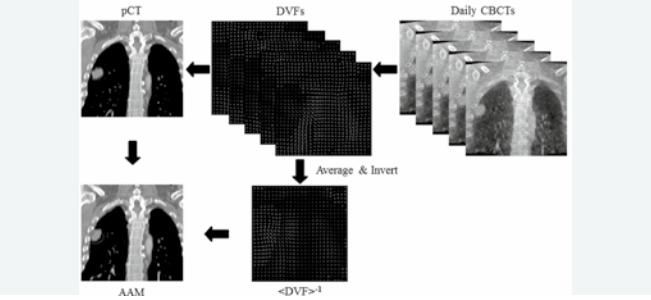
Over the course of RT, the target(s) and surrounding normal tissue can change relative positions causing geometric uncertainties that limit treatment accuracy and precision. The purpose of this work was to develop a population based statistical model of these inter-fraction geometric variations. To that end, deformable image registrations (DIR) between the planning CT and first week CBCTs of 235 lung cancer patients were used to generate DVFs representing the geometric variations of lung cancer patients. Using a second DIR step, the average DVF per patient was mapped to an average patient CT. Subsequently, the dominant modes of systematic geometric variations were extracted using Principal Component Analysis (PCA). For evaluation a leave-one-out cross-validation was performed. Fifty and 112 components were needed to describe correspondingly 75% and 90% of the variance. An overall systematic variation of 3.6mm SD was observed and could be described with an accuracy of about 1.0mm with the PCA model. Such a model can serve as a basis for probability based treatment planning in lung cancer patients.

Treatment plan modification

Differential baseline shifts between primary tumor and involved lymph nodes in locally advanced lung cancer patients compromise the accuracy of RT. The purpose of this study was to evaluate the performance of an average anatomy model (AAM) derived from repeat imaging and DIR to reduce these geometrical uncertainties. An AAM was generated by first averaging five DVFs resulting from cone beam CT (CBCT) to planning CT (pCT) DIR and second by applying the inverse of the average DVF to the pCT (see figure). The proposed method was evaluated on 15 locally advanced lung cancer patients receiving daily motion compensated CBCT and a repeat CT (rCT) for adaptive RT. Reduction of systematic baseline shifts of the primary tumor were quantified for the fractions used to build the AAM as well as over the whole treatment and compared to the performance of the rCT. The systematic baseline shifts over the five fractions prior to the rCT used to build the AAM reduced from 5.9 mm vector length relative to the pCT to 2.3 and 4.2 mm relative to the AAM and rCT, respectively. The overall systematic errors in the left-right, cranio-caudal, and anterior-posterior directions were [3.4,3.8,3.3] mm, [2.3,2.9,2.6] mm, and [2.3,3.1,2.7] mm for the pCT, AAM, and rCT, respectively. In conclusion, AAM mitigates systematic errors occurring during treatment due to differential baseline shifts between the primary tumor and involved lymph nodes similar to (or even better than) rCT. This model has the potential to be used as an efficient and accurate alternative for rCT in adaptive RT of locally advanced lung cancer patients, obviating the need for rescanning and recontouring.

Outcome Modeling

Recently, heart dose was shown to be associated to survival in conventionally treated lung cancer patients. The purpose of this study was to investigate potential associations between heart dose and non-cancer death, in early stage non-small cell lung cancer (NSCLC) patients treated with stereotactic body radiation therapy (SBRT). To that end, 803 patients with early stage NSCLC receiving SBRT were analyzed. All patients were registered to an average anatomy, their planned dose deformed accordingly, and dosimetric parameters for heart substructures were obtained. Multivariate Cox regression was used to identify doses to heart substructures with a significant association with non-cancer death. Multivariate analysis showed that the maximum dose on the left atrium (median 6.5Gy EQD2, range=0.009-197, HR=1.005, p-value=0.035), and the dose to 90% of the superior vena cava (median 0.59Gy EQD2, range=0.003-70, HR=1.025, p-value=0.008) were significantly associated with non-cancer death. In conclusion, doses to mainly the upper region of the heart were significantly associated with non-cancer death.



Schematic illustration of generating an AAM to account for systematic errors caused by differential baseline shifts. Daily CBCTs of the first N fractions are deformed to the pCT and the inverse of the average DVF is applied to the pCT to generate the AAM, which can then be used for adaptive replanning.

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Receptors for matrix adhesion

The main objective of our group is to study the mechanisms involved in cell adhesion. Specifically, we are interested in characterizing the interactions that take place between cells and the extracellular matrix (ECM) and determining their significance.

Role of RGD-binding integrins in cancer

Integrins are heterodimeric αβ transmembrane receptors that link the ECM to the intracellular cytoskeleton. Depending on the combination of α- and β-subunits, integrins recognize and engage with specific ECM components. For instance, the integrins α5β1, αvβ3, αvβ5, and αvβ6 recognize the Arg-Gly-Asp (RGD) sequence of ECM proteins such as fibronectin, vitronectin, and latent TGF-β (Fig.1). These integrins are found to be expressed on tumor cells of various tumor types and their expression is correlated with disease progression and decreased patient survival. Several inhibitors of RGD-binding integrins are being tested in clinical trials, of which cilengitide (αvβ3/αvβ5 antagonist) was the first to enter a phase III trial for glioblastoma. Unfortunately, the results of this trial were disappointing, as the use of the antagonist did not lead to increased patient survival. This finding underlies the need to better understand the molecular mechanisms that are controlled by RGD-binding integrins. We are currently following different strategies to learn more about the role of RGD-binding integrins in cell adhesion and migration to gain a better understanding on how they contribute to cancer progression.
First of all, we observe that although RGD-binding integrins share many similarities, they exhibit a distinct subcellular localization and might therefore contribute to cancer progression in different ways. We make use of CRISPR/Cas9 genome editing and retroviral transduction of cDNAs to replace individual integrin subunits in cells with mutants or chimeras consisting of an extracellular domain of one integrin subunit, fused to the cytoplasmic domain of another, in order to understand whether the differences in subcellular localization arise from differences in integrin ligand-binding properties and/or binding to different cytoplasmic adaptors. We will study the adhesive and migratory properties of the epithelial cells that either express or lack RGD-binding integrins, or that express mutants or chimeras, both in response to growth factor and mechanical stimulation. Secondly, we are conducting proteomic screens to further identify and compare the interactomes of different RGD-binding integrins in different epithelial cell lines. The contribution of (novel) interactome components to cell adhesion and migration will be further analyzed by deleting these components in epithelial cell lines using CRISPR/Cas9.
Together, these studies will help us to better understand the common and unique characteristics of the different RGD-binding integrins.

The role of integrin α3β1 in skin tumorigenesis

The laminin receptor integrin α3β1 is expressed in a variety of epithelial cell types. In the skin, α3β1 is present in basal keratinocytes, where it plays a relatively minor role in the adhesion of these cells to laminin-332 in the underlying basement membrane. Most, if not all, of the stable adhesion of basal keratinocytes to laminin-332 is mediated by the hemidesmosomal integrin α6β4 (see below). Using a mouse model, in which integrin α3 has been deleted in the basal layer of epidermis (Krt14-Cre; *Itga3*$^{fl/fl}$), we have previously shown that α3β1 is an important tumor promoting element in chemically induced skin carcinogenesis (DMBA/TPA treatment). To understand the molecular mechanisms underlying the tumor promoting function of α3β1, we are investigating its role in supporting various tumorigenesis-related signaling pathways, as well as its role in controlling the homeostasis of cell proliferation and differentiation. For these studies, we make use of the already mentioned Krt14-Cre; *Itga3*$^{fl/fl}$ mouse model, as well as a model, in which integrin α3 can be conditionally deleted from cells in the hair bulge (Krt19-Cre; *Itga3*$^{fl/fl}$), which is the *bona fide* reservoir of precursor cells for chemically-induced tumors. The introduction of mT/mG reporter in the latter mouse strain further enables us to follow the fate of α3-deficient cells and track the origin of induced skin tumors *in vivo*. Additionally, we have established a series of α3β1 wild-type and knockout transformed and 'normal' keratinocyte cell lines, isolated from our mouse strains. We use these cell lines for controlled studies of α3β1-dependent signaling in two- and three-dimensional cell culture.

Investigations are also carried out to determine whether the expression of α3β1 integrin is associated with human clinical conditions, more specifically, with different stages of progression of skin lesions. Preliminary analysis of the collected biopsies of the lesional and non-lesional skin from patients with Bowen disease and squamous cell carcinomas indicates that α3β1 is overexpressed in benign lesions and tends to be downregulated at transition to SCCs.

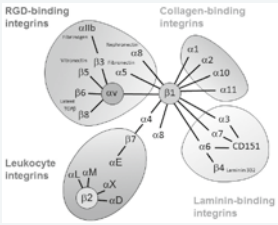

Figure 1
Integrins and their ligands

Regulation of hemidesmosome formation

Keratin-associated hemidesmosomes (HDs) are protein complexes in basal keratinocytes which play an essential role in maintaining epidermal-dermal cohesion. HDs are disassembled during wound healing to allow migration of keratinocytes over the wound bed. We are interested in how the assembly and disassembly of HDs is regulated in normal and transformed keratinocytes. Previously, we have shown that HD dynamics and cell migration of normal keratinocytes is regulated by serine/threonine phosphorylation of integrin β4. However, in carcinoma cells that only form rudimentary HDs or do not form them at all, β4 is also phosphorylated on several tyrosine residues. The significance of these phosphorylation events in HD disassembly is currently being investigated. Furthermore, we study the role of CD151, an established component of HDs, in the formation of HDs. Our investigations revealed that CD151 contributes to α6β4 clustering at the basal membrane, which is an important step in HD formation. Finally, we are utilizing proteomic screens to identify possible new players in the regulation of HD dynamics. Several interesting novel interactors were identified and their significance in regulating HD dynamics is currently being investigated.

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Publications

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Genomic instability and carcinogenesis

Genomic instability, a hallmark of human cancer, has been attributed to defective DNA maintenance and cell cycle control mechanisms. Our research focuses on mutagenesis resulting from *(1)* defective DNA mismatch and crosslink repair pathways, and *(2)* perturbed DNA replication as a consequence of defective G_1/S control. The principle tools include gene modification in murine embryonic stem cells (ESC) and other cell types, and analyses of the phenotypic consequences in cell lines and mice.

DNA MISMATCH REPAIR

Inherited defects in DNA mismatch repair (MMR) genes underlie the cancer predisposition Lynch syndrome (LS), which manifests as early onset colorectal and endometrial cancer. MMR corrects DNA replication errors, which are recognized by MSH2/MSH6 or MSH2/MSH3 dimers. Recruitment of another dimer, MLH1/PMS2, promotes exonucleolytic removal and resynthesis of the error-containing strand.
MMR proteins also recognize mismatches arising upon replication of damaged bases such as O^6- or S^6-methylguanine, that can be formed by methylating compounds or the guanine analog 6-thioguanine (6TG), respectively. However, in this case, repetitive removal by MMR of the incorporated nucleotide rather than the lesion itself causes DNA breakage and cell death. Thus, defective MMR increases spontaneous mutagenesis and confers resistance to methylating agents.

Oligonucleotide-directed gene modification

We have developed a gene modification technique in mouse embryonic stem cells (ESCs) that allows any desired single base-pair substitution without the need for prior generation of a DNA double-stranded break. The method uses short synthetic oligodeoxyribonucleotides (ssODN) that are complementary to the endogenous target sequence except for the centrally located nucleotide that comprises the desired modification (Aarts and Te Riele, NAR 2010;38:6956). Gene modification involves annealing of the ssODN to its complementary sequence in the replication fork and subsequent integration. However, the mismatch at the position of the mutating nucleotide elicits a MMR reaction that restricts gene modification to a frequency of 10^{-7} (Dekker *et al.*, NAR 2003;31:e27). ESCs can be made permissive for 'oligo targeting' by *transient* suppression of *MSH2* (Aarts *et al.*, NAR 2006;34:e147) or *MLH1* (Dekker *et al.*, Mutation Res 2011;715:52), increasing the frequency to 10^{-5} but at the cost of spontaneous, potentially confounding mutations. We found the effect of MMR can also be avoided when the mutating nucleotide in the ssODN is a locked nucleic acid (LNA). LNA-modified ssODNs (LMOs) of only 25 nucleotides allow highly accurate base-pair substitution at frequencies of 10^{-4} in wild-type ESCs, while MMR suppresses off-target effects (Van Ravesteyn *et al.*, PNAS 2016;113:4122). Also in *Escherichia coli* the LMO design evades MMR during λ Red-mediated gene editing.

Unclassified variants of MMR genes

We use oligo targeting to study so-called *'variants of uncertain (clinical) significance'* (VUS) of MMR genes that are found in suspected LS patients. Evidently deleterious germ-line defects in MMR genes (*e.g.*, protein-deleting or -truncating) allow for the clinical diagnosis LS. In contrast, carriers of a VUS (usually a missense mutation *affecting a single amino acid*) cannot be properly counseled as long as it is uncertain whether the variant is disease-causing or innocuous.

We originally used oligo targeting to recreate suspected *MSH2* and *MSH6* gene variants in ESCs, which were then assayed for MMR capacity. Of twelve VUS, five partially or fully abrogated MMR activity and could be classified as pathogenic (Wielders *et al.*, Human Mutation 2011;32:389-96, Plos ONE 2013;8:e74766, J Med Genet 2014;51:245, Familial Cancer 2017;16:221-9). Although reliable, the throughput of this approach is low. Therefore, we have developed a novel high content cellular assay, termed "oligonucleotide-directed mutation screening" (ODMS) (Houlleberghs *et al.* PNAS 2016;113:4128, PLoS Genet 2017;13:e1006765). Briefly, ESCs are exposed to a ssODN designed to introduce the VUS of interest in a small subset (±0.01%) of cells. Should the VUS be deleterious, modified cells survive exposure to 6TG and form colonies. Should the mutation not affect MMR, no colonies appear. We have validated this protocol by demonstrating the correct detection of 25/25 proven pathogenic MMR gene variants, whereas not one of 24 proven non-pathogenic variants was detected. Subsequently, we investigated the phenotype of 149 MMR gene VUS and found 64 VUS to inactivate MMR and hence to be causative of LS. Among these, six variants attenuated but not fully abrogated MMR activity and may therefore have a lower penetrance than fully deleterious mutations.

A novel mouse model for Lynch syndrome

We have made a novel mouse model in which, similar to LS patients, MSH2-defective crypts arise amidst an excess of MMR-proficient crypts (ratio 1:20) (Wojciechowicz et al. *Gastroenterology* 2014;147:1064). Half of these animals spontaneously developed MSH2-deficient intestinal tumors after ±1.5 year. Exposure of *"Msh2-Lynch"* mice to the methylating agent temozolomide caused 5-fold expansion of MSH2-deficient crypts and dramatically accelerated intestinal tumorigenesis, which now developed at ± 4 months in all animals. Exposure to methylating agents is clearly a risk factor for tumor development in LS patients. Currently, we are trying strategies to achieve the reverse: reduction of the number of MSH2-defective crypts in order to reduce cancer risk in LS patients.

CRISPR/Cas9-assisted gene editing

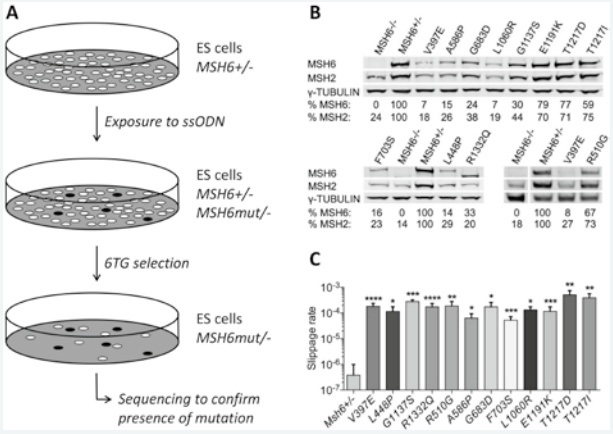
Base-pair substitutions can also be effectuated by oligonucleotide-templated repair of a CRISPR/Cas9-induced site-specific DNA double-strand break. We have identified a remarkable role of DNA MMR in this process and found novel ways to avoid off-target effects.

LOSS OF G_1/S CONTROL

Loss of G_1/S control is frequently seen in tumors. Genetic ablation of the retinoblastoma (Rb) proteins pRB, p107 and p130 disrupts G_1/S control, causing unscheduled S-phase entry. However, additional events are needed for oncogenic transformation. To identify these, we study the requirements for mitogen- and anchorage-independent proliferation of Rb-protein-deficient cells.

Mitogen independence

Mouse embryonic fibroblasts (MEFs) completely devoid of Rb proteins (TKO MEFs) still need mitogens for proliferation: mitogen-deprived TKO MEFs enter S-phase, but suffer from severe replication stress manifested by slow fork progression, reduced origin firing and accumulation of DNA double-strand breaks (DSBs) (Van Harn *et al.*, Genes Dev 2010;24:1377). Together with induction of $p27^{KIP1}$, activation of the DNA Damage Response (DDR) and induction of $p21^{CIP1}$ causes a G_2-like arrest (Foijer *et al.*, Cancer Cell 2005;8:455). We are currently performing screens to identify genetic events that attenuate this response and allow mitogen-independent proliferation.



Oligonucleotide-directed mutation screening to identify pathogenic *MSH6* variants.

A. *Msh6* $^{+/-}$ mESCs (lacking one copy of *Msh6*) were exposed to ssODNs that introduce the mutation of interest into the *Msh6*$^{+}$ allele with an efficiency of 10^{-3}-10^{-4}. Cells that lost MMR activity will form 6TG-resistant colonies. PCR and sequence analysis were used to distinguish colonies arising from loss of heterozygosity or introduction of the planned mutation, the latter indicative for pathogenicity.

B. Western blot analysis of detected variants showing that single base-pair substitution may or may not affect protein level.

C. All detected variants showed elevated levels of microsatellite instability at a G_{10} slippage reporter.

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Imaging technology in radiation oncology

Delivery techniques in radiotherapy have reached unprecedented levels of accuracy. The introduction of MRI-guided radiotherapy systems such as the MR-Linac create the opportunity to improve the accuracy even further. We address the development of MRI techniques for guiding radiotherapy and work on improving target definition in radiotherapy by application of MRI and quantitative imaging methods for tumor characterization.

Quantitative imaging for radiotherapy dose painting and follow-up

To improve target definition and tumor characterization for dose painting, strategies to integrate anatomical MRI in the radiotherapy workflow are designed and applied to a range of tumor sites.
For radiotherapy dose painting, we investigate quantitative MRI techniques. For diagnostic scanning platforms we now have integrated T1 and T2 mapping as well as diffusion-weighted MRI and dynamic contrast-enhanced MRI in scanning protocols. In a multicenter study of 3 institutes we demonstrated the high accuracy and precision of a fast T2 mapping sequence that allows for quantitative T2 imaging at a spatial resolution similar to diagnostic T2-weighted exams (figure 1). For dynamic contrast-enhanced MRI, accurate quantification is notoriously hard. We work on developing more robust acquisition and analysis techniques. In a collaboration with 6 institutes from Europe and the US, we showed that subtle differences in algorithms used to implement the Tofts tracer kinetics model, limit the possibility for combining/comparing results from different institutes. Careful cross-algorithm quality-assurance must therefore be utilized. These findings have influenced the design of the IQ-EMBRACE trial, a multi-center imaging study of patients receiving chemoradiotherapy for cervical cancer that we initiated in collaboration with Aarhus University.
The same techniques are now developed for the integrated MRI-linear accelerator. This device improves radiation accuracy by daily MR image guidance of external beam radiotherapy.
As patients will receive an MRI exam during each treatment fraction, the use of quantitative imaging provides a great opportunity for response monitoring and the acquisition of data for imaging biomarker discovery.

Dose painting for prostate cancer

The FLAME trial, a multi-center phase III randomized trial of dose escalation in prostate cancer using external-beam radiotherapy, has finalized inclusion. In this study, a focal boost to the visible tumor inside the prostate to a dose of 95 Gy was given and compared to the standard treatment of 77 Gy to the gland. In total 571 patients have been randomized and we now wait for the data to mature.
As we found that manual delineation of the tumor based on multi-parametric MRI is prone to interobserver variability, we developed a delineation model, using a set of imaging features

derived from T2-weighted, diffusion-weighted and dynamic contrast-enhanced MRI. To improve its performance we added a prevalence map to the model, reflecting the a-priori likelihood of finding cancer in a particular location. Also, the reported status of prostate biopsies was included. The model predicts probability of cancer presence on a voxel-by-voxel level. We validated this with whole-mount section histopathology in cohorts from two institutes.
The tumor probability maps may be used to improve accuracy of the delineation of tumors inside the prostate. However, the dose painting paradigm allows a non-binary modulation of the dose based on the likelihood of tumor presence. We determined the robustness of this approach in a test-retest study where patients received a multi-parametric MRI exam twice on separate days prior to treatment (figure 2). Both MRI exams were used to generate tumor probability maps and dose painting prescription maps. For both sets, treatment plans were generated in a research version of the treatment planning system Pinnacle, in which the prescription maps were imported. The voxel-by-voxel comparison showed interclass correlation coefficients above 0.8 for all steps of the process, indicating that dose painting based on tumor probability maps is stable.

MRI-guided radiotherapy

To improve the precision of dose delivery in the clinic, the department of Radiation Oncology introduces MRI guidance for radiotherapy. As part of the MR-linac consortium an integrated MRI-linear accelerator has been installed at the NKI. This year, we started imaging of patients on the MR-Linac in the Umbrella study. The aim of this study is to optimize MRI sequences, develop sequences for quantitative imaging and generate imaging data that can be used as input for testing and further development of MR-guided radiotherapy workflows.
A key aspect of an MR-Linac treatment is that it enables daily online adaptive strategies to accommodate the changes that occur in a patient. This implies that new treatment plans will be generated each day at the MR-Linac. The complexity of these techniques makes independent patient-specific dosimetric verification and quality assurance (QA) highly desirable. Electronic portal imaging dosimetry (EPID dosimetry) has the potential to provide an independent real-time verification of the entire treatment chain. The presence of the MRI housing between the patient and the EPID and the impact of the magnetic field on the dose distributions and on the EPID create challenges that need to be resolved. A back-projection algorithm was developed that incorporates the presence of the MRI housing and the characteristics of the EPID panel were determined. These are critical steps to move to a functional EPID dosimetry solution for MR-guided radiotherapy.

Brachytherapy of rectal cancer

One of the applications where in-room MRI-guidance is expected to provide a benefit, is the treatment of rectal cancer with radiotherapy. An alternative approach to minimize the irradiated volume in rectal cancer and reach extremely high doses in the tumor, is the use of endoluminal brachytherapy. This technique is investigated in collaboration with the Leiden University Medical Center in an Alpe d'HuZes funded project. In contrast to external-beam radiotherapy, image guidance is not as far developed for brachytherapy. As a first step, we therefore investigated the dosimetric benefit of repeat CT-based treatment planning at each application in patients who received high-dose-rate endorectal brachytherapy (HDREBT) to boost the dose, replacing surgery after external beam radiotherapy. Using a single CT-based treatment plan for all fractions could result in a suboptimal treatment at later fractions. Therefore, repeat CT imaging should be the minimal standard practice in HDREBT for rectal cancer to determine whether an intervention would be necessary. Replanning based on repeat CT imaging resulted in more conformal treatment plans and is therefore recommended. To improve image guidance, the benefit of MRI is currently investigated in the OPPER trial. At Leiden UMC recently the first patient was included, receiving 4 brachytherapy applications instead of a regular 5x5Gy external-beam radiotherapy treatment. NKI intends to participate in this study and will treat patients in the MR-Linac room, which has been adapted to facilitate MR-guided brachytherapy.

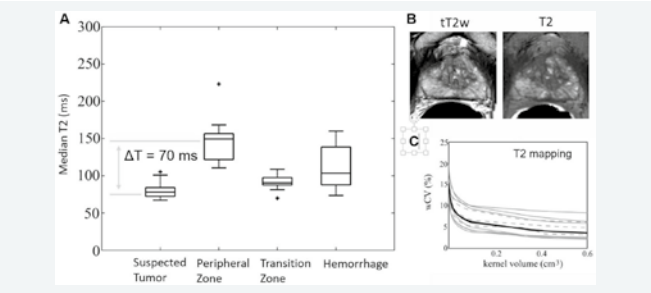

Figure 1. Quantitative T2 mapping of prostate cancer. A: T2 values in tumor and healthy parts of the prostate; B: T2-weighted image (left) and quantitative T2 map (right). C: the repeatability of T2 mapping as function of kernal volume, reflecting the precision at which T2 can be determined in a given volume of interest.

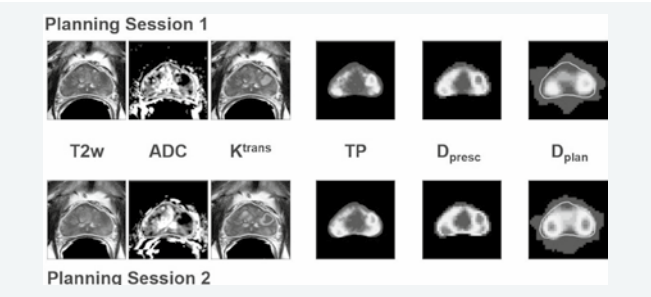

Figure 2. Test-retest of dose painting by numbers for prostate cancer. From left to right: T2-weighted MRI, apparent diffusion coefficient from diffusion-weighted MRI, K^{trans} from dynamic contrast-enhanced MRI; probability of tumor presence; prescribed dose; planned dose.

V

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Publications

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Functional genomics of urological cancers

Individualized therapy in bladder cancer: molecular targets and biomarkers

Bladder cancer is a common cancer, with a worldwide prevalence of 2.7 million patients. Although bladder cancer is often superficial at diagnosis, 30-40% of patients present with more advanced disease or progress to more aggressive disease. For patients with locally advanced or metastatic bladder cancer, platinum-based chemotherapy is the mainstay of treatment. Unfortunately, virtually all patients with metastatic cancer and a substantial proportion of patients with locally advanced bladder cancer will eventually present with platinum-refractory disease. In recent years, immunotherapy has shown to be active in bladder cancer. Impressive responses are seen, however only a minority of patients benefits from these treatments and it is unclear which patients respond. We aim to advance the development of a personalized approach bladder cancer by exploring novel molecular targets, mechanisms of resistance and biomarkers that can guide systemic therapy. Through the large number of bladder cancer patients and broad availability of early phase clinical trials with molecularly targeted therapies at the NKI-AVL, discoveries can rapidly be translated into clinical trials.

Genetic determinants of response to neo-adjuvant platinum-based therapy

Pathologic complete response to neo-adjuvant platinum-containing chemotherapy (NAC) is a strong prognostic determinant for patients with muscle-invasive bladder cancer (MIBC). Despite comprehensive molecular characterization of bladder cancer, associations of molecular alterations with clinical outcome and treatment response are still largely unknown. Recently, we found *ERBB2* mutations to be associated with complete response to neoadjuvant chemotherapy. *ERCC2* missense mutations, previously found associated with response to NAC, were enriched in responders, however this association did not reach statistical significance in our cohort. In addition, we analysed a group of complete responders and non-responders to NAC for DNA copy number alterations. Copy number gain of the *E2F3* locus was enriched in responders, whereas copy number gain of the *MYC* locus and copy number loss of the *CDKN2A* locus were both associated with non-response. In order to provide a definitive answer on the association of genetic aberrations with response to NAC in bladder cancer, we assembled a validation cohort composed of pre-chemotherapy bladder cancer samples from multiple centers. These samples will be genetically analyzed for copy number alterations and mutations in *ERCC2*, *ERBB2* and several other genes that have been reported to be associated with NAC response.

Circulating cell-free tumour DNA

Molecular pathways activated in bladder cancer could provide targets for new treatments. Establishing the most relevant

target in metastatic cancer can be a challenge for various reasons: 1) Metastases can be hard to biopsy due to proximity to vital structures. 2) A biopsy will provide information for only one location, which may not represent the bulk of the metastatic burden. 3) Therapy can induce genetic changes or select for certain genetic aberrations that were of low abundance in the pre-treatment tumour. Therefore, the ideal molecular test to guide treatment would represent the bulk of the metastatic burden at the moment of treatment initiation and would be relatively easy to obtain. Cell-free tumour DNA circulates in the plasma of cancer patients and can comprise as much as 1-10% or more of total circulating DNA in patients with advanced stage malignancies. Circulating tumour DNA (ctDNA) contains information on tumour mutations and possibly reflects metastatic burden. The relative abundance of mutations has been shown to change as a result of therapy and could possibly serve to guide treatment. Perhaps more importantly, specific mutations in ctDNA could reflect changes in abundance of specific clones, making it possible to adapt molecularly targeted therapies to dominant clones. Urinary cell-free DNA is another source of easily accessible DNA to provide a mutation spectrum of the primary tumour and potentially also of metastatic burden. In our ctDNA project, we longitudinally collected cell-free DNA in the urine and blood of bladder cancer patients treated with systemic therapy to establish the dynamics of genetic alterations during treatment. Samples were analysed by our collaborators in Cambridge (Rosenfeld lab) using the Tam-seq method and low-coverage WGS (Whole Genome Sequencing). Tumor-specific mutations were found in urine as well as in blood. Patients who failed to clear mutant DNA in peripheral fluids had a higher chance of recurring early. Additionally, we found evidence of clonal evolution during therapy.

Enhancement of sensitivity to FGFR-inhibitors

The *FGFR3* gene is activated in 10-15% of advanced bladder cancers, and FGFR inhibitors are currently tested in clinical trials. To find potential drug targets that can act synergistically with FGFR inhibition, we performed a synthetic lethality screen for the FGFR inhibitor AZD4547 using an shRNA library targeting the human kinome in the UCC cell line RT112 (*FGFR3-TACC3* translocation). We identified multiple members of the PI3K pathway and found that inhibition of PIK3CA acts synergistically with FGFR inhibition in multiple UCC and lung cancer cell lines having *FGFR* mutations. Consistently, we observed an elevated PI3K-AKT pathway activity resulting from EGFR or ERBB3 reactivation caused by FGFR inhibition as the underlying molecular mechanism of the synergy. Our data show that feedback pathways activated by FGFR inhibition converge on the PI3K pathway. These findings provide a strong rationale to test FGFR inhibitors in combination with PI3K inhibitors in cancers harboring genetic activation of FGFR genes.

Genetic mechanisms of resistance to androgen receptor inhibitors

Novel androgen receptor (AR) inhibitors have clinical benefit in castration-resistant prostate cancer patients. Still, cancer cells eventually develop resistance to these therapies. We are investigating genetic resistance to these drugs through several means. Functional genetic screens are used to identify mechanisms of resistance. After in vitro and in vivo validation, these mechanisms can then be tested on clinical samples of patients undergoing AR inhibitor treatment. These clinical samples are being collected through the CPCT network. In addition, plasma is collected to analyze development of genetic resistance throughout treatment.

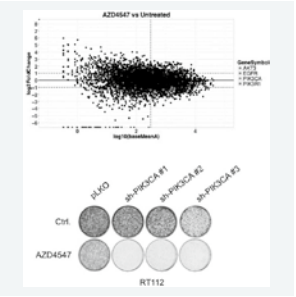

Figure 1. A functional genetic screen identifies the PI3K pathway as a determinant of resistance to FGFR inhibitors in *FGFR* mutant urothelial cell carcinoma. *Top*: members of the PI3K pathway are identified as increasing sensitivity to FGFR inhibition upon knockdown in the RT112 cell line. *Bottom*: knockdown of PIK3CA by 3 independent hairpins increased sensitivity to the FGFR inhibitor AZD4547.

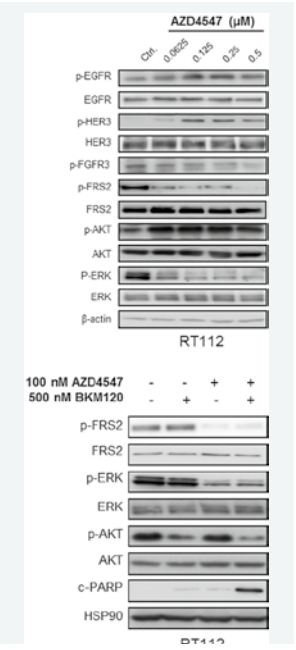

Figure 2. Biochemical analysis in RT112 cells indicated: *Top:* the reactivation of EGFR and ERBB3 in association with elevated PI3K-AKT signaling after treating 1 week with 50 mM AZD4547. *Bottom*: Synergistic response of RT112 to combinations of FGFR (AZD4547) and PI3K (BKM120) inhibitors.

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Cancer survivorship

Today, 10 million people in Europe survived cancer for 5 years or longer, being at risk for a range of adverse effects. It is estimated that only one in five people with cancer survive in good health. However, our understanding of health decline (symptom development, deteriorated quality of life, functional decline, disease progression and onset of comorbidity) after cancer is still in its infancy. Our research objective is to understand the impact of cancer, treatment and supportive care strategies on physical and psychosocial functioning of cancer survivors.

Observational studies

The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) Registry

In 2009 we initiated the PROFILES registry for the study of the physical and psychosocial impact of cancer and its treatment. Today we have evaluated and published about patient reported outcomes (PRO's) of more than 20.000 cancer patients and (long term) survivors. In 2016 we obtained a large investment grant from NWO to upgrade the PROFILES registry to facilitate studies of the *mechanisms* of declining health after cancer. Specific innovative features of the upgraded PROFILES infrastructure include 1) Data collection of novel biological markers, 2) Objective ambulatory monitoring of physical and physiological functioning with an ambulatory biosensor; 3) Assessment of dietary intake with an online food diary; 4) Measurement of changes in body mass index and body composition; 5) Online neuropsychological assessment of cognitive functioning. In 2017 we have started the new, extended data collection. Specific populations of interest within the PROFILES registry are colorectal, gynecological and thyroid cancer patients, lymphoma patients, and patients with advanced cancer.

International development of quality of life questionnaires

We have developed four disease-specific EORTC QoL questionnaires for patients with (non) Hodgkin lymphoma or chronic lymphocytic leukaemia. In 2017 our international phase I-III development was published and we started with the phase IV international validation study of the EORTC QLQ-HL27 (Hodgkin), QLQ-NHL-HG29 (High Grade Non-Hodgkin), QLQ-NHL-LG20 (Low Grade Non-Hodgkin) and QLQ-CLL17 (Chronic Lymphocytic Leukaemia).
Current survivorship questionnaires tend to focus on psychosocial issues, whereas the EORTC cancer survivorship questionnaire we are developing also includes physical and practical functioning. In Phase I we have interviewed 575 disease free cancer survivors with 11 types of cancer from nine different countries. Together with a systematic literature review this resulted in the identification of 122 generic cancer survivors issues and on average 26 cancer site-specific issues per tumor type. In 2017 we started with phase III of

the development of the EORTC survivorship questionnaire. We will develop a generic EORTC cancer survivorship 'core questionnaire' which can be used as a stand-alone questionnaire or in combination with a site specific (survivor) module.

Intervention studies

Cancer Survivorship Care Plans for patients with endometrial or ovarian cancer

This pragmatic cluster RCT was conducted to longitudinally assess the impact of an automatically generated survivorship care plan (SCP) on patient-reported outcomes in routine clinical practice. Twelve hospitals were randomly assigned to SCP care or usual care. Newly diagnosed patients with endometrial or ovarian cancer completed questionnaires after diagnosis (n = 395; 75% response), 6 months (n = 282), and 12 months (n = 248). We previously reported that our trial showed no evidence of a benefit of SCPs on satisfaction with information and care in women with endometrial cancer, but increased patients' concerns. In 2017 we published that in women with ovarian cancer no overall differences were observed between the trial arms on satisfaction with information provision, satisfaction with care or health care utilization. Regarding illness perceptions, patients in the 'SCP care' arm had lower beliefs that the treatment would help to cure their disease. Our trial results suggest that ovarian cancer patients may not benefit from an SCP.

Web-based treatment decision aid for early-stage prostate cancer

A web-based prostate cancer treatment Decision Aid (DA) was developed to fit clinical workflow. A cluster RCT included 18 hospitals, of which nine were randomized to implement the DA. Patient recruitment was established previously and 1-year follow-up questionnaires have been collected in 2017. One year after treatment was chosen, regret was experienced rarely, and most men were satisfied with their treatment and the information received. Including a DA in treatment counseling did not result in different outcomes twelve months after treatment was chosen, compared to the control group.

Effectiveness of patient-reported outcome feedback and a web-based intervention on lymphoma patients' self-management skills

The objective of the multicentre Lymphoma InterVEntion (LIVE) RCT is to examine whether feedback to patients on their PROs and access to the web-based self-management intervention *Living with lymphoma*will increase self-management skills and satisfaction with information and reduce psychological distress. Patients who have been diagnosed with HL or NHL will be selected for participation. Patients are invited via their haemato-oncologist 6 to 15 months after diagnosis. The intervention is based on cognitive-behavioural therapy components and includes information, assignments, assessments, and videos. Changes in outcomes from baseline to 16 weeks, 12 and 24 months post-intervention will be measured. Primary outcomes are self-management skills, satisfaction with information, and psychological distress. Patient recruitment has started in 2016 and is expected to be completed early 2018. Pilot evaluation among 64 invited patients showed that all patients wished to receive feedback on their QoL, whereas most (81%) wanted feedback on their functioning, fatigue, neuropathy, anxiety, and depressive symptoms. 97% viewed it as being useful, with reassurance and knowledge about their own functioning in relation to what is "normal" being the most frequently mentioned reasons.

Ongoing initiatives include:

- ENdometrial cancer SURvivors' follow-up carE (ENSURE): Less is more? Randomized controlled trial to evaluate patient satisfaction and cost-effectiveness of a reduced follow-up schedule'.
- Stimulating evidence based, personalized and tailored information provision to improve decision making after oesophageal cancer diagnosis together with the Academic Medical Center.
- ICT4CANCER: facilitating self-management and personalized access to supportive care in cancer survivors together with VU Medical Center
- GERiatric Screening in the treatment of elderly patients with Ovarian Carcinoma (GERSOC)

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Early stage technology assessment, operations research and cancer rehabilitation

In this group three research topics are covered: Early Stage Technology Assessment, Improving Oncology Services and Cancer Rehabilitation.

Early Stage Technology Assessment

As healthcare costs are continuously increasing and demographics and technologic developments in oncology cause especially high service and financial burdens on health systems, sustainability of future oncology services will inevitably become an issue. Gradually we can expect Health Technology Assessment (HTA) not only to be involved in policy and coverage decisions, but also in an earlier stage in the translational research process.

From 2003 through 2006, a technology assessment study was conducted by Valesca Retèl on the introduction of the MammaPrint (a 70-gene micro array test) as a prognostic tool in the treatment of node negative breast cancer (the RASTER-study) and as a side study of the European randomized controlled trial the MINDACT-study.
We will end the series of Cost Effectiveness Analyses of the MammaPrint with the incorporation of the results of MINDACT trial, which the proposal has been approved by BIG consortium and EORTC for 2017/2018. Danalyn Bing was appointed to perform this in a PhD study. She will also cover an early HTA of alternative strategies for managing low grade DCIS within the PRECISION project.

In 2015 an early stage technology assessment of TIL-transfer technology in advanced melanoma started in a Coverage with Evidence Development project until 2019. In 2017 two additional CED projects (high dose chemotherapy for BRCA1-like breast cancer and HIPEC stomach) have started with HTA involvement of our group.
Valesca Retèl works as post-doc 50% employed by NKI and 50% for the Health Technology and Services Research group at the University of Twente. She is coordinating the CED programs in the AVL and is primary investigator in the TANGO (Technology Assessment of Next Generation Sequencing) project that was awarded € 1.6 million in the Personalized Medicine GGG program of ZonMw (in which Wim van Harten is co-investigator).

In 2016 Anna Miquel Cases finalized the early stage technology assessment in the application of diagnostic/prognostic markers in neo-adjuvant breast cancer treatment. This was part of the CTMM program BREASTCARE. Ann-Jean Beck works on technology assessments of various interventions in Head & Neck survivorship care. Melanie Lindenberg is evaluating early stage translational technologies in oncology including image guided interventions and Personalized Cancer Treatment. Nora Franzen is employed as PhD student on a private grant to perform an exploratory health economic study on alternative patent- and

pricing models in view of extremely rising drug costs. Riin Ots performed a follow up study on effects of high drug prices in 17 European countries. Furthermore a range of supportive HTA activities was performed such as Cost Effectiveness analyses on OV-Hipec and Confocal Microscopy in skin cancer. Wim van Harten chairs a OECI working group on health economics.

Improving Oncology Services

Benchmarking is a possibly powerful tool to inform management on improvement options and patients on the quality of services. In 2013 the EU-subsidized project BENCH-CAN started to develop and pilot a European benchmarking system on Comprehensive Cancer Care. As final publications of BenchCan Anke Wind submitted 2 papers on benchmarking of cancer centers and on pathway development. She defended her PhD thesis in April 2017. Bruno Vieira is performing a PhD study in close cooperation with the University of Twente on operations management techniques in improving various aspects of Radiotherapy capacity use.

Rehabilitation, Physical Activity and Cancer

Survivorship care and rehabilitation are important elements of a cancer centre's program. In a stepwise approach various rehab and survivorship services have been developed and by late 2017 an NKI cancer survivorship and rehab ("Quality of Life") centre will open its doors. A major Alpe d'Huzes/KWF project was started early 2011, focusing on patient empowerment, return to work, tele-monitoring and mplementation of relevant findings and programs related to physical exercise and supported by innovative IT (ACARE2). As a final project, a PhD student co-supervised by Wim van Harten and Rosella Hermens works at IQ-Healthcare in Nijmegen on the structured implementation of ACARE projects' findings in ten Dutch hospitals. As a follow up Laura Kooij (co supervised by Wim Groen and Wim van Harten) performs research into e-health interventions and survivorship care, such as IT-supported shared care and video consultation.

Following up on the ACARE2 project a grant was obtained from KWF for an RCT involving a web-based and blended intervention on physical activity in breast and prostate cancer survivors. The project involves a postdoc position (Wim Groen, who is also co-PI), and a PhD position (Inge Ruitenberg, from May onwards Hester van de Wiel) focusing on aspects that influence effectiveness from both physical as well as psychological perspectives. Additionally a cost effectiveness analysis will be performed. Lastly the HEART study proposal was honored by KWF (Wim Groen is PI). This project will focus mainly on cardiovascular aspects (cardiac MRI and echocardiography) in a follow up study of both the PACES and PACT study. PACES and PACT were large Dutch randomized controlled trials investigating the effects of physical exercise during chemotherapy.

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Cancer epidemiology

Introduction

The cancer epidemiology group is currently concentrating on two principal research lines: (1) the etiology of hormonerelated cancers, with a focus on gene-environment interactions; (2) the long-term health consequences of cancer treatment, particularly in terms of the risk of developing second malignancies or cardiovascular disease.

Late effects of cancer treatment

Now that curative treatment is available for a substantial group of cancer patients, it is increasingly important to evaluate how the occurrence of late complications of treatment affects their long-term survival. We aim to evaluate the risk of second malignant neoplasms (SMNs) and cardiovascular disease (CVD) after radio- and chemotherapy for Hodgkin lymphoma (n=8,500), non-Hodgkin lymphoma (n=3,100), testicular cancer (n=7,100) and breast cancer (n-100,000) over a period of up to 40 years after primary treatment.

As part of a program grant awarded in 2011 a comprehensive assessment is made of the late effects of treatment for Hodgkin lymphoma (HL) in close collaboration with Berthe Aleman, Radiation Oncology. Previously we showed that HL survivors experience substantially increased risks of developing SMNs and CVD. It is unclear, however, to which extent this affects long-term survival after treatment for HL. Therefore, in 2017, we examined long-term treatment-related excess mortality from adverse events in HL patients in our multicenter cohort comprising 4,047 HL patients, diagnosed before age 51 and treated between 1965 and 2000. After a median follow-up of 22 years since HL treatment, 1,793 patients had died (19.5% from HL, 32.5% from solid tumors, 15.5% from cardiac diseases, 7.0% from NHL/leukemia). The standardized mortality ratio (SMR) for causes other than HL was strongly increased: 8.2-fold that of the general population. The cohort experienced 149 excess deaths per 10,000 patients per year. The SMR and absolute excess mortality (AEM) for causes of death other than HL increased throughout follow-up: after ≥35 years the SMR was 19.2, translating to 506 excess deaths per 10,000 patients/year. Even 35 years after treatment, HL patients experienced elevated SMRs and AEMs from solid tumors and cardiac diseases. While the SMR for solid tumors remained stable during follow-up, the SMR for cardiac diseases (overall SMR=9.8, AEM 29.4) increased during follow-up (SMR at ≥35 years 28.8, p-trend<0.001)). The risk of death from solid cancers was significantly increased for patients treated with supradiaphragmatic radiotherapy (Relative risk (RR), adjusted for sex, age and follow-up time: 2.1), infradiaphragmatic radiotherapy (RR=1.3), and procarbazine (RR=1.3). Risk of death from cardiac diseases was also increased among patients treated with supradiaphragmatic radiotherapy (RR=4.1) and, additionally, in patients who received anthracyclines (RR=1.5). The SMR for infectious causes (2.9% of all deaths) was 6.5-fold increased.

Interestingly. both splenectomy (RR=2.1, p=0.041) and spleen radiotherapy (RR=3.2, p=0.001) were associated with increased risk of death due to infectious causes, compared to patients not receiving such treatment.

To study the risk of heart failure in HL survivors, a case-control study was performed, including 91 patients with heart failure and 278 matched controls. A nonlinear radiation dose-response relationship with upward curvature was derived for mean heart dose (MHD), resulting in rate ratios of 1.2 and 2.5 at MHDs of 20 and 30 Gy, respectively. Anthracycline-containing CT increased heart failure rate 2.8-fold, without evidence for interaction with radiation dose. In patients treated without anthracyclines, modelled 20-year cumulative risk of heart failure following MHDs of 0-25 Gy, 26-30 and ≥31 Gy were 0.9%, 1.9% and 3.6%, respectively, and in patients treated with anthracyclines these risks were 3.4%, 6.8% and 12.9%, respectively. These findings can be used to predict CVD risk for HL patients before treatment, during RT planning and during follow-up.

With a large grant from KWF-Alpe d'HuZes, the Dutch BETER consortium (Better care after Hodgkin Lymphoma: Evaluation of long-term Treatment Effects and screening Recommendations) is developing a nationwide survivorship care program for HL survivors. The project is coordinated by the NKI. So far, survivorship clinics have started in fourteen hospitals, including the NKI, while eight other centers will follow in the course of 2018. Apart from those in two newly participating centers, the identification of survivors is nearly complete, resulting in approximately 7900 HL survivors and 3100 NHL survivors of whom approximately 70% are eligible for the BETER program. In 2017, the formally approved screening guidelines were included in the Dutch national database for medical guidelines for screening and treatment.

In our multicenter testicular cancer (TC) cohort, established and expanded under a 2011 KWF grant, we evaluated risk of diabetes associated with para-aortic irradiation compared to orchidectomy alone among 2,998 1-year TC survivors treated before 50 years of age between 1976-2007. During follow-up, 161 TC survivors were diagnosed with diabetes after a median interval of 23.6 years. Compared to patients treated with orchidectomy only, patients treated with para-aortic radiotherapy had a 1.7-fold (95%CI:1.1-2.6) higher risk of diabetes. The excess hazard increased with 0.23 with every 10 Gray increase in the prescribed radiation dose (P=0.004). The 30-year cumulative incidence of diabetes was 16.7% after a para-aortic prescribed radiation dose >26 Gray compared to 9.5% among patients without para-aortic radiotherapy. We also evaluated risk of solid cancers after treatment for testicular cancer among 5,848 one-year survivors treated for TC before 50 years of age between 1976-2006. After a median follow-up of 14.1 years, 350 solid SMNs were observed, translating into a significantly 1.8-fold increased risk compared to the general population. Non-seminoma patients experienced increased risk of cancers of the thyroid, lung, stomach, pancreas, colon, bladder and of melanoma and soft tissue sarcoma, whereas seminoma patients experienced increased risk of cancers of the small intestine, pancreas, and urinary bladder. Remarkably, chemotherapy was associated with significantly increased risk of solid cancers (hazard ratio 2.4), and the risk of a solid cancer increased with 22% per cycle of platinum-containing

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chemotherapy (P-value for linear trend <0.001). The risk of gastrointestinal solid cancers even increased with 53% for each additional cycle. The risk of infradiaphragmatic solid cancers was also strongly associated with infradiaphragmatic irradiation: the risk increased with 6% per Gray prescribed radiation dose to an infradiaphragmatic field (P-value for linear trend <0.001). Our study is the first to provide evidence for a dose-response relationship between the number of platinum-containing chemotherapy cycles and solid cancer risk in TC patients. This is not only relevant for TC survivors but also for other cancer patients, since platinum is used in primary treatment of various malignancies, including head-and neck, stomach, colorectal, and cervical cancer.

To evaluate long-term cardiovascular morbidity and mortality in survivors of breast cancer treated with traditional or contemporary regimens, we have previously conducted a large hospital-based cohort study among breast cancer patients treated between 1970 and 2009 in the NKI or the Erasmus MC (n=14,645). This study showed increased risks of several CVDs. To identify more detailed risk factors for CVD we conducted three case-control studies, nested in this large cohort of breast cancer survivors. Cases are patients who developed either myocardial infarction (MI), heart failure (HF) or valvular heart disease (VHD) after breast cancer treatment. Controls are patients diagnosed with breast cancer who did not develop MI, HF/CMP, or VHD after BC treatment. They are individually matched to the cases on age at BC diagnosis and date of diagnosis. For 183 MI cases and 183 controls detailed treatment information has been collected from the medical records up to the time of diagnosis of MI, or for controls, for at least the length of time elapsed between BC diagnosis and MI diagnosis in the corresponding case. Radiation dose to the heart and to specific structures of the heart and dose-volume parameters were estimated by S. Darby, C. Taylor and F. Duane, Oxford University, based on detailed treatment information using virtual simulation and computed tomography planning. Median age at BC of cases and controls was 50 years. Median mean heart dose (MHD) was 9.5 Gy (range: 0.3-35.2 Gy). Median time to MI was 14 years. We found that MI rate increased linearly with increasing MHD (excess rate ratio (ERR) per Gy: 6.5%). Patients receiving ≥20 Gy MHD had a 3.4-fold higher MI rate than unirradiated patients. ERRs were higher for younger women, but the difference was not statistically significant ($ERR_{<45years}$: 24.6%/Gy, $ERR_{\geq 50years}$: 2.5%/Gy, $p_{interaction}$=0.07). Whole heart dose-volume parameters did not modify the dose-response relationship significantly. These results are consistent with the previously published linear dose-response relationship between MI rate and MHD in breast cancer survivors. Results of the HF and VHD case-control study are expected in 2018.

Recently the Harbor study (Identifying subgroups with High CARdiovascular risk in Breast cancer survivORs), which we set up in close collaboration with our colleagues in the University Medical Centre Groningen, was completed in the AVL. 324 Breast cancer survivors treated in the AVL, who were either 5-7 of 10-12 years after diagnosis at their study visit (response 64%), underwent an extensive cardiovascular screening. Currently results are being analyzed to evaluate the prevalence of subclinical CVD among breast cancer survivors who were treated with or without anthracycline-based chemotherapy (with or without trastuzumab, endocrine therapy and radiotherapy).

In our nationwide cohort study among families tested for a *BRCA1/2* mutation (HEBON study; 44,616 relatives, including 38,710 women (5,983 BRCA1/2 mutation carriers) and 5,397 men (including 1,853 *BRCA1/2* mutation carriers), we are studying whether 1) hormonal/life-style factors modify cancer risk in *BRCA1/2* families, and 2) common genetic alterations are associated with the risk of breast cancer among *BRCA1/2* carriers. In 2017 five large research projects started/continued within HEBON conducted by NKI, Erasmus Medical Center, Leiden University Medical Center and Vrije University Medical Center, in addition to many smaller studies in the other five participating Dutch Academic Medical Centers.

Use of oral contraceptive preparations (OCPs) has been associated with reduced ovarian cancer risk, but its association with breast cancer risk is unclear. We estimated breast cancer risk associations from data on 6,030 BRCA1 and 3,809 BRCA2 mutation carriers using age-dependent Cox regression, stratified by study and birth cohort. Prospective, left-truncated retrospective and full-cohort retrospective analyses were performed. For BRCA1 mutation carriers, there was no association between OCP use and breast cancer risk from the prospective analysis (Hazard Ratio (HR)=1.08;95% Confidence Interval (CI) 0.75-1.56), but an estimated 26% (95%CI 6%-51%) and 39% (95%CI 23%-58%) increased risk from the left-truncated and full-cohort retrospective analyses, respectively. For BRCA2 mutation carriers, there was an association with OCP use from the prospective analysis (HR=1.75;95%CI 1.03-2.97), but retrospective findings were inconsistent (left-truncated: HR=1.06;95%CI 0.85-1.33; full-cohort: HR=1.52;95%CI 1.28-1.81). There was some evidence of increasing risk with duration of use, especially before first full-term pregnancy. Based on the least biased, prospective analysis, OCP use was not associated with increased breast cancer risk for BRCA1 mutation carriers. As these analyses estimated risk for mostly middle-aged women (mean age 43.3), a risk association at younger ages cannot be ruled out. While prospective analyses found an association with OCP use for BRCA2 mutation carriers, there was no increased risk with duration or recency of use rendering a causal association less likely.

In a genome-wide association study using 21,468 ER-negative cases and 100,594 controls combined with 18,908 BRCA1 mutation carriers (9,414 with breast cancer), we identified independent associations with ten variants at nine new loci, replicated associations with 10 of 11 variants previously reported in ER-negative disease or BRCA1 mutation carriers and observed consistent associations with ER-negative disease for 105 susceptibility variants identified by other studies. These 125 variants explain approximately 16% of the familial risk of this breast cancer subtype. These findings may lead to improved risk prediction and inform further fine-mapping and functional work to better understand the biological basis of ER-negative breast cancer.

In our prospective DESnet cohort of 12,182 women exposed to diethylstilbestrol in utero (DES) we examined non-CCA invasive cervical cancer risk as this is still unclear. We took screening behavior carefully into account. The incidence of CIN1 was increased (Standardized Incidence Ratio (SIR) = 2.8, 95% CI 2.3-3.4), but no increased risk was observed for CIN2 + (CIN2,

CIN3 or invasive cancer) compared to the screened general population (SIR = 1.1, 95% CI 0.95-1.4). Women with DES-related malformations had increased risks of both CIN1 and CIN2 +, but the CIN2+ increased risk was largely restricted to intensively screened women. We concluded that the increased risk of CIN1 among DES daughters was probably mainly due to screening, while a true small risk increase for non-CCA cervical cancer among DES daughters with DES-related malformations could not be excluded.

The aim of the Nightingale Study, a cohort of 59,947 nurses, is to assess the association between shift work and risk of breast cancer. We have been conducting the first round of follow-up to update information on shift work, reproductive history, sleep habits and lifestyle since 2011, and to better assess circadian disruption. So far, 51% of the population participated and reminder letters are still being sent out. These data will allow us to further study the potential effects of circadian disruption on cancer risk among a highly exposed population.

The aim of the nationwide OMEGA study is to assess the long-term risk of hormone-related cancers after fertility treatment, such as ovarian stimulation for in-vitro fertilization (IVF). The cohort comprises 19,158 women treated with IVF and 5,950 women treated with subfertility treatments other than IVF between 1983 and 2000 (OMEGA I). The cohort has been expanded with 11,680 IVF-treated women treated between 1996 and 2001 and 4,063 women treated with subfertility treatments other than IVF (OMEGA-II), resulting in a cohort of over 40,000 women. Currently analyses are performed to investigate risk of invasive and borderline ovarian tumors and endometrial cancer.

We established the OMEGA children's cohort comprising all live born children of women included in OMEGA I and II; 24,269 children conceived by assisted reproductive technology (ART, i.e. IVF or intracytoplasmic sperm injection (ICSI)) and 23,421 non-ART conceived children (conceived naturally or through hormones with/without intrauterine insemination, but no ART). The children's cohort has been linked to the Netherlands Cancer Registry, yielding 231 incident cancers after a median follow-up of 21 years. Overall cancer risk was not increased in ART-conceived children, neither compared with naturally-conceived children from subfertile women (hazard ratio (HR):1.10) nor with the general population. From 18 years onwards the HR of cancer in ART-conceived versus naturally-conceived individuals was 1.25 (95%CI=0.73-2.13). Slightly but non-significantly increased risks were observed in children conceived by ICSI or cryopreservation (HR:1.52, 95%CI=0.81-2.85, and HR:1.80, 95%CI=0.65-4.95, respectively). Risks of lymphoblastic leukaemia (HR:2.44, 95%CI=0.81-7.37) and melanoma (HR:1.86, 95%CI=0.66-5.27) were non-significantly increased for ART-conceived compared with naturally-conceived children. Recently, funding has been obtained to pool the OMEGA children's cohort with other national ART children cohorts enabling the investigation of cancer risk in more depth by performing subgroup analyses and investigate risks of specific tumor types.

We obtained approval from PALGA and VUmc to collaborate in our BBMRI study to develop an improved standard procedure for linking epidemiological cohorts or biobanks with disease registries through use of the pseudonimized national identification number (burger service nummer, BSN), to ensure valid linkages with optimal privacy protection. Approval from UMCU and NCR is expected soon. We linked OMEGA responders to the questionnaire from VUmc with PALGA using pseudonimized BSN. We expect to complete this study within a few months.

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Publications

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Chromatin dynamics

Chromatin and Epigenetics

Each time a cell divides the genetic information encoded in the genome is duplicated and segregated between the two daughter cells. In addition, cells can inherit non-genetic or "epigenetic" information. Epigenetic refers to variations in function that are heritable without an underlying change in DNA sequence. For example, during the development of a human body, a single genome gives rise to a diverse range of cells with very different functions and shapes. These cell types can subsequently be maintained during cell divisions later in life when the initial signal that instructed the formation of the cell type may no longer be present. In addition to normal development, epigenetic inheritance underlies processes ranging from oncology to aging to evolution, and is therefore highly relevant for many areas of biology. The research in the van Leeuwen lab is centered around two key topics in the field of epigenetics: 1. How do epigenetic regulators control gene expression in normal development and cancer? 2. What is epigenetic information, how stable is it, and how is it transmitted and copied?

Epigenetic regulation of gene expression

Switching genes on or off and keeping them in that state involves 'packaging' of the DNA in the nucleus by wrapping it around proteins called histones. This packaged form of DNA is called chromatin. Histones carry different chemical modifications that affect the packaging state of chromatin, which in turn affects the ease with which the cellular machinery can access the DNA code and regulate gene expression. The van Leeuwen lab is investigating the stability and dynamics of chromatin states and how the accessibility instructions are involved in epigenetic memory. By taking advantage of budding yeast and the mouse as model systems and CRISPR-Cas9 tools in human cells the van Leeuwen lab is developing new tools to investigate the basic principles of chromatin-based gene regulation.

Histone dynamics and inheritance

It is widely believed that the long-lived histone proteins that package eukaryotic genomes can carry non-genetic or epigenetic information and thus transmit information about genome activity from one cell generation to the next. However, inheritance of genomic packaging status is hard to study and still poorly understood. Studies on the behavior of long-lived proteins in dividing cells have been hampered by the lack of biochemical and genetic technologies to analyze them. To solve this problem, we develop tools to simultaneously monitor old and new proteins in living cells. One of the tools we developed is Recombination-Induced Tag Exchange (RITE). Using RITE in combination with genomics and proteomics methods in yeast, we found that histone protein inheritance can vary along the genome, that histone proteins may walk along active regions, and that histone proteins carrying epigenetic information can be replaced by new naïve histone proteins, potentially erasing

information. Since the inheritance and dynamics of histones are expected to influence the epigenetic landscape and epigenetic memory, we are searching for the mechanisms responsible for these processes. Our current investigations are aimed at determining the rules, mechanisms, and functions of histone protein turnover and inheritance in human cells.

Role and regulation of histone methylation

Errors in the chemical modifications of histones, such as acetylation and methylation, can lead to changes in gene expression and cause cancer. We are particularly interested in histone methylation, which plays a critical role in maintaining cell identity and in tumor development. Here we use budding yeast as a discovery platform, and translate our knowledge to mouse models and human cells. We previously discovered a histone methyltransferase Dot1, which can add one, two, or three methyl groups to lysine 79 of histone H3 (H3K79). Dot1 influences chromatin structure and the DNA damage response, and has been implicated in oncogenic transformation in mammals. A major goal of our research is to understand the regulation of H3K79 methylation and its function in gene control and DNA damage response. Our previous work showed that Dot1 acts in a non-processive manner. This uncommon mechanism affects the function of the methylated lysine and determines how methylation can be regulated, for example by trans-histone crosstalk to ubiquitination of histone H2B. In yeast, the degree of methylation of H3K79 increases progressively on histones, which together with results obtained by mathematical modeling suggests that H3K79 methylation constitutes a timer mechanism. Using the RITE tool, we found that genomic locations that show high turnover of histones show lower degrees of H3K79 methylation, indicating that histone turnover and inheritance fine tune the levels of H3K79 methylation. We recently developed a powerful high-throughput barcode-sequencing method called Epi-ID. This method allows us to directly interrogate chromatin status on a barcoded locus in thousands of yeast mutants on parallel. These studies are facilitated by our yeast robotics infrastructure that enables high-throughput manipulation of yeast colonies and genetic crosses. Using Epi-ID, we delineated the regulome of H3K79 methylation in yeast and discovered several new mechanisms of regulation, some with potential relevance in human cells. Candidate regulators are currently being studied further in yeast as well as human cells and mouse models. We are particularly interested in the role of DOT1L and H3K79 methylation regulators in T- and B-cell malignancies and normal lymphocyte development. We team up with the group of Heinz Jacobs to connect epigenetic processes to lymphocyte biology.

Epi-Decoder

Gene regulation involves interactions of specific genomic loci with many different proteins. How these interactions are orchestrated at any given location over time is largely unknown because systematically measuring protein-DNA interactions at a specific locus in the genome is challenging. To address this problem, we developed Epi-Decoder, a Tag-ChIP-Barcode-Seq technology in yeast. Epi-Decoder is orthogonal to proteomics approaches because it does not rely on mass spectrometry but instead takes advantage of DNA sequencing. We expect that Epi-Decoder will enable the delineation of complex and dynamic protein-DNA interactions across many regions of the genome.

Together, our studies will provide a deep molecular understanding of the inheritance and dynamics of protein-based information in dividing cells and the impact of chromatin-based information on gene regulation in normal development and disease.

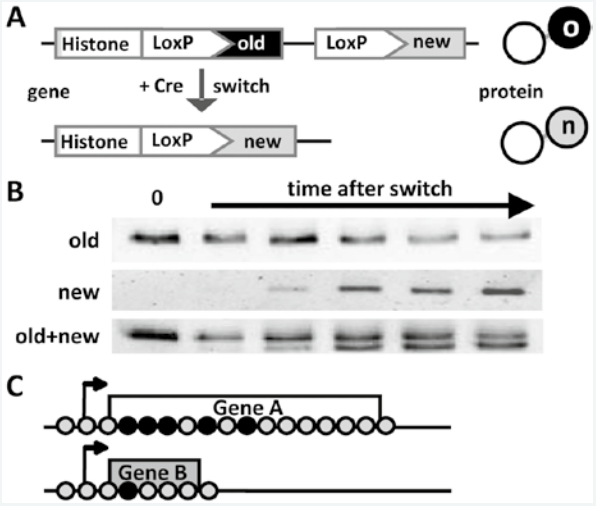

Figure 1. Recombination-induced tag exchange (RITE) distinguishes Old from New chromatin proteins in replicating cells.

Figure 2. Trans-histone crosstalk: monoubiquitination of H2B lysine 123 promotes methylation of H3 lysine 79 by Dot1.

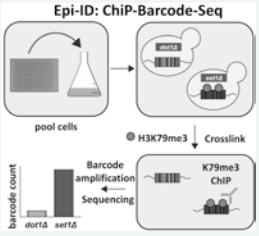

Figure 3. Epi-ID allows for screening of many yeast mutants in parallel for changes in chromatin at a barcoded reporter locus. Immunoprecipitated barcodes counted by DNA sequencing report on the abundance of the chromatin modification of interest in each mutant.

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Publications

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Role of polycomb-group genes in transcriptional repression, stem cell fate and tumorigenesis

Our lab has a long-standing interest in epigenetic gene regulation dictated by chromatin modifications. We study the mechanism of transcriptional repression by Polycomb-group (Pc-G) protein complexes, and the effects of deregulation of Pc-G genes on development, cell cycle control, cancer formation and stem cell maintenance. In addition, we are performing large-scale genetic screens in primary cells and in cancer-predisposed mice to identify cancer-relevant networks of oncogenes and tumor-suppressor genes.

Functional characterization of Pc-G protein complexes

Repressive Pc-G proteins and counteracting Trithorax-group (Trx-G) of nucleosome remodeling factors are involved in maintenance of proper gene expression patterns during development at the level of chromatin structure. At least two biochemical distinct evolutionary highly conserved Pc-G protein complexes can be distinguished. The first (PRC2) contains EzH1/EzH2 (Histone H3 methylases), Su(z)12, Eed and histone deacetylases. The second complex (PRC1) is represented by several subcomplexes all carrying the central Bmi1/Ring1B or Mel18/Ring1B ubiquitin E3 ligase that can monoubiquitinate H2A or H2Ax at K119. We focused on key PRC1 and PRC2 enzymes in gain- and loss-of-function studies in mice. Conditional Ring1b and Bmi1 loss-of-function experiments indicate an essential role for maintenance of Pc-G repression in development and stem cell maintenance. An outstanding question is how the activity of PcG enzymes is regulated; we showed that phosphorylation of Bmi1 is required for E3 ligase activity of PRC1and its action in double strand break repair. We also showed that the deubequitinating enzyme Usp3 can remove the K119ub mark and conditional loss of USP3 in mice leads to increased DNA damage and chromosomal instability and leads to increased cancer incidence and hematopoietic stem cell defects. An emerging theme is the unique functions of dynamically changing Pc-G protein complexes during differentiation. In this regard, we demonstrated a specific role for the chromodomain helicase Chd4 associating with PRC2 to define a specific narrow developmental time window for inhibiting astroglial differentiation in the mouse brain.

Connections between Pc-G gene repression, control of stem cell fate and cancer

We originally identified Bmi1 as a cMyc-cooperating lymphoma-inducing oncogene in mice. We have recently exploited new conditional knockout and transgenic mouse models to extend the observed wide-spread Pc-G deregulation to models of solid cancer. This indicated important roles for overexpression of both Bmi1 and Ezh2 in breast-, prostate- and non-small cell lung cancer as well as in glioblastoma. In contrast, using tissue specific loss of function for Bmi1, Ezh2 or the essential PRC2 component Eed in mice we recently showed profound

effects on stem cell/progenitor compartments in the breast, small intestine and brain, often associated with premature induction of proliferation arrest and aberrant differentiation, highlighting a dual role for Pc-G in controlling both proliferation and differentiation. To select the critical cancer-inducing Bmi1 target genes among the many Pc-G targets in the genome we performed high-throughput ChIP to define a conserved set of Bmi1 targets in mouse and human glioblastoma cells. We subsequently used these to generate a custom shRNAi library that was used in in vivo glioma-inducing shRNAi screens to select shRNAs that are specifically gained or lost. This robust screening method yielded novel tumor suppressors and candidate oncogenes several of which could be independently validated and which form the basis for investigating possible new intervention strategies exploiting glioma-subtype specific synthetic lethal interactions (figure 1). In light of the widespread deregulation of Pc-G in diverse cancers we are currently investigating using both small molecule inhibitors and in parallel inducible shRNAi for Bmi1 and Ezh2 their possible use in preclinical intervention studies in mouse models for basal breast cancer, colon cancer, glioblastoma and lung cancer. These studies recently highlighted the highly context-dependent action of Pc-G in cancer, dictating either an oncogenic or, conversely, a tumor-suppressive role: in glioblastoma models prolonged Ezh2 inhibition induced an aggressive stem cell like epigenetic state (figure 2), whereas in non-small cell lung cancer mutant for KRas and P53, Ezh2 inhibition or Eed deletion induced a switch to an aggressive invasive mucinous adenocarcinoma. These results emphasize preclinical testing in appropriate models and caution in how to use Ezh2 inhibitors that are currently entering into clinical trials.

Genome wide Chromatin profiling using va novel transposon-reporter system

In collaboration with the Wessels and Van Steensel labs we have developed high-throughput chromatin profiling by using Thousands of PiggyBac transposon-based Reporters In Parallel (TRIP) in Embryonic stem cells. The power of this approach lies in combining different (inducible) transcriptional reporters in transposons with random barcoding and high throughput sequencing to study genome-wide position effects and influences of local chromatin and epigenetic states on reporter expression. The modular and flexible set up of TRIP allows for the efficient probing of different features of chromatin context on a wide variety of molecular processes including transcription, chromatin dynamics, DNA methylation effects and RNA splicing and stability. As an example, we recently used TRIP to test the genome-wide influence of epigenomic context on CRISPR-Cas9 activity.

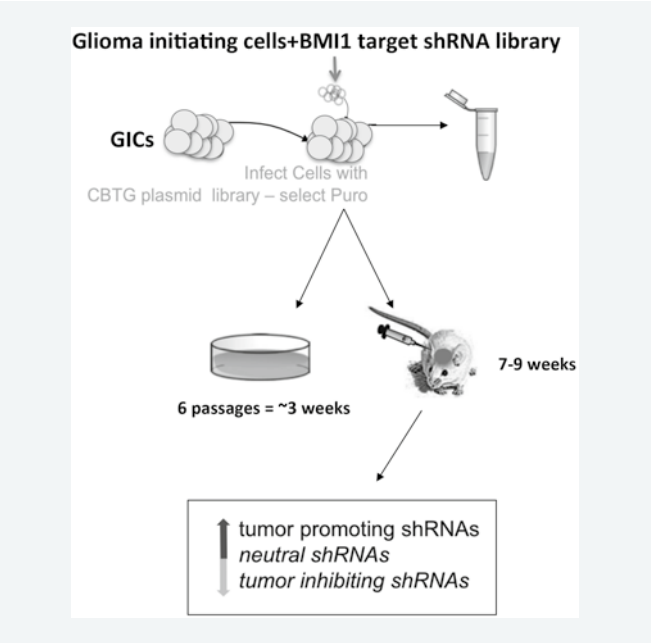

Figure 1: In vivo shRNA screen for Bmi1 target genes implicated in Glioblastoma formation. Using stringent ChIP-seq a comprehensive library of Bmi1 target genes was obtained and used to build a custom shRNAi library to screen for enriched or counter selected shRNA's in a mouse model for glioblastoma, selectively yielding novel tumor suppressors and oncogenic pathways relevant for in vivo tumor formation.

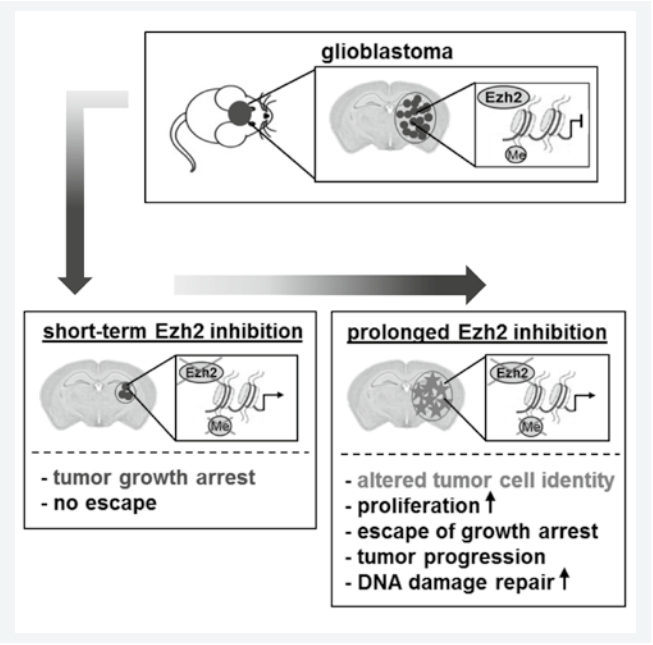

Figure 2: Context-dependent role of Ezh2 in Glioblastoma. Prolonged Ezh2 inhibition in Glioblastoma results in an altered tumor cell identity and tumor progression, unlike short-term Ezh2 inhibition, suggesting that well-balanced drug dosing is important.

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Publications

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#co-senior

Intravital microscopy of cancer plasticity

Our group studies the identity, behavior, and fate of cells that drive tumor initiation, progression, metastasis and the development of therapy resistance. These populations of cells are difficult to study since they are rare, and their behavior (e.g. migration) and traits (e.g. stemness) change over time. To be able to study these dangerous cells, we have developed intravital microscopy techniques to visualize individual cells in real-time in living animals, often referred to as intravital microscopy. In order to trace specific cell types (e.g. stem cells, EMT cells, proliferative cells) within primary tumors and in metastases in distant organs for several weeks, we combine genetic mouse models for breast and colorectal cancer with fluorescent mouse models in which the identity, behavior and/or lineage is labeled by fluorescent colors.

Gaining prolonged optical access to living tissue through imaging windows

In the intravital imaging field it is common to surgically expose tissues that are located deep inside animals such as breast, intestinal and liver tissue, which limits these experiments to a few hours. However, tumor development, metastasis and the development of therapy resistance are processes that take place over weeks and months, so studying them requires both intravital microscopy and visual access to tissue over prolonged times. Therefore, we invented the mammary imaging window to get prolonged visual access to breast tissue, and the abdominal imaging window to get access to intestinal tissue, but also e.g. liver metastases. To mark and track individual cells and lineages over time, we also developed methods to fluorescently label and trace individual cells and progeny over long periods and during multiple imaging sessions.

Tumor initiation revealed at the single cell level

We investigate tumor initiation by visualizing the pathological events during development and homeostasis of breast and intestinal tissues. The intestinal epithelium is a repetitive sheet of crypt and villus units with stem cells (SCs) at the bottom of the crypts. SCs are long-lived, able to self-renew and differentiate into specialized cells to drive tissue homeostasis and tissue repair, and in addition are considered to be crucial for the initiation of tumors. Deletion of the tumor suppressor gene adenomatous polyposis coli (APC) (initiating alteration in >80% of all human colorectal tumors) in intestinal SCs leads to adenoma formation, while deletion of this gene in differentiated cells does not. However, not every SC that loses APC will initiate a tumor. In collaboration with the labs of Ben Simons, Hugo Snippert and Alexander van Oudenaarden at the Hubrecht Institute in Utrecht, we use intravital microscopy, mathematical modelling, and single cell sequencing to investigate how the dynamic behavior and fate of these SCs can be manipulated to reduce colorectal cancer initiation. Currently we are investigating whether we can manipulate the elimination

of mutant (APC-negative) stem cells by changing stem cell competition and crypt fusion by changing diet (e.g. calorie restriction).

During puberty, the mouse mammary gland develops into a highly branched epithelial network. Using a combination of unbiased lineage tracing, modelling and intravital microscopy, we revealed the identity, behavior and fate of the mammary stem cells (MaSCs) that drive mammary morphogenesis. Our study showed that these MaSCs are very heterogeneous and that the behavior of MaSCs is not directly linked to a single expression profile. Currently, we are investigating the identity, behavior and fate of cancer stem cells (the cancer counterpart of SCs) during the growth and progression of mammary tumors, and during the development of therapy resistance.

Intravital imaging of dissemination and metastasis formation

Metastasis is a multistep process in which only a minority of cells within a tumor acquire traits and are surrounded by microenvironments that enable them to disseminate and form distant metastases. Using intravital microscopy, we have studied the role of epithelial-to-mesenchymal transition (EMT) during metastasis. We have established a genetic breast cancer mouse model in which cells change color upon EMT. We found that epithelial-mesenchymal plasticity supports migration but additionally eliminates stemness-enhanced metastatic outgrowth differences. Currently we use this model to study the role of EMT in the development of chemotherapy resistance.

We have also studied the metastatic spread of colorectal cancer. We have dissected the adenoma to carcinoma progression sequence *in vivo* by using an orthotopic organoid PDX transplantation model of human colon organoids engineered to harbor different CRC mutation combinations. We have demonstrated that sequential accumulation of oncogenic mutations in Wnt, EGFR, P53, and TGF-β signaling pathways facilitates efficient tumor growth, migration, and metastatic colonization. We showed that reconstitution of specific niche signals can restore metastatic growth potential of tumor cells lacking one of the oncogenic mutations. Our findings imply that the ability to metastasize -i.e. to colonize distant sites- is the direct consequence of the loss of dependency on specific niche signals. Currently we are investigating whether cancer cells need to acquire a stem cell state to efficiently metastasize to distant sites.

Cellular mechanisms that drive therapy resistance

Tumors contain heterogeneous populations of cancer cells with different sensitivities to therapy. The microenvironment of non-responding clones will dramatically change upon the therapy-induced massive cell death of the surrounding responding clones. We are currently investigating the microenvironmental changes upon cancer cell death and whether these changes can enhance the growth and dissemination of cells that are intrinsically non-responsive to the therapy. For this, we study BRCA1-deficient tumors in which a minority of cells have gained resistance to PARP-inhibitor treatment due to loss of 53BP1. This model enables us to induce the microenvironmental change upon PARP-inhibitor-mediated cell death in the BRCA1 cancer cells, and test how this affect the migratory and metastatic behavior of the non-responsive 53BP1-negative BRCA1 cancer cells.

Breast cancer is a heterogeneous disease, and much effort has been invested to identify molecular breast cancer subtypes, in an attempt to better guide treatment decisions and to improve treatment outcomes. However, techniques currently used in diagnostics are based on bulk measurements that obscure intra-tumoral heterogeneity, and will be dominated by the most prevalent tumor cell clones and stromal components. Therefore, the potential influence of tumor heterogeneity on the classification of breast cancer in molecular subtypes is unknown, and therefore the subsequent prognosis and choice of treatment may be suboptimal. In collaboration with the labs of van Oudenaarden, Wessels, and Voest, we are identifying this molecular heterogeneity of human breast tumors by single cell mRNA sequencing aiming at the development of improved stratification methods in order to improve treatment decisions.

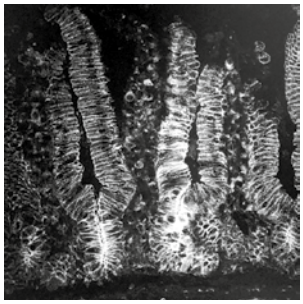

Figure 1. Intestinal villi: section of intestinal villi labeled with E-cadherin and EdU

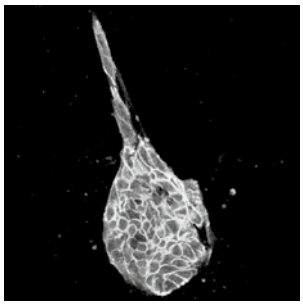

Figure 2. Mammary organoid: mammary organoid genetically labeled with E-cadherin-CFP and cytoplasmic YFP

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Chromatin Genomics

Gene expression is controlled by promoters and many other regulatory elements, and by packaging of DNA into chromatin. All of these components work in concert, and it is a major challenge to unravel their complex interplay. In addition, the spatial organization of interphase chromosomes is thought to be of key importance for genome expression and maintenance. In order to gain insight into these fundamental processes, we develop and apply new genomics techniques to reveal the interplay of chromatin and regulatory elements, and to visualize the architecture of chromosomes inside the nucleus. We use mostly mammalian cultured cells as model systems.

New genomics assays to study chromatin and gene regulation

Most existing genome-wide tools to study gene regulation are descriptive and correlative by nature, and do not permit the inference of causal relationships. Therefore, we develop new methods to assay mechanism and function, while maintaining a genome-wide view.

We have developed SuRE, a genome-wide method to study how regulatory elements are functioning when taken out of their natural chromatin context. In SuRE more than 10^8 random genomic DNA fragments, each 0.2-2kb in size, are tested for their ability to act autonomously as an enhancer or promoter (depending on the design of the assay). When applied to the human genome, the nature and scale of the SuRE data allowed us to construct a genome-wide map of autonomous promoter activity. The lab of Harmen Bussemaker (Columbia University) then developed an algorithm to precisely delineate sub-regions within promoters that are relevant for their activity, based on the SuRE data. In a variant approach, we are assaying thousands of combinations of enhancers and promoters in order to understand the underlying 'compatibility' rules. The throughput and data structure provided by SuRE facilitate genome-wide dissection of transcriptional regulation of the human genome. We are also applying SuRE to compare the genomes from several human individuals, in order to study the impact of human genetic variation on gene regulation.

In addition, we are systematically tethering transcriptional activators and repressors to many individual loci throughout the genome, using transposon integrations as well as dCas9 techniques. These approaches will help us to understand the interplay between chromatin context, nuclear lamina interactions (see below) and gene activity.

Furthermore, we have conducted a comprehensive genome-wide study of the nucleocytoplasmic kinetics of mRNA in *Drosophila* cells by metabolic labeling in combination with cellular fractionation. By mathematical modeling of these data we determined rates of transcription, export and cytoplasmic

decay for >5,000 genes. We characterized these kinetic rates and investigated links with mRNA features, RNA-binding proteins (RBPs) and chromatin states. The data provide insights into the genome-wide nucleocytoplasmic kinetics of mRNA and should be generally applicable to other cell systems.

Together, these new tools enable us and others to systematically dissect gene regulation and the role of chromatin and chromosome organization.

Facilitating genome editing experiments

We previously developed a cheap and simple assay to monitor the efficacy of genome editing by CRISPR/Cas9 (Brinkman et al, Nucl Acids Res 2014). The assay, named TIDE, only requires a pair of PCR reactions and two standard capillary sequencing runs. A specially developed decomposition algorithm then identifies the major induced insertions and deletions, and accurately determines their frequency in a cell population. We are hosting an interactive web tool for automated analysis of TIDE experiments (http://tide.nki.nl). This web server is widely used by the research community, with >1000 visits per week. We recently extended this service with TIDER, a variant of the technology that can quantify "designer" CRISPR/Cas9 editing events such as oligonucleotide-templated nucleotide substitutions.

DNA repair kinetics and the role of chromatin.

When a break occurs in the genome, how quickly is it repaired, how accurate is the repair, and how does this depend on the local chromatin context? We have set up an inducible Cas9 system in human cells to trigger a double-strand break (DSB) at a single genomic locus of choice, and then employ next-generation sequencing, direct detection of broken DNA ends and mathematical modeling to determine the kinetics and fidelity of DSB repair at this locus. Our results indicate that repair of Cas9-induced breaks takes several hours and is mostly mutagenic. Most likely, the unusually slow kinetics and high error rates are explained by strong adherence of Cas9 to the DSB ends. Our kinetic modeling approach can be combined with manipulation of chromatin components to study how DSB kinetics and fidelity are precisely modulated by the local chromatin environment. In addition, we are implementing a variant of our TRIP method to extend this approach to many genomic locations in parallel. The results are expected to provide new insights in the impact of chromatin context on the process of DSB repair.

Interactions of the genome with the nuclear lamina and other compartments

The nuclear lamina (NL) is a protein layer at the nucleoplasmic surface of the nuclear envelope. By DamID mapping we previously found that the genome of mammalian cells is associated with the NL through ~1,300 large Lamina-Associated Domains (LADs). By integrating maps of LADs with our SuRE data we identified hundreds of genes that appear to be repressed inside LADs, because their promoters become active when moved from the LAD environment into a plasmid. Another set of genes is much less sensitive to the LAD context. Our aim is to understand how these differences are encoded in the promoter sequence.

Together with the lab of Daniel Peeper we found that oncogene-induced senescence (OIS) is accompanied by massive rearrangements of NL–genome interactions. In particular, constitutive LADs (those shared by all cell types) are detached upon OIS, suggesting the loss of a specific mechanism that targets these regions to the NL. In another collaborative study, we observed that a small human artificial chromosome in mouse cells partially retains the NL interactions and overall folding.

As part of the NIH 4D Nucleome consortium we are generating a collection of publicly available high-resolution maps of NL contacts in various cell lines, and we have begun to map association of the genome with other nuclear compartments, such as nucleoli and pericentric heterochromatin domains. Computational integration with other datasets generated by the consortium should yield a comprehensive view of the spatial organization and compartmentalization of the human and mouse genome. Collectively, these studies highlight principles of the dynamic spatial architecture of chromosomes in relation to gene regulation.

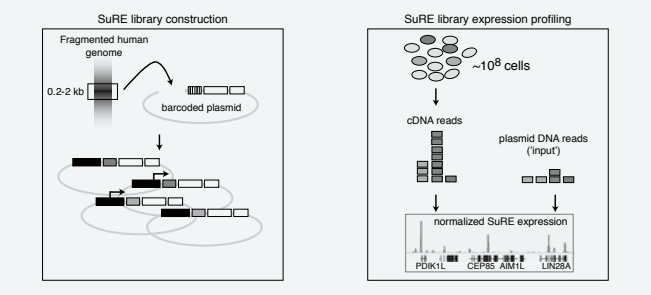

Figure 1. Overview of the SuRE method. Left panel: more than 100 million fragments of human DNA are cloned into a barcoded reporter vector. Right panel: this library is transfected into human cells and the barcodes are counted in the mRNA to infer the promoter activity of each fragment.

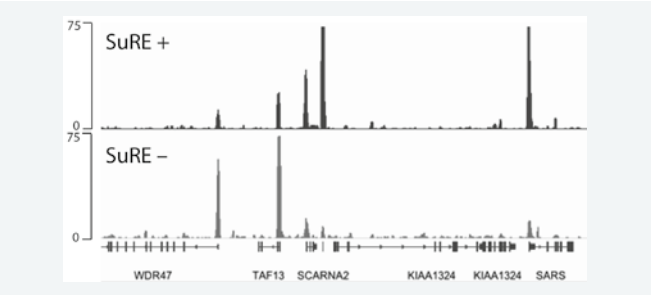

Figure 2. Example of a SuRE profile in the forward (+) and reverse (-) direction along a ~25 kb region of the human genome. Autonomous activity is clearly detectable for multiple promoters in this region.

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Pre-clinical studies to evaluate novel treatments for glioblastoma

Glioblastoma (GBM) is a uniformly fatal disease. The location and invasive nature of GBM renders complete surgical resection impossible. Although radiotherapy is important for disease management, side effects prohibit the delivery of curative doses. Despite the successful introduction of novel targeted therapeutics in some other solid cancer types, clinical trials in GBM have all failed. The mission of our preclinical research group is to develop and validate more effective pharmacotherapies for this disease. One of the spearheads of our research is aimed at highlighting the important role of the blood-brain barrier (BBB) in treatment failures. Although disruption of the blood-brain barrier (BBB) is common, this grossly affects areas of the tumor that are amenable to surgical resection. However, the non-resectable tumor cells that have colonized the surrounding normal brain tissue are protected by the BBB and are the source of the inevitable recurrence. Just a few mainly small hydrophobic drugs display some efficacy against GBM. In particular, drug transporting proteins like ABCB1 and ABCG2 hinder the entry of most of the other effective anticancer agents, including many of the targeted agents. Thus, in order to develop more successful pharmacotherapies, our research aims to identify (potentially useful) agents that are none or weak substrate of these drug transporters. Alternatively, we are trying to improve drug penetration into brain tumors by using drug efflux pump inhibitors or carrier systems.
Other hurdles to effective pharmacotherapies are the combined activation of multiple oncogenic pathways and intra-tumor heterogeneity. With multiple aberrant signaling pathways being the drivers of GBM, single target-single agent pharmacotherapies are likely to fail, even when using drugs that can penetrate the BBB. Consequently, we are exploring combinations of targeted agent that should cause concomitant inhibition of the common glioma associated oncogenic signaling pathways. Moreover, as radiotherapy is the cornerstone of the standard therapy, we are also actively investigating the options of radiosensitization by small molecule drugs.

Targeting aberrant signaling pathways in glioblastoma

The PI3K-mTor pathway is frequently activated in GBM and offers several druggable targets. We have explored a series of PI3K - mTOR inhibitors, including rapamycin, AZD8055, NVP-BEZ235 and ZSTK474. As shown by transwell assays and ABC-transporter knockout mice, only the PI3K inhibitor ZSTK474 was not a substrate of the ABC-transporters and had a good BBB penetration. We were able to show target inhibition (pAkt and pS6) in normal brain of wildtype mice at clinically relevant plasma concentrations and in vivo in brain tumors. However, both in transplantable and spontaneous mouse models, we observed only a very modest antitumor efficacy. Notably, other signal transduction routes such as the MAPK pathway were still active. The fact that GBM harbors several over-active signaling

pathways, stresses the need of multi-targeted combination therapies.
In line with this idea we performed a similar set of experiments with a range of MEK inhibitors that are already approved or in advanced clinical development. Taking into account the BBB penetration and the range of clinically relevant plasma concentrations, we propose PD0325901 as the most promising candidate for such combination treatments. Next to PI3K-mTor and the MAPK pathway, the CDK4/6-Rb pathway is also activated in the majority of GBM. Palbociclib and abemaciclib are inhibitors of CDK4/6 and currently tested as single agents in GBM. Although both are good substrates of the ABC transporters limiting their brain penetration, we are now exploring the potential of triple-targeted (PI3K/MAPK/CDK4/6) combination therapy for treatment of GBM.

Radiosensitization of GBM

Because the G1/S checkpoint is usually abrogated, GBMs are more dependent on the G2 checkpoint to maintain sufficient genome integrity. Chk1 and Wee1 are major nodes in the molecular switch that determines whether cell may progress to mitosis. Perturbation of the G2 checkpoint in combination with chemoradiation may lead to enhanced cell death by causing mitotic catastrophy and is being considered as a strategy for radiosensitization. We have evaluated the BBB penetration of the Wee1 inhibitors AZD1775 and PD166285. Although AZD1775 is in clinical development, this agent is an excellent substrate of ABCB1 and ABCG2 with a very low BBB penetration and therefore not a very good candidate for treatment of GBM.

GBM invasion

One of the main reasons why GBM's are so difficult to treat is the remarkable capacity of glioma cells to invade deeply into the surrounding normal brain where they find shelter against therapy. Understanding how glioma cells invade is therefore an important first step to develop treatments that tackle this disastrous feature of GBM. In collaboration with the research group of Rene Bernards we have discovered that GBM cells produce a variety of collagens thus laying their own groundwork of rigid connective tissue, which they can use as grip for invasion. Moreover, we identified the transcription factor Interferon Regulatory Factor 3 (IRF3) as a master regulator in collagen production. Although this finding made IRF3 a potentially interesting protein to target therapeutically, drugs that directly target IRF3 are not available. Fortunately, however, IRF3 had been described to be regulated by casein kinase 2 (CK2) and inhibitory drugs are available. Indeed, we found the inhibition of CK2 by the small molecule drug CX4945 markedly reduced the invasion capacity of GBM in mice. Treating invasion by inhibition of CK2 may be an interesting therapeutic strategy for GBM, although it may not have a direct impact on survival of GBM patients, since spreading has already occurred at the time of diagnosis. However, we will explore the potential of CK2 inhibition in combination with chemoradiation therapy. Considering that invasion and proliferation are mutually exclusive, switching invasive cells to a proliferative phenotype may render them more vulnerable to anti-proliferative chemoradiation therapy.

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Targeted radiosensitization

Increased understanding of the molecular mechanisms underlying tumor and normal cell radiosensitivity has led to the identification of a variety of potential targets for rational intervention. Our research aims to translate such novel combination strategies from bench to bedside with a focus on cell death and DNA repair/response modulation and radio-immunotherapy.

Manipulation of cell death

Based on our previously described synergistic interaction between pro-apoptotic receptor agonists and DNA damaging agents, we study combined treatment effects of APG880, a second generation hexameric TRAIL-receptor agonist, and radiation in a panel of human colon cancer cell lines and colon cancer-derived organoids. Nanomolar concentrations of APG880 induce apoptosis in a time- and dose-dependent. Combined treatment with radiation results in synergistic levels of apoptosis and reduced clonogenic survival, indicating radiosensitization. Ongoing studies focus on underlying molecular mechanisms of this interaction. Preliminary data indicate a radiation-induced increase of DR4 and DR5 expression in the models studied.
In collaboration with Wouter Moolenaar and Olaf van Tellingen (Department Clinical Chemistry), we study the combination of CP121, an alkyl-phospholipid (APL) analog, and radiation in vitro and in a preclinical orthotopic intracranial model of glioblastoma. We also examined the possible role of lipid flippases in mediating transbilayer transport of APL-like lysophospholipids (notably lysoPC and lysoPE). The uptake of fluorescent lysophospholipids (TopFluor-LPC and -LPE) was monitored over time in wild-type HAP1 and CDC50A -/- cells using single-cell live imaging. Knockout of the flippase subunit CDC50a slows and attenuates the uptake of fluorescent lysoLPC and lysoPE. This suggests that CDC50a mediates, at least in large part, the active uptake of cytotoxic APLs, similarly to natural lysophospholipids.

DNA damage response modulators

DNA damage repair and response inhibition are promising strategies to potentiate radio- or chemotherapy. Among such approaches, PARP inhibitors are particularly attractive as radio-enhancers due to the cellular replication-dependent radiosensitizing and vasodilatory properties. Potent radiosensitization capacity combined with a favorable low systemic toxicity profile provides a strong rational for radiotherapy PARP inhibitors combinations. Three collaborative phase I-II studies evaluating the safety and tolerability of the PARP inhibitor olaparib, in combination with radiotherapy in locally advanced breast cancer (with G Sonke), non-small cell lung cancer (NSCLC; with Michel van den Heuvel) and HNSCC (with Michiel van den Brekel) are recruiting patients to test this combination in the clinic.
Biomarkers that assess the activity of drugs or the combination

are important to guide such trials. In collaboration with Jan Schellens (Department Clinical Pharmacology), we developed and evaluated a PARP inhibitor pharmacodynamics assay that allows sensitive assessment of PARP inhibitor activity. In a healthy volunteer study we determined that the sensitivity and accuracy to quantify PARP inhibition exceeded those of the established PAR pharmacodynamic assay by several fold. Implemented in clinical combination trials, the assay showed superior detection of PARP inhibition in patients treated with the PARP inhibitor olaparib and establishes strong PARP inhibitory activities at low daily doses (figure 1).
In a preclinical homologous recombination-proficient breast cancer model, G Borst found that neoadjuvant olaparib decreased the hypoxic tumor fraction and improved radioresponsiveness in vivo. Translation into clinical studies is required to confirm these preclinical findings.

Radio-immunotherapy

The combination of radiotherapy and immunomodulation has been recognized as an effective strategy to enhance local tumor control and induce abscopal effects in selected cases. In collaboration with Inge Verbrugge (Division Tumor Biology and Immunology), we examined to which extent T cell (co)stimulation and/or stereotactic body radiation therapy (SBRT) could further enhance the therapeutic efficacy of T cell checkpoint blockade in pre-clinical mouse (breast) tumor models. We found that, while combining SBRT with PD-1 blockade and CD137 agonism is highly effective in local tumor control, tumors implanted outside the radiotherapy field were not eliminated. Mechanistic follow-up studies revealed gene signatures associated with a 'CTL-permissive' tumor micro-environment. By adding clinically-relevant interventions, we succeeded at mimicking this permissive micro-environment and improving abscopal tumor control. Our future studies are aimed at delineating the cellular and molecular bottlenecks of radiotherapy that impair systemic immunity in mouse tumor models with distinct immunogenicity.

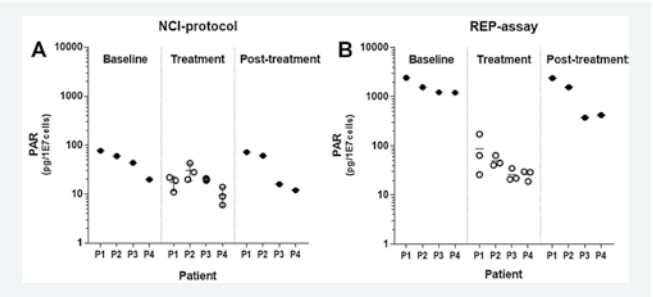
Identification and exploitation of DNA repair defects

Recent genomic data demonstrate the role of DNA damage response and repair in tumorigenesis or patient outcome in an increasing number of cancer types. DNA damage repair pathway defects inherent to some cancers may therefore define radiotherapy outcome. Previously, we identified DNA repair defects in HNSCC and tested opportunities to exploit those by the combination of radiation and PARP inhibitors. To allow the identification of such defects in clinical material, we tested and developed multiple genetic biomarkers in collaboration with the HNSCC department. In preliminary studies these showed promise, identifying a subgroup of patients with different outcome parameters that warrant validation in an independent cohort.

Preclinical lung toxicity models

Increased normal tissue toxicity counteracts any dose intensification by combination with novel targeted combination strategies. The in-house image-guided small animal irradiator (µIGRT) provides the opportunity to target tissues of interests in a manner that resembles the situation in the clinic when targeting tumors.Using sensitive preclinical models, novel radiation combination strategies can be carefully assessed by analyzing histologic, radiologic and functional endpoints.

Together with Jan-Jakob Sonke's group we focused on the sensitive assessment of radiation-induced lung damage guided by CT imaging in longitudinal studies. This will help to address the therapeutic value of radiation combination strategies.



The REP-assay detects strong inhibitor activity at low olaparib doses in NSCLC patients treated with olaparib combined with concurrent chemoradiation. Blood was drawn from four NSCLC trial patients and assayed in parallel according to the NCI-protocol (A) or REP-assay (B) that applies 8 Gy irradiation as indicated.

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Personalized Medicine by employing tumor organoids and genomics

Emile Voest is medical director of the Netherlands Cancer Institute, medical oncologist and translational scientist. In addition to his clinical and managerial responsibilities he is leading his own research group. His laboratory group is devoted to bringing personalized medicine to patients and is focused on the identification of biomarkers that predict treatment efficacy. The results from these studies are subsequently translated in clinical studies. These translational approaches are performed across tumor types with emphasis on epithelial tumors.

Genomics, immunotherapy and (tumor)organoids

Genomic guided personalized medicine

In 2017, we further accelerated and facilitated DNA guided personalized medicine. The collaborative consortium that was co-founded by me in 2010 now includes more than 40 hospitals including all academic cancer centers. In 2017 almost 2000 patients with metastatic cancer (of any kind) underwent biopsies to obtain fresh tumor material at the start of new systemic treatment and were whole genome sequenced (WGS) in conjunction with clinical outcome data. The Hartwig Medical Foundation (HMF, also co-founded by me in April 2015) is a not-for-profit foundation that has created an unprecedented database of genomic and clinical data and treatment outcome that may be used by the scientific community. The Hartwig Medical Foundation will not perform research itself but merely supports research. In addition to WGS the Hartwig has now started with RNA sequencing of the full data set.
In addition to the national CPCT/HMF I have made a connection with the AACR GENIE initiative and published on the program of data sharing. Furthermore, these initiatives also brought to light that the medical oncology community also needs support and guidance in interpreting the genetic data. We therefore proposed ways on how to implement multidisciplinary tumor boards on genomics.

In the CPCT/HMF initiative we frequently found potentially actionable mutations or amplifications in tumors of patients for which approved drugs were available but not part of the reimbursement system because it was not on the approved EMA label. Therefore we initiated the Drug Rediscovery Protocol, in short the DRUP study. In this multi-pharma (10 companies to date), multi-drug (19 drugs to date), multi-center (27 centers to date) study we now have created a platform through which patients can get access to approved medication based on a genomic profile coupled to a tumor type. These drugs are provided for free by pharma and the number of drugs and hospitals are expanding. In 2017, we received and reviewed >350 patient submissions of which 140 patients will be actively treated with targeted agents. In the first analysis we have encountered a clinical benefit ratio (defined as complete or partial remission or stable disease >16 weeks) of ~40%. This is surprisingly high and reflects that patient selection is key in

such a personalized medicine approach. Also, we will perform data sharing with other international initiatives (e.g. TAPUR/CAPTUR) that were based on our protocol.

Genomics guided personalized medicine has also important ethical consequences and little is known about this. We therefore started a project, in collaboration with Annelien Breedenoord, to identify the needs and wishes of patients who are offered DNA sequencing including germ line data. This will help to prepare and inform patients better for important decisions and also improve our informed consent procedures. Several publications came out in 2017 addressing these important issues such as "Am I my family's keeper?" "Duty to hunt" and how to handle unsollicted findings. We are currently also conducting a large survey amongst >700 patients to identify potential wishes and problems. We have now included >200 patients who completed a lengthy and detailed survey. This will be extremely valuable for the future education of our patients but also doctors.

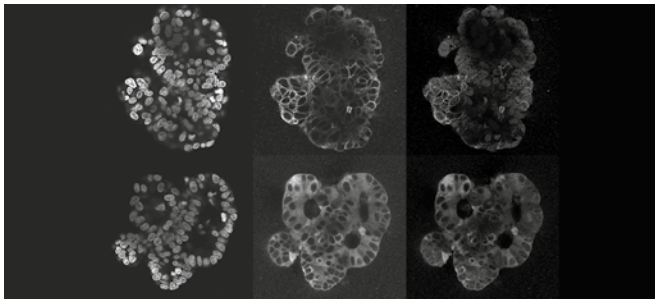
Immunotherapy

Several trials and translational studies have been initiated in 2016. The NICHE trial is a unique study that investigates the use of neoadjuvant immunotherapy in colorectal cancer. First results are now coming in which allows the assessment of safety and initial outcome. We also invested a great deal of time and energy in obtaining paired biopsies from melanoma or lung patients treated with immunotherapy. This is extremely challenging but we feel that (with the help of the Nefkens Foundation) this will be very rewarding in better understanding resistance pathways. Large scale efforts to analyze WGS data of >100 patients treated with immunotherapy and for whom we have clinical outcome data are underway. These data will be subsequently ompared with the data set of now 39 paired biopsies of patients treated with immunotherapy. We intend to generate a data set of 100 paired biopsies.
A very exciting translational study to generate better understanding of which tumors are recognized by T cells comes from using organoids to induce an immune response on PBMC. In colorectal cancer and NSCLC we have seen PBMC responses when exposed to autologous tumor organoids. These T cells can be expanded for further research and even in the future for T cell treatment. This creates a very interesting platform to study resistance to T cells.

Organoids as a tool to personalize medicine

Finally, in the context of our personalized medicine efforts and in collaboration with the Hubrecht Institute we have investigated whether organoids derived from tumors from individual patients have the capacity to predict treatment responses. Based on seminal studies from the group of Hans Clevers to which my group also contributed, we now have protocols for culturing various types of cancer. Next we have initiated several clinical trials to investigate the value of these organoids as predictive tools. These trials include validation studies in patients with chemotherapy and targeted therapy in lung and colorectal cancer (TUMOROID), organoid-guided experimental treatment studies (SENSOR) and more. These studies are now expanded with breast cancer. We also used the organoid platform to screen for the functionality of fusion genes that, in collaboration with Wigard Kloosterman, were identified by RNA sequencing in a large set of colorectal cancer patients.

In summary, my group is strongly committed to understand the genetic make up of tumors and to use this knowledge from DNA and RNA to better predict the responsiveness of cancer cells to treatment.



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Molecular pathology of breast cancer

Breast cancer is a heterogeneous disease. Accurate pathological and molecular analyses are key to make accurate predictions regarding prognosis and response to treatment. We aim to find, validate, and implement biomarkers to optimize precise and personalized predictions regarding prognosis and treatment response.

Finding the balance between over and undertreatment of breast Ductal Carcinoma In Situ (DCIS)

A major concern in breast cancer management is the overdiagnosis and hence overtreatment of ductal carcinoma in situ (DCIS), a common breast cancer precursor. However, most DCIS lesions will never make it to fatal disease. Such lesions actually do not need treatment. To distinguish which DCIS lesions may ever turn into potentially lethal disease and which ones do not, it is first essential to estimate the magnitude of the risk of overtreatment. Therefore, we conducted epidemiological studies to evaluate the risk of subsequent ipsilateral and contralateral invasive breast cancer. To assess the prognostic role of screen detection, we studied mortality in a population-based cohort of 9,799 women treated for primary DCIS between 1989 and 2004 in the Netherlands with a median follow-up of 9.8 years and made a comparison with the general population. The absolute breast cancer mortality rates were low and declined over time. Increased relative risk of death from breast cancer was found especially in patients 40 years at DCIS diagnosis. For women older than 50 years, the risk of breast cancer death was low and did not counterbalance the risk of lower rates found for other causes of death, indicating a healthy user effect among women older than 50 years diagnosed with DCIS. In addition, we are identifying biomarkers associated with progression of DCIS into breast cancer. Therefore, we compared DCIS samples from 200 patients developing ipsilateral breast cancer with 500 matched DCIS samples of women without invasive recurrence during a ten year follow up period. Staining for ER, PR, HER2, COX2, p16, and p53 has been performed. Gene expression profiling and mutation panel sequencing is ongoing. We are also studying the immune infiltrate of DCIS, aiming at the detection of T-cells, B-cells, mast cells, neutrophils, macrophages, plasma cells and NK-cells. Ultimately, we aim to develop an individualized risk prediction model for DCIS patients by integrating the data to distinguish indolent from aggressive DCIS. This will eventually be essential to guide DCIS management. We hypothesize that it will be safe to offer women with innocent DCIS lesions active surveillance only. Validation of such a model can be performed in our ongoing prospective DCIS study, the Low-Risk DCIS (LORD) trial. This is a randomized controlled, phase 3, non-inferiority trial to evaluate the safety of active surveillance in 1,240 women with low risk DCIS. The LORD trial is coordinated by the BOOG and EORTC. The trial is open since summer 2017 and the first patients have been randomized. In 2017, we received the Cancer Research UK Grand Challenge Award, funded in partnership with KWF Dutch Cancer Society for

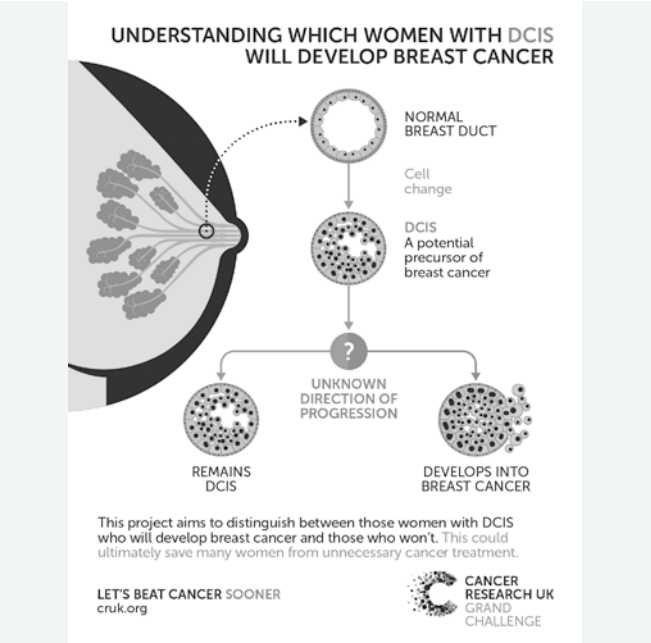
our PRECISION Initiative. This is the acronym for 'PREvent dCIS Invasive Overtreatment Now' (see also www.dcisprecision.org). For this, we synergize with international top experts to solve the DCIS dilemma as depicted in the figure. In this initiative, we will profoundly characterize three large retrospective DCIS series to learn how to distinguish which DCIS lesions will develop into invasive breast cancer and which ones never will.

Mechanisms of response and resistance in patient-derived xenograft models of triple-negative breast cancer

We have generated patient-derived xenograft (PDX) models for BRCA1-deficient triple negative breast cancer (TNBC) and used these to test response to alkylating agents and PARP inhibitors. Initially, these models respond well to such treatments, but eventually resistance develops frequently. Resistance mechanisms include genetic rearrangements or demethylation of the BRCA1 promoter. Both mechanisms restore full length BRCA1 expression. Strikingly, response was not directly correlated to BRCA1 expression in a series of 24 TNBC PDX models treated with cisplatin (collaboration with the Curie Institute, Paris, France). In a small subset of these models, response did correlate with RAD51 focus formation. Additional analyses of candidate predictive factors are ongoing, as well as validation of the results in mice.

Development of clinically useful molecular tests to predict chemotherapy response of primary breast cancers

Within the neoadjuvant chemotherapy program, we aim to develop tests predicting response to preoperative chemotherapy. Since 2004 we collect pre-treatment biopsy material and clinical data from all patients scheduled to receive neoadjuvant chemotherapy in the NKI-AVL, resulting now in a database and sample collection of 1,700 patients. A clinical biomarker test developed in this program, the BRCA1-like MLPA assay, is now used in three clinical trials to select patients for high dose chemotherapy (in collaboration with Petra Nederlof). In close collaboration with the computational cancer biology group (Lodewyk Wessels) we identified three major tumor processes in triple negative breast cancer that allow us to stratify tumors into subtypes associated with response to chemotherapy and long-term survival. These subtypes could be validated in an adjuvantly treated cohort from the NKI-AVL. Especially tumors with a high proliferation and high expression of immunity related genes showed very high response rates in the neoadjuvant setting (79% pCR, n=28) and excellent long-term survival in the adjuvant dataset (no recurrences, n= 24). In another project we performed deep sequencing of matched samples taken before and after neoadjuvant chemotherapy of 21 patients. By comparing somatic mutations, copy number alterations and gene expression levels between 'before' and 'after' samples from the same patient, we aim to study the effect of chemotherapy on breast tumors and to identify potential resistance mechanisms. In collaboration with the medical oncology department (Gabe Sonke) we aim to identify biomarkers for trastuzumab response (primary endpoint is pathologic complete response in the breast and lymph nodes). For this purpose, we will analyze mutation data, gene expression data and protein data of the primary tumor (pretreatment) in a cohort of ~100 patients with stage II or III HER2-positive breast cancer. The data will be analyzed with a systems biology approach for studying drug response in cancer (collaboration with Lodewyk Wessels).



The PRECISION Initiative funded by Cancer Research UK in partnership with the KWF Dutch Cancer Society aims to distinguish between those women with DCIS who will develop breast cancer and thos who won't. This could ultimately save many women from unnecessary cancer treatment. See for further details www.dcisprecision.org.

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Computational cancer biology

The Computational Cancer Biology group develops novel computational approaches and performs state-of-the-art analyses of a wide array of data types to further our basic understanding of cancer and to translate these findings to the clinic. A number of exemplary projects are presented below in more detail.

Weighted Orthogonal Nonnegative (WON) PARAFAC: A sparse parallel factor analysis on multiple cancer genomics data types identifies generalizable genomic factors

In the quest for personalized medicine, the idea of integrating genomics data for better understanding drug response in cancer cells gains traction. However, the high dimensionality of these data types forms a significant barrier to obtaining interpretable response models. While interpretability is an important requirement, accuracy of response prediction is arguably even more important. Moreover, as large cancer cell line collections have been molecularly and pharmacologically profiled, a significant challenge remains the successful transfer of predictive models from the in vitro domain to the in vivo setting. We developed Weighted Orthogonal Nonnegative (WON) PARAFAC, a method for obtaining sparse and interpretable factors by compressing linked molecular data, like mutation, copy number and gene expression data. The factors represent 'hidden' processes in the cell lines, that give rise to the observed molecular data. By relating the factors to the gene expression, tumor cell type annotation and to the drug response of the cell lines, we can reveal the identity of the biological processes underlying the factors, the cell types these processes are active in and the effect they have on drug response. Employing the molecular data from the GDSC1000, we identified 130 factors that sufficiently capture the variation in the molecular data, and we interpreted these factors through pathway and tissue type enrichment analyses. We employed these factors to predict drug response and found its performance comparable to elastic net regression employing all molecular data. However, the drug response predictor derived from cell lines is superior to elastic net regression in predicting drug response on in-vivo PDX models (Figure 1). This demonstrates that the compressed factors identified by WON-PARAFAC are not only good predictors of in vitro response, but, more importantly, provide a robust mechanism to directly transfer in vitro predictors to the in vivo setting and, hopefully, ultimately, to the human setting.

TRIP technology enabled genome-wide Cas9 targeting reveals epigenomic effects and insertions dependent on staggered cleavage

As CRISPR/Cas9 emerges as a prime tool for precise genome editing in eukaryotic cells, it becomes increasingly important to know and control variables influencing Cas9 efficiency. While guide RNA sequence effects have been extensively studied, the

impact of the regulatory landscape on Cas9 targeting remains poorly understood. In this study, we collaborated with the Van Lohuizen lab and employed the TRIP (Thousands of Reporters Integrated in Parallel) to generate ~1k barcoded reporters to multiplex Cas9 targeting and profile mutation frequency and patterns across the genomes of mouse embryonic stem (mES) cells. We observed that Cas9 efficiency was strongly dependent on genomic location but could not establish an association with regulatory context, which was possibly masked by extensive epigenetic changes characterising the unusually long S-phase of the mES cell cycle. Additionally, we determined that most Cas9-induced insertions arose from template-dependent repair of DSBs with 1bp 5' overhangs. Our results reveal that insertions are driven by staggered cleavage, which could be leveraged to increase knock-in efficiency and control over the orientation of an insert into host DNA.

Estimating hierarchies amongst data types to inform the structure of multi-stage TANDEM models

We developed TANDEM, a two-stage approach to predicting drug response in cancer cell lines. In the first stage, TANDEM explains response using upstream features (mutations, copy number, methylation and cancer type) and the second stage explains the remainder using downstream features (gene expression). Applying TANDEM to 934 cell lines profiled across 265 drugs, we show that the resulting models are more interpretable, while retaining the same predictive performance as classic approaches that do not employ a two-stage hierarchy. Several follow-up questions stem from this work. First, we classified the data sets into an upstream and downstream category, partially motivated by the central dogma. However, does the data support such a structure? Second, we did not define a hierarchy amongst the upstream data types, so the question arises whether there is a natural hierarchy between these data types and if so, what the structure of that hierarchy would be. Finally, if a new data type, like proteomics data, is added to the analyses, where should we place that data type in the hierarchy? To answer these questions, we employed matrix correlations to quantify how much information is shared between two datasets with corresponding samples, such as mutation and gene expression data of the same tumors. The RV coefficient measures matrix correlation by comparing whether the samples have a similar configuration (e.g. clustering) in both datasets. We extended the RV coefficient to be applicable to binary data and for partial matrix correlations, both of which we tested on artificial and the cell line pharmacogenomics data. We could reach several conclusions (Figure 2). First, the information shared between drug response and upstream data (mutation, copy number, methylation and cancer type) is fully contained in gene expression indicating that the original TANDEM hierarchy is also supported by the data. Second, there is no clear hierarchy amongst the upstream data, i.e. mutation, copy number, methylation and cancer type. Third, proteomics data is an independent predictor of drug response in the presence of gene expression. While gene expression is more predictive of drug response, there is no clear hierarchy between these two data types. This implies that when proteomics is added to the current TANDEM models, a three-stage model should be employed with the upstream data in the first stage, followed by proteomics in the second stage and gene expression in the final stage. As there is no clear hierarchical order between gene expression and proteomics, a TANDEM model with gene expression in the second and proteomics in the final stage is also a plausible option. Employing such configurations, we have demonstrated that SLFN11 is a gene expression marker of response to DNA damaging agents which is exclusively present in the gene expression data, while protein levels of ABC transporters are excellent biomarkers of drug response exclusively detectable in the proteomics data.

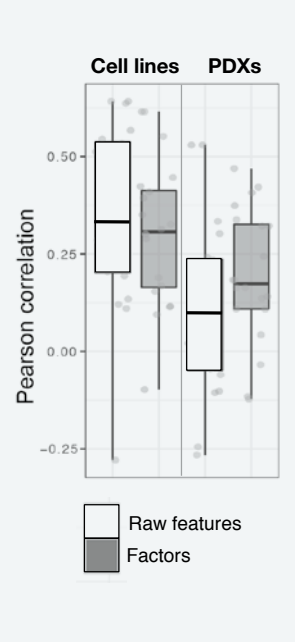

Figure 1. This figure displays box plots of the Pearson correlation of the predicted and actual response in cell lines (left two boxplots) and PDX models (right two boxplots) based on the raw features (white boxes) and compressed features from the WON-PARAFAC model. The raw features show a large drop in performance when moving from cell lines to PDX models, while the compressed features show only a small drop in performance, demonstrating the transferability of the compressed features between model systems.

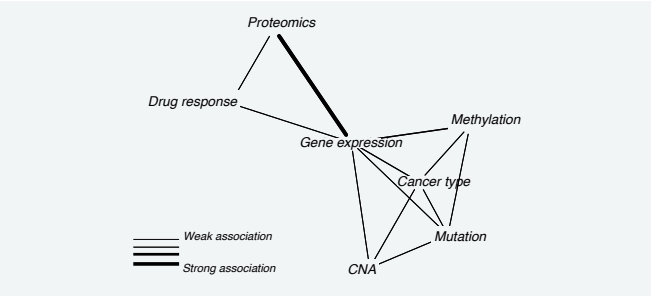

Figure 2. The conditional dependence graph as determined by the PC algorithm on all data types (gene expression, protein expression, mutation, copy number, methylation, cancer type and drug response data) derived from a collection of 266 cell lines. This graph reveals the hierarchical structure between data types. The lines connecting data types reflect the strength of the association between the different data types. From this figure we conclude that 1) the upstream data types (mutation, copy number, methylation, cancer type) do not display a clear hierarchical structure; 2) all information regarding drug response that is present in the upstream data is contained in the gene expression data and 3) the proteomics data is an independent predictor of drug response in the presence of gene expression, and vice versa.

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Improving treatment responses in Head and Neck cancer

Seventy percent of all head and neck squamous cell carcinoma (HNSCC) patients present with advanced staged disease with an overall 5-year survival of approximately 40-50% in case of radical and often mutilating surgery and/or (chemo-) radiation therapy. The addition of high-dose cisplatin to radiotherapy (CCRT) increases the percentage of ≥ grade 3 acute toxicity up to 89%, in stark contrast to the 6.5% of patients that actually experience a 5-year survival benefit after CCRT. Apart from cisplatin and some other classic chemotherapeutic agents, only cetuximab has been shown to increase the response to radiotherapy in HNSCC, while Olaparib, a PARP-inhibitor, is currently tested for its clinical efficacy in HNSCC patients. It remains a major challenge in head and neck cancer to find novel compound based treatment schemes that help to achieve higher cure rates while preserving function of nearby tissues and organs at risk.

Microenvironment of HNSCC

HNSCCs can be categorized by two distinct aetiologies: tobacco and/or alcohol use in combination with genetic predisposition, or infection and activity of viral oncogenes. In addition, head and neck cancers are characterized by a microenvironment invaded by various immune cells that each may play a role in treatment response and resistance. For example, HPV positive oropharyngeal HNSCC tumors are described to have increased numbers of tumor infiltrating CD8+ and FOXp3+ lymphocytes compared to HPV-negative tumors, correlating to favorable clinical outcome in HPV positive HNSCC. Consequently, tumor-specific lymphocytes (T cells) are target for treatment opportunities to improve clinical outcome in patients with advanced disease.

In the laboratory, we aim to assess hypoxia as a determinant for T cell capacity in human tumors. The net effect of hypoxia or HIF1a accumulation on T-cell differentiation or effector function in human malignant solid tumors in vivo is unknown, and may very well differ per T-cell subset. Tumor hypoxia may interfere with the effect of aPD1 on adaptive immunity, due to 1. hypoxia-mediated altered local T cell fate (gene transcription and/or RNA translation), and 2. the local balance between different T cell subsets and myeloid cells. When we will be able to reveal key consequences of hypoxia on T cell capacity both at steady-state and after immunotherapy in clinical setting, the results of our study may have large implications for the development of combination treatments that aim to further enhance tumor-specific T cell activity and consequently treatment response in HNSCC during check-point blockade therapy.

To improve clinical outcome in our patients, we designed the phase Ib/II "*IM*CISION" trial (EudraCT 2016_002366_31) concerning toxicity and feasibility of T-cell checkpoint inhibitors nivolumab w/wo ipilimumab neoadjuvant to major surgery in head and neck patients with advanced disease. This trial started February 2017 at the department of Head and Neck Surgery and

Oncology of the Antoni van Leeuwenhoek Hospital. In order to address the above described translational research, patients HX4-PET guided tumor biopsies will be taken to the laboratory to assess the influence of hypoxia on T-cell capacity before and after immunotherapy.

Anti-cancer drugs and HNSCC

Automated drug screens were used to identify novel radiosensitizing compounds to improve drug based RT outcome in patients with head and neck cancer. Different chemical libraries were tested for their biological effects on different HNSCC cell lines. Compounds were tested at multiple concentrations, either with or without additional radiation, for their potential radiosensitizing effects based on a fluorescence metabolic read-out. We identified a promising lead compound that showed selective radiosensitizing activity against a panel of HNSCC cell lines, while having no effect on cell viability in the absence of radiotherapy. This effect was confirmed by a colony forming assay with a DEF (dose-enhancement factor) of 1.8. The target of our lead compound was found to be ATM, part of the DNA repair pathway. In addition, our compound did outperforme Olaparib in several (but not all) HNSCC cell lines. We are currently testing our novel ATM inhibitor in mice. These studies are performed in collaboration with the Division of Chemical Immunology of Jacques Neefjes and Huib Ovaa in het LUMC in Leiden, the Netherlands, and should define better options for radiotherapy of HNSCC patients.

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Hormone receptors in cancer

Hormone receptor blockade represents one of the first and most-successful targeted therapeutics in cancer. In most breast cancers and prostate cancers, hormonal therapy forms the very backbone of systemic treatment both in the adjuvant setting and in the treatment of metastatic disease. Still, resistance to hormonal therapeutics is commonly observed, and it is of vital relevance to better understand hormonal signalling in these two most-frequently diagnosed tumor types.
We study hormone receptor action in breast and prostate cancer, with the ultimate goal to personalize clinical decision-making, optimize treatment selection and minimize over-treatment. By expanding our knowledge on steroid hormone receptor function in breast and prostate cancer, as well as elucidating mechanisms of treatment resistance, we aim to achieve tailored endocrine treatment selection, selecting the most-suitable therapy for the individual patient.

Effects of hormonal breast cancer treatment and response prediction

Each year, 1.7 million women are diagnosed with breast cancer. About 75% of all breast tumors are Estrogen Receptor (ERα)-positive and are thought to depend on hormonal stimuli for tumor cell proliferation. Consequently, ERα is considered an ideal drug target and most therapeutics are aimed to block this hormone-dependent transcription factor, but resistance to treatment is common.
In collaboration with the group of Paul van Diest (UMC Utrecht), we studied paired primary breast cancers and metastatic samples from the same patient (Schrijver et al., 2017). In line with previous reports, we found selective loss of ERα expression in ~20% of cases who received adjuvant endocrine therapy. Interestingly, we also observed a selective loss of Androgen Receptor protein expression in the metastases from patients, previously treated with ERα-inhibiting therapy. These findings suggest a functional connection between these two steroid hormone receptors. In fact, Androgen Receptor and ERα do functionally interact in breast cancer (Severson and Zwart, 2017) and we found both receptors to share chromatin binding features at the same genomic regions, in cell lines and human tumor tissue (Severson, Kim, Joosten et al., in press).

Interestingly, other ERα interactors strongly deviate in chromatin binding features between cell lines and human tissue. According to the current cell line-based dogma, ERα requires pioneer factor FOXA1 for chromatin binding, and ~95% of all ERα sites are found at enhancer elements. In collaboration with Sabine Linn and Lodewyk Wessels, we show in human tumor tissue that over half of all ERα chromatin sites not shared with FOXA1 (Severson, Kim, Joosten et al., in press) (see figure 1). Most importantly, FOXA1-devoid ERα sites were strongly promoter-enriched, providing compelling evidence that current cell line models do not recapitulate ERα genomic features as observed in human tumors.

Since anti-hormonal therapy for breast cancer is intrinsically systemic, other tissue types that express ERα are affected as well, including endometrial cells that represent the inner cell layer of the uterus. Consequently, tamoxifen treatment increases the endometrial cancer risk with a factor of 2-7 fold, dependent on the duration of treatment. In collaboration with Floor van Leeuwen, we profiled ERα genomic binding in human endometrial tumors, where we compared ERα sites of spontaneous endometrial cancers with those that originated after years of tamoxifen exposure for the treatment of breast cancer (Droog et al., 2017). Interestingly, large-scale genomic relocation of ERα was observed in the endometrial tumors originating in presence of tamoxifen. These tamoxifen-specific sites were normally not ERα-occupied in endometrial cells, but were found strongly bound by ERα in breast tumors (figure 2). These findings suggest that tamoxifen reprograms ERα function in the uterus, regulating oncogenic programs that are regularly active in breast tumors. With this, we provide a potential explanation of the oncogenic effects of tamoxifen in endometrial cancer development.

Androgen Receptor chromatin binding and protein complex in prostate cancer

Prostate cancer is the second most prevalent malignancy in men, in which the Androgen Receptor (AR) is considered the sole-driving factor in cancer development and progression. To increase our understanding of the AR protein interaction network, we performed mass spectrometry analyses in prostate cancer LNCaP cells, in close collaboration with Andre Bergman and Maarten Altelaar. These analyses revealed 66 high-confidence AR-interacting proteins, endogenously expressed in LNCaP cells (Stelloo et al., 2017). Using publicly available CRISPR/Cas9 knockout data, we identified these 66 proteins as specifically critical for LNCaP cell proliferation, while not affecting proliferation of cell lines that were derived from other tissues. As genomic subcomplexes of AR may deviate on a genome-wide scale, interactors that were most-critical for LNCaP proliferation were profiled using ChIP-seq. Using unsupervised hierarchical clustering, we identified three distinct genomic subcomplexes of AR action that deviated specifically based on interactions with FOXA1 and HOXB13; both previously recognised as critical players for AR action in prostate cancer. Using AR ChIP-seq data from human healthy prostate specimens, we showed that AR binds the chromatin at sites devoid of FOXA1 and HOXB13. In prostate cancer, AR is relocated by FOXA1 and HOXB13 to other loci, potentially driving oncogenic processes in this context.

Currently, we are expanding on these analyses by studying paired healthy prostate specimens and prostate cancers from the same patient, providing genomic selectivity of chromatin binding for AR, HOXB13, FOXA1, CTCF and histone modification H3K27ac. With these analyses, we aim to better understand AR action in a physiologically relevant context, increasing our knowledge of this critical hormone-driven transcription factor in prostate cancer development and to better annotate direct interplay of AR with other factors that are critically involved in this process.

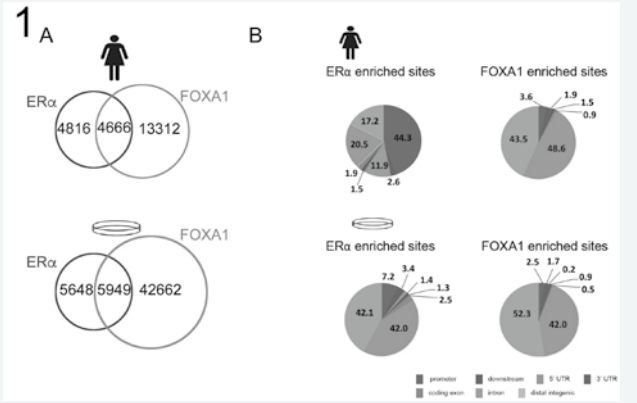


Figure 1. Deviating genomic distributions of Estrogen Receptor between tumors and cell lines.
A. Shared and unique binding sites between Estrogen Receptor and FOXA1, as identified in tumors and cell lines. All sites identified in >50% of tested samples were considered.
B. Genomic location of differential peaks. While Estrogen Receptor-enriched peaks in tumors are strongly promoter-enriched, this is not found in cell lines.

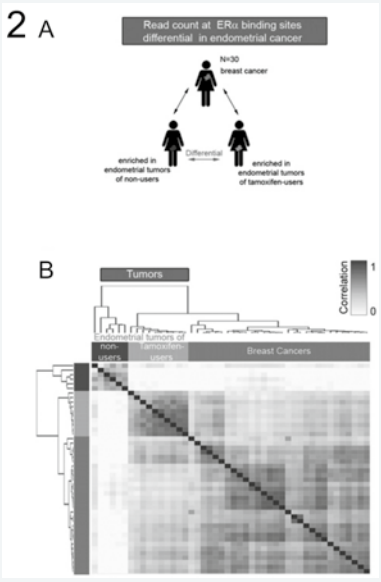
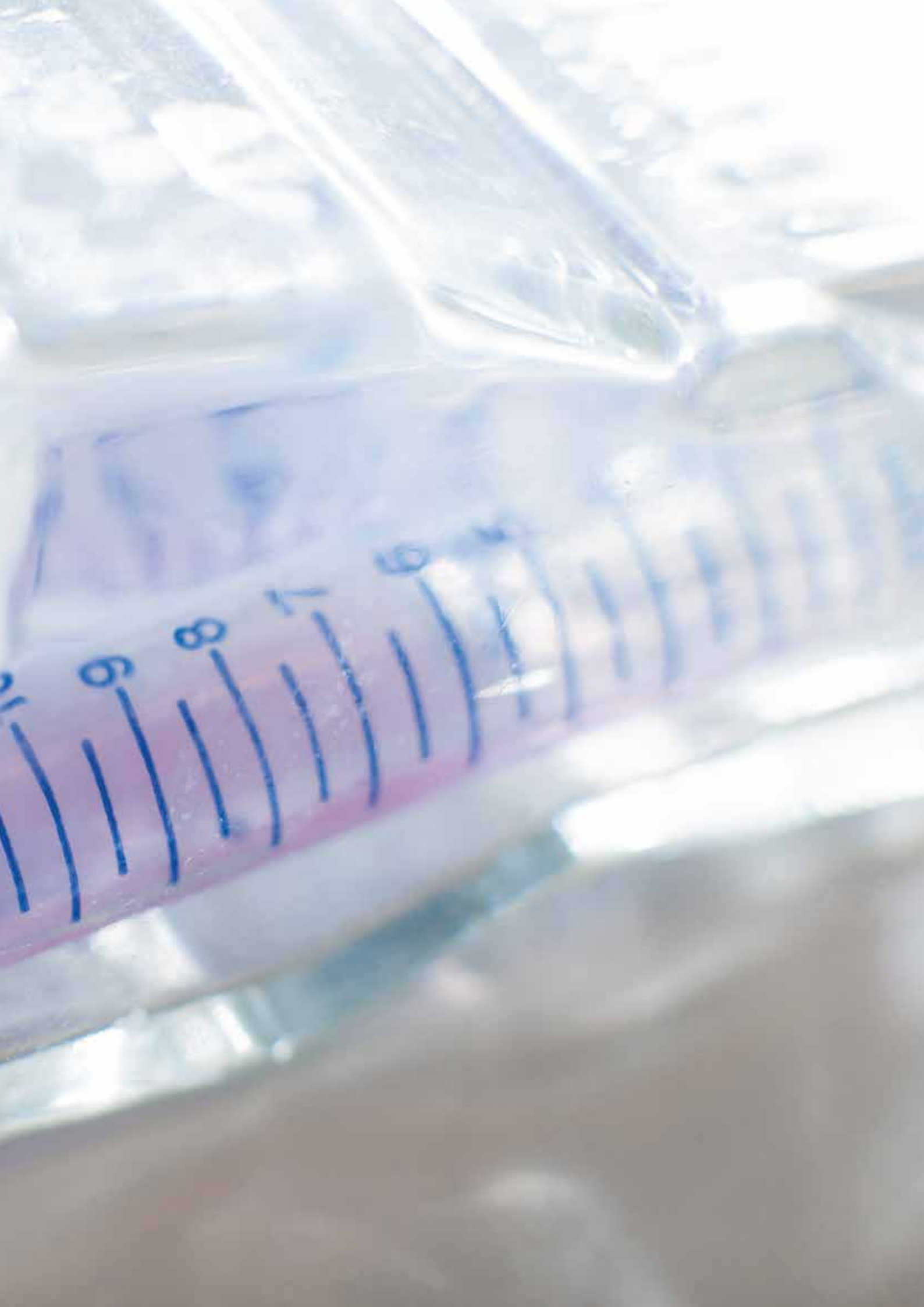


Figure 2. ERα in tamoxifen-associated endometrial tumors binds genomic regions formally bound by ERα in breast cancer. Comparative analysis of ERα-binding sites in endometrial and breast tumor tissue.
A. Analysis setup. ERα binding in breast cancer at the differential sites in the two endometrial cancer groups was evaluated.
B. Heatmap visualization of the correlation matrix, based on ERα ChIP-seq read count at differential ERα-binding sites found between endometrial tumors of tamoxifen users and nonusers. ERα sites in endometrial tumors of tamoxifen users correlate with ERα profiles as observed in breast tumors.



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Division of Diagnostic Oncology

The division of Diagnostic Oncology comprises the departments of Clinical Chemistry, Clinical Physics, Pathology, Family Cancer Clinic, Radiology and Nuclear Medicine. Diverse as the departments are, they share a common focus: improvement of diagnostic procedures and implementation of latest technologies in order to guide treatment as much as possible. Due to the fact that this division plays a key-role in almost all research topics of the NKI-AVL, such as image guided surgery, immunotherapy, personalized medicine and basic science, the number of oral presentations and publications has again increased significantly over the past year. In addition, collaboration with national and international organizations are not only a sign of success, but also underline its current outstanding performance. It resulted again in many granted projects and in several theses defended successfully this year.

DEPARTMENT OF CLINICAL CHEMISTRY

In addition to the daily routine - performing laboratory tests needed for the diagnostics and the monitoring of the tumor diseases - the department of clinical chemistry is involved in research projects as well as clinically oriented projects. The department of clinical chemistry is the bridge between basal research and the more clinical research with the aim to implement innovative diagnostic tests. Furthermore, we investigate new applications for recently designed assays. With these developments, we can improve the support to the clinician in the diagnosis and treatment of the disease.

LIQUID BIOPSIES

An important focus of the department is translational research and implementation of innovative diagnostics into clinical practice. Such an innovative approach to cancer diagnostics are liquid biopsies. Liquid biopsies are increasingly used in clinical care, for which our department is involved in biobank initiatives and numerous studies. In 2017, we have organized, in collaboration with the UMCG and the Erasmus MC, the first national ctDNA day as a start for further national standardization and discussion on the use and structured implementation of ctDNA. One of the spin off initiatives from this day is a multicenter national consortium which has submitted a proposal for clinical validation of ctDNA in the ZonMW personalized medicine call in 2017. In 2017 Daan Vessies started as a PhD student on molecular biomarkers in blood and body fluids. In collaboration with the department of Pathology we have started to explore the impact of liquid biopsies on the current diagnostics processes and how to combine different biosources in routine clinical care.

Liquid biopsies in Lung Cancer

All projects on lung cancer are running in collaboration with the departments of Thoracic Oncology, Pathology and Pharmacy.
In the recent years an extensive biobank of plasma, serum and other body fluids of patients with lung cancer has been built.
Apart from the analysis of ctDNA for routine patient care new techniques and approaches are being validated and implemented in clinical care. We evaluated 86 patients under first line TKI's. We aimed to determine whether ctDNA could be a predictor of progressive disease and compare its performance to imaging. Analysis of the dynamics of the primary driver was a good predictor of onset of progressive disease 80-120 days earlier than routine CT evaluation.
The sensitivity of mutation detection could be enhanced by the analysis of multiple biosources. To test this hypothesis, we analyzed pleural effusions and serum in a retrospective cohort of KRAS and EGFR positive patients. This evaluation showed an increase in sensitivity for the combined analysis of plasma and pleural effusion. Analysis of pleural effusions identified primary driver mutations and the presence of EGFRT790M in samples lacking sufficient cells for standard molecular analysis. The advantage of analyzing multiple bio-sources will further be explored to determine its place and value in standard diagnostics.
In 2017, we biobanked and evaluated plasma samples for the LEMA trial which aims to evaluate early molecular profiling in patients diagnosed presenting with lung cancer. In 2017 more than 150 plasma samples were analyzed using ddPCR. In collaboration with Roche we are evaluating the possibilities of sequencing plasma for point mutations, translocations and copy number variations. An approach which also will be highly relevant for application in clinical care. We are evaluating the possibilities to use ddPCR for the detection of other genetic aberrations such as translocations and copy number variations in plasma.

Liquid biopsies in Colorectal Cancer

All colorectal studies are in collaboration with Remond Fijneman, PLCRC and the Department of Pathology

We are processing and storing an increasing number blood samples from national biobank initiatives such as PLCRC. In 2017 the ORCA study (longitudinal evaluation of ctDNA in Ras wild-type non-liver limited metastatic colorectal cancer patients) was initiated for which we process the plasma samples and implemented Sysmex BEAMing for the evaluation of changes in RAS status. With additional funding from Health Holland, we are comparing six different, currently commercially available platforms for ctDNA analyses. These platforms range from PCR based approaches to NGS analysis of ctDNA. We aim to compare sensitivity, variation and total costs of analysis in patient samples and constructed reference samples. Evaluating these systems will shed light on the performance of different techniques for the evaluation of ctDNA and which platform is most fit to answer a specific clinical question. In collaboration with the Maxima Medical Centre, we initiated an explorative analysis of ctDNA analysis of patients receiving pressurized intra-peritoneal aerosol chemotherapy for peritoneal metastasis. In this pilot, we aim to analyse ctDNA levels at short time intervals before, during and after the procedure.

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Liquid biopsies in other tumor types

In collaboration with Michiel van der Heijden and Cambridge university, cell free urine, urine cell pellet and plasma were analyzed from patients with bladder cancer using Tam-Seq. This study showed an increase in the detection of mutations when different biosources for ctDNA were combined. In addition, specific mutations in these biosources were followed using patient specific ddPCR assays.
In collaboration with the department of radiotherapy and Jan Paul de Boer, we are evaluating the use of ctDNA for therapy efficacy and the use of ctDNA as a marker to select patients at risk for recurrence. For the latter question, we are collaborating with Rick Haas and Jos Elbers for soft-tissue sarcomas and head and neck cancer.

Other projects on liquid biopsies

In collaboration with Tom Wurdinger and Michel van den Heuvel, we are evaluating the impact of pre-analytical variables on the TEP algorithm developed in the VUmc. We aim to address the effect of pre-analytical handling on the prediction of the algorithm as well as understanding the biological processes in the platelets during the pre-analytical phase.

DEVELOPMENT OF TUMOR BIOMARKER METHODS

In collaboration with Olaf van Tellingen, Margot Tesselaar, Henk van der Poel, Floris Pos, Michel van den Heuvel, Jelle ten Hoeve, Vincent van der Noort

One focus of the department of clinical chemistry is the development of new analytical methods for (tumor) biomarker analysis.
Recently a liquid chromatography tandem mass spectrometry (LC-MS/MS) based assay was developed for the analysis of serotonin, a marker for neuroendocrine tumors. This method was used to investigate the relevance of the blood matrixes whole blood, platelet-rich plasma and serum that are all used in daily practice. It was shown for the first time that serotonin determined in these matrixes was interchangeable. The assay has now been implemented for routine serotonin analysis in daily patient care.
Furthermore, we are working on the development of sensitive and specific assays for steroids. Androgens, a class of steroid hormones, are important drivers of prostate cancer and primary therapy of more advance disease is focused on reducing the endogenous androgen concentration. Currently, the limited analytical sensitivity and specificity of routinely used immunoassays for these compounds significantly limits monitoring of androgen levels in prostate cancer patients.
Another project aims to develop a finger prick PSA method that allows patient self-management of a finger prick blood sample collection. Furthermore, the method should not compromise the analytical performance of our current routine PSA test, requires limited pre-analytical sample handling and allow automated PSA analysis on our routine PSA analyzer. First we have developed and validated a PSA method that requires just 200 µL of blood on our automated PSA analyzer. Secondly, since no suitable finger prick blood collection device was commercially available we developed in collaboration with the TU Delft a finger prick blood collection device. At this point we are preparing a trial to investigate 1) Does the finger prick self-management sample collection device results in a suitable blood sample for PSA

analyses and 2) Are PSA concentrations obtained with the finger prick PSA method comparable to PSA concentrations obtained from venipuncture collected blood as is performed in routine clinical practice.

CLINICAL VALIDATION OF CANCER MONITORING USING CIRCULATING BIOMARKERS

In collaboration with Michel van den Heuvel, Jelle ten Hoeve, Vincent van der Noort, Paul Baas

Most diagnostic tests performed at the AKL are used for monitoring of treatment and disease. For monitoring cancer, oncological biomarkers, also known as tumourmarkers, are used. Unfortunately for many oncological biomarkers used in daily practice, such as the Cyfra 21.1, SCC, NSE, CEA markers for lung cancer, objective insights in what consecutive obtained results (longitudinal biomarkers) clinically mean is lacking. We are aiming to design new approaches to allow clinical validation of such longitudinal (tumor) biomarkers. For this purpose we have developed a new way of studying such data and a graphical presentation; the BReC-plot. Next we developed IT infrastructure to be able to generate these plots in a flexible way and design and study longitudinal biomarker based medical tests. The developed interface; BReC-plot Generator, is available for the NKI-AVL and can be used to study all sorts of longitudinal biomarkers for specific patient cohorts.
When we used the BReC-plot application to study metastatic non-small cell lung cancer patients, we could design a test that right after start of Nivolumab treatment identifies about 50% of the patients with high certainty that do not respond to this treatment. Future research is in progress to confirm these findings in independent cohorts and perform similar diagnostic validation of longitudinal tumour biomarkers for other tumour biomarkers, treatments and cancers.

CLINICAL VALIDATION OF BIOMARKERS

Gastro-enteropancreatic neuroendocrine tumours (GEP-NET)

In collaboration with Margot Tesselaar, Division of Medical Oncology; Irvin Modlin, Mark Kidd, Wren Laboratories, Branford CT

Wren Labs has developed the NETest, an In Vitro MultiAnalyte with Algorithm Analyses test service, targeted gene expression profile of RNA isolated from peripheral blood. NETesting is intended to aid in the identification of active disease and therefore provide an assessment of treatment responses in neuroendocrine tumor patients. We collected in 2014 and 2015 blood samples of 21 healthy volunteers, 153 patients with NET, 77 patients with colorectal carcinoma and 106 patients with melanoma. Preliminary results showed that at 95% specificity a sensitivity of 82% was observed when comparing healthy volunteers with NET-patients.
We started to collect sequential blood samples in patients with NEN to investigate whether those samples can identify disease status (PD, SD or CR) during follow-up. Furthermore we started to collect samples to identify melanoma specific transcripts that differentiate NEN from melanoma in order to evaluate the difference in biological behavior between the different patient groups (melanoma versus NEN).

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HE4

In collaboration with Gynecologic Oncology (Christianne Lok, Anna Stiekema, Pien Lof)

Ovarian cancer is the leading cause of death in women with of gynaecologic cancer. CA125 is the most commonly used tumor marker in the diagnosis of ovarian cancer, but has limitations in both sensitivity and specificity. In recent years, we compared Human epididymal secretory protein (HE4) with CA-125. HE4 demonstrated the highest discrimination between benign and malignant pelvic masses compared to ROMA, Risk of Malignancy Index and CA125 alone. In 2017, we started a prospective observational multicentre study, "HE4-Prediction". The primary objective of this study is to evaluate the biomarker HE4 as second step after the RMI score, in the triage of patients with an ovarian mass. Secondary outcomes are cost-effectiveness and quality of life. Nine institute are collaborating with this study.

Risk reducing salpingo-oophorectomy: physical and psychological consequences

In collaboration with Gynecologic Oncology (Marc van Beurden, Ravi Vermeulen) and Division of Psychological Research and Epidemiology (Neil Aaronson)

The pathophysiological changes that occur after Risk reducing salpingo-oophorectomy (RRSO) are largely unknown. Therefore, we prospectively collected blood samples and questionnaires of women who underwent RRSO. The objective of our study is to improve our knowledge about vasomotor, mood and sexual complaints and its relationship with pathophysiological changes. Prospectively, we included 147 pre- and postmenopausal women who underwent a RRSO. We collected blood samples and questionnaires about quality of life, sexuality and menopausal complaints.

We investigated whether higher pre-surgical AMH levels are related to: (1) the severity of post-RRSO menopausal symptoms, in general, and the perceived burden of hot flushes and night sweats, in particular; (2) sexual functioning; and (3) psychological distress (depression and anxiety). In addition to AMH-levels, we investigated the possible association between post-RRSO symptoms and a range of sociodemographic and clinical variables. We found that AMH was not a significant predictor of change in symptoms following RRSO. Regular menses prior to RRSO, earlier receipt of chemotherapy and being in a relationship were significantly, but relatively weakly associated with changes in outcomes six weeks and/or seven months after RRSO.

BIOBANK

In collaboration with the Core Facility - Molecular Pathology & Biobanking (Annegien Broeks)

In 2011, we started with the biobank for storage of serum and whole blood for future investigations in a broad research area. Every new patient in the NKI-AVL is asked by an informed consent to donate 2 tubes of blood. In the following years, we also started with storing EDTA-plasma for research of circulating tumor DNA and tumor educated platelets (TEP) for research of RNA-transcripts. Furthermore, other body fluids such as cerebrospinal fluids, pleural fluids, ascites and urine are stored in the biobank. If investigators wanted to start a biobank, or wanted to use human specimens, they have to go the Translational Research Portal (TRP), where they can find all the required information and where the online registration will be done.

In 2017 we expect to collect totally 18,500 requests: 6,300 serum samples; 3,300 cell free plasma for ctDNA; 3,900 tumor educated plasma's; 2,400 whole blood samples for germ line DNA; 2,200 other materials such as cerebrospinal fluid, urine samples and other blood samples.
We also collect, process and store blood samples from multicenter studies, for which the NKI is the responsible biobank. In 2017, we expect to receive 550 blood samples of patients with colorectal cancer, 100 samples of patients with lung cancer and 150 samples of several other tumor groups.

THE NETHERLANDS CANCER INSTITUTE FAMILY CANCER CLINIC

Frans Hogervorst, Efraim Rosenberg, Petra Nederlof, Maartje Vogel, Mohamed Achachah, Abderrahim Ajouaou, Majella Boutmy-de Lange, Rashmie Debipersad, Daphne Dieduksman, Mobien Kasiem, Ruben Moritz, Rob Plug, Roelof Pruntel, Rubayte Rahman and Esther Scheerman. Lizet van der Kolk, Marielle Ruijs, Fred Menko, Muriel Adank, Fonnet Bleeker, Petra Cohn-Hokke, Sophie van der Velden, Anja van Rens, Marijke Hagmeijer, Daoud Ait Moha, Kiki Jeanson, Elly Kaats, Eveline Bleiker and Daniela Hahn

Over the last few years the number of families who have been referred for clinical genetic evaluation at the Family Cancer Clinic of our hospital has risen to over 1400 patients yearly. For most families the indication for referral is a possible genetic predisposition for breast and/or ovarian cancer. Other indications include suspected non-polyposis colorectal cancer (Lynch syndrome), colorectal polyposis syndromes, Li-Fraumeni syndrome and a possible genetic predisposition for stomach cancer, renal cancer, melanoma and pancreatic cancer. BOADICEA, a risk assessment model specifically for breast and /or ovarian cancer, has been introduced in the daily counselling practice.
Increasingly, results of DNA-analysis have implications for the treatment of cancer. For example, women with ovarian cancer who carry a mutation in the BRCA1- or BRCA2-gene, may benefit from treatment with PARP-inhibitors. This development results in more referrals and, sometimes, a different way of genetic counselling.

The DNA-diagnostic laboratory of the Family Cancer Clinic

The Raad voor Accreditatie visited our department to audit our Quality Management System which we (DNA-diagnostic laboratory of the Family Cancer Clinic) have since 2001. As from April 2017, we are not a CCKL accredited laboratory but an ISO 15189 accredited laboratory.
The implementation of Next Generation Sequencing (NGS) for the BRCA1/2 genes in 2016 made it possible to offer BRCA testing for germline and somatic DNA, isolated from blood cells and more importantly FFPE fixed tumor or normal cells. This is of great value for us as our laboratory screened more than 6800 families for germline mutations in the BRCA1/2 genes since the start in 1995. These families have received genetic counseling at our Family Cancer Clinic. In addition to BRCA1 and 2 mutations

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we also search for the CHEK2 1100delC mutation. The 1100delC mutation in CHEK2 is as frequent as BRCA 1 and 2 mutations together and is considered to be a moderate risk variant. It is relatively frequent in the Netherlands. The report of rapid testing for BRCA1/2 is available within 2-3 weeks after request. Routine testing is generally reported between 3-5 weeks.
The introduction of BRCA testing by NGS is also important for patients with ovarian cancer. Patients having either a germline or somatic mutation in these two genes can be considered treatment by PARP inhibitors. This is a major step forward in the treatment of ovarian cancer. Furthermore, several clinical trials require rapid testing of tumor DNA for a BRCA1 specific or a BRCAness profile. In this respect, we are able to offer a complete test panel for BRCAness: germline and somatic BRCA1/2 testing, BRCA1 promotor methylation and CNV seq to assess the genomic tumor profile for BRCAness features. The BRCAness testing is performed in close collaboration with Petra Nederlof, head Molecular Diagnostics. In addition, we performed >120 BRCA1/2 mutation tests on FFPE tissues from high risk families in which we previously were unable to detect germline B1/2 mutations. For this purpose we analyze DNA isolated from normal and tumor FFPE tissue. Several tumors with BRCA1/2 germline or somatic only mutations have been identified. This gives us the opportunity to distinguish between germline and somatic mutations which may influence the (screenings) options after counselling.
For families with suspicion for Lynch Syndrome, we start with testing for microsatellite instability in the tumor DNA. This test contains a multiplex of 5 mononucleotide markers. We also perform immunohistochemistry for the mismatch repair genes which is carried out in collaboration with P. Snaebjornsson, pathologist. MSI-High and/or absent MMR staining in the tumor is an indication for MLH1 and sometimes MSH2 promotor methylation testing. About 50% of the microsatellite instable (MSI-high) tumors with absent staining of MLH1 have a methylated MLH1 promoter. In rare cases a germline deletion of the 3'region of EPCAM results in MSH2 promotor methylation. In case no methylation is detected, so no indication for a somatic cause of the MSI-high pattern, the patient is referred to the clinical genetics department as this may indicate a possible hereditary predisposition. This result has direct consequences for the patient and it family members. For germline testing we perform Sanger sequencing for analysis of mismatch repair genes MLH1, MSH2 and MSH6 and screen for large genomic rearrangements by MLPA. NGS testing for the MMR including PMS2 has been started Q4 of 2017. Other genes and panels will follow after a careful selection procedure of the technical platforms in 2018.

Research projects

The Family Cancer Clinic contributes data to several multi-center national and international research projects, e.g. HEBON Resource (Hereditary Breast and Ovarian Cancer Research Group Netherlands see Division Psychosocial Research and Epidemiology), DNA-profiling by CNV seq or BRCAness of breast and ovarian cancer patients (in close collaboration with E. Lips, Division of Molecular Pathology), and the BCAC and CIMBA consortiums which focus on the contribution of SNPs to cancer risk, (HEBON resource, M. Rookus, dept of Psychosocial Research and Epidemiology (PSOE)). In this respect we also contribute to two EU HORIZON 2020 studies,

BRIDGES and BCAST, both focus on the further molecular analysis of non BRCA1/2 breast cancer prone families and tumors resp. M.K. Schmidt from the dept Mol Pathology is PI of BCAST. Furthermore, we participate in studies which assess the biological significance of so called unclassified variants (DNA changes of which it is uncertain whether they be pathogenic mutations or polymorphisms) in collaboration with the dept Tumor Biology and Immunology (H. te Riele, E. Rosenberg and F. Bleeker in the nationwide INVUSE consortium on MMR UVs), with the dept Molecular Pathology (J. Jonkers and P. Bouwman on BRCA1 UVs) in national and international collaborations with other DNA-diagnostic and research labs, e.g. LUMC (M. Vreeswijk on BRCA2 UVs), internationally in ENIGMA for BRA1/2 UVs (member Hogervorst) and psychosocial studies, in collaboration with the PSOE (E. Bleiker) and clinical and genetic research in families with gastrointestinal cancer, including stomach cancer and pancreatic cancer (A. Cats, Division of Medical Oncology). Furthermore, E. Rosenberg is involved in the molecular characterization of colon tumors which were found in Hodgkin patients (collaboration with P. Snaebjornsson (Pathology) and M. Leerdam (Division of Medical Oncology)
The study on the clinical significance of variants within the BRCA1 and BRCA2 genes and a study on male breast cancer are ongoing (both in collaboration with prof. dr. C. van Asperen).

In close cooperation between the PSOE (E. Bleiker), Family Cancer Clinic (F. Menko) and the national organizations Erfocentrum and Levenmetkanker new methods for informing family members are developed and evaluated aimed at improving the communication of cancer risk and better use of preventive measures. For colorectal cancer families with Lynch-like syndrome a project has been set up for the detection of causative variants in DNA mismatch repair genes (H. te Riele, M. van Leerdam, E. Bleeker) and this subject is explored in close cooperation with the ErasmusMC group in Rotterdam (Dinjens). The possible hereditary background of a large group of patients with multiple primary tumours is evaluated in cooperation with Lok (NKI) and Maher (Cambridge, UK).
TP53-mutation carriers from Li-Fraumeni syndrome families are screened by total body MRI in the NKI. Data will be collected on the MRI-results and on the psychosocial impact of this screening tool (M. Ruijs, E. Bleiker, G. Sonke (Division of Medical Oncology) and C. Loo (Division of Radiology)). L. van der Kolk, E. Bleiker and Lok (Division of Gynaecology) collaborate in a project (funded by Astra Zeneca) investigating the effect of online information prior to the genetic counseling (Genova Project). The goal of this study is to increase the efficiency of the counseling (measuring the duration of the face to face contact) while maintaining the degree of satisfaction and knowledge and without increasing perceived stress.
In 2017 a unique prospective breast cancer study was granted by Pink Ribbon/KWF (In close cooperation with M.J. Hooning and A. Hollestelle (Erasmus MC), and M. Schmidt, and M. Adank (NKI-AVL)) to assess all aspects of breast cancer in women from families with a CHEK2 c.1100delC mutation. The major aims of this nationwide study, partly under consent HEBON, is to prospectively assess (contralateral) breast cancer risk, evaluate screening, survival and breast cancer tumor biology in carrier and non-carrier women in CHEK2-positive families.

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DEPARTMENT OF NUCLEAR MEDICINE

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In collaboration with: Hester Oldenburg, Emiel Rutgers, Marie-Jeanne Vrancken Peters, Frederieke van Duijnhoven, Henk van der Poel, Bas van Rijn, Martin Klop, Alexander van Ackooij, John Haanen, Egbert Smit, Paul Baas, Joop de Langen, Margot Tesselaar, Jan Paul de Boer, Uulke van der Heide, Jeroen van de Kamer, Marcel Verheij, Jose Belderbos, Michiel van den Brekel, Regina Beets-Tan

In 2017, the department of nuclear medicine was involved in many research projects in close collaboration with clinical and pre-clinical departments. Topics of study were related to image guided surgery, immunotherapy and personalized medicine. This resulted in many scientific papers, oral presentations and a successfully defended thesis of Suzana Teixeira. Ongoing topics of research performed in close collaboration with the NET-group of University Medical Centre Utrecht (Prof. Marnix Lam, Prof. Gerlof Valk) and Zentralklinik Bad Berka (Prof. Richard Baum) were theranostics and radiomics in neuroendocrine tumors. Regarding immoPET, again new initiatives were launched in close collaboration with the departments of Thoracix Oncology (NKI-AVL) and nuclear medicine of the Free University in Amsterdam and the University Medical Center in Groningen. Two projects were granted by KWF and ZonMW (pi's Wouter Vogel and Erik Vegt). Finally, the project on Cherenkov light imaging, a close collaboration with Lightpoint Medical, Philips and the University of Twente (Prof. Cees Slump) and granted by KWF/STW, has been started and the first results will be presented at the end of this year.

Imaging in urogenital malignancies

FDG-PET/CT imaging has high potential for pelvic and distant staging of penile cancer, but published data regarding its clinical accuracy and impact are scarce. The only dedicated study of this subject was published in 2009 by our group. In 2017 we have done an extensive literature review and designed a study to confirm the utility of PET in a much larger cohort of patients. Also, we are studying the use of PET in bladder cancer.

Imaging in upper gastrointestinal malignancies

Both FDG-PET/CT and diagnostic laparoscopy (DLS) were recently included in the new Dutch guidelines for the treatment of gastric cancer, as staging modalities for advanced (T3-4) tumors. We received a grant from ZonMW to evaluate the impact and cost-effectiveness of FDG-PET/CT and DLS in patients with advanced gastric cancer, in cooperation with UMCU and RadboudUMC. This 'PLASTIC' study is a multicenter study including patients from all gastric cancer centers in the Netherlands, which will be open from 2017 til 2019.

Image-guided radiotherapy

Modern image-guided radiotherapy increasingly relies on functional imaging with PET- and SPECT-scans, for example to better select patients for treatment with curative intent or to define target volumes that need to receive specific dose levels. This development leads to new requirements for

the availability and quality of relevant imaging procedures. We performed a national patterns-of-care evaluation in the Netherlands, in collaboration with UMCU. The results of this study illustrated that access to functional imaging with PET/CT (and mpMR) for radiotherapy purposes can now be considered standard of care in the Netherlands. However, it was concluded that these procedures should be supported by collaborating technologists from the two departments and by facilities for multimodal delineation, and that for several specific clinical situations the interpretation of images may benefit from further standardization. To further support safe and adequate introduction of these procedures, a subsequent study was performed to determine the best training methods for observers in PET/CT based radiotherapy target definition for NSCLC. This study concluded that training should be intensified with repetitive supervised delineations, to reach optimal accuracy and observer agreement. A notable demonstration of functional imaging for radiotherapy planning is the discovery of a currently unknown macroscopic salivary gland location in the retropharyngeal area, that had never been detected by standard anatomical imaging modalities. This new knowledge will be tested in toxicity evaluations, and may contribute to better quality of life after radiotherapy of the head and neck for future patients. To further optimize the balance between tumor control and toxicity, we aim to involve lymph drainage patterns in the definition of elective nodal fields.

Neuroendocrine tumors

^{68}Gallium-DOTATATE PET/CT imaging is standard for diagnostic assessment in neuroendocrine tumor (NET) management in our institute. Current research focusses on optimization of NET imaging. In a clinical trial investigating the influence of lanreotide on ^{68}Ga-DOTATATE PET/CT the last patient has been included and data analysis is ongoing. Retrospectively the influence of the peptide that is radiolabeled on scan quality is being investigated. Furthermore, the predictive value of ^{68}Ga-DOTATATE PET/CT on progression free- and overall survival is evaluated.

In 2016 treatment of metastatic NET with ^{177}Lutetium-DOTATATE was started in our institute. Dosimetry is expected to optimize treatment and to move towards personalized medicine. In this view, a research collaboration with DOSIsoft (France) has been started to evaluate dosimetry in ^{177}Lu-DOTATATE therapy in patients treated in the AVL. In collaboration with the Zentralklinik Bad Berka (Germany), the association between dosimetry and uptake on diagnostic molecular imaging and survival after ^{177}Lu treatment were retrospectively evaluated.

Immuno-PET

With the introduction of new immune modulating therapies, molecular imaging has gained an important role in selecting patients and assessing response. Immuno-PET using Zirconium-89 (^{89}Zr) coupled to new therapeutics enables *in vivo* evaluation of biodistribution and tumour targeting. This approach was implemented as substudy of the BP28920 (M13CEA) phase I trial with CEA-IL2v (NCT02004106). The results of this recently completed study confirmed CEA-mediated tumour accumulation of CEA-IL2v at dosages above 20mg. Physiological uptake was seen in the spleen, live rand lymphoid tissues, independent of CEA-status. Repeated imaging during therapy (cycle 1 versus cycle 4) indicated an altered

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biodistribution and tumour accumulation during treatment. For the first time, it was shown that Immuno-PET during different stages of therapy improves the understanding of drug pharmacokinetics. At present new studies are being initiated with PD-L1 and PD-1 directed imaging in lung cancer, melanoma and glioblastoma. For very specific clinical questions Immuno-PET is presently also used in a clinical setting. If for instance intrapatient heterogeneity of Her-2 expression is expected, or when lesions cannot be biopsied, ^{89}Zr-Trastuzumab PET can be performed to give insight into Her2-status of lesions. Based on the accumulation patterns on the PET therapy can be adjusted for that specific patient.

Intraoperative Cherenkov imaging

In 2016, the KWF-STW project 'Cerenkov Luminescence Imaging (CLI) during prostate cancer surgery using Gallium-68 PSMA' started to address this very problem. Complete surgical excision remains challenging, especially in stage T3 tumours, as the surgeon is unable to distinguish between cancerous and non-cancerous tissue during surgery. In a substantial number of men (11-38%) cancer is left behind. The proposed research is intended to combine two emerging technologies, CLI and ^{68}Ga-PSMA, to assess whether they provide a feasible intra-operative imaging technique for prostate cancer surgery.

The radiotracer ^{68}Ga-PSMA is already successfully used at our department to detect prostate cancer using the large PET-scanners. With this radiolabelled small molecule we are able to detect small prostate cancer lesions (>5mm) with high sensitivity. However, the large PET-scanners used for the diagnosis and follow-up are impractical for use in an operating room. In addition to ionizing radiation, certain isotopes also produce a very low intensity light signal (cherenkov light). Our collaborative partner Lightpoint Medical Ltd was the first company in the world to develop an approved CLI device for cancer surgery. After an initial feasibility study to assess breast cancer margins with Fluor-18 (^{18}F) FDG at Guys Hospital London, we are planning to use this technique to assess surgical margins in prostate cancer. Currently, the first technical validations are being performed in close collaboration with our second project partner the Twente University. The initial results suggest that the light yield of the isotope is 15-20x higher compared to the ^{18}F signal, suggesting that application of this technique for prostate cancer surgery is within reach.

Cisplatin imaging

Cisplatin based chemotherapy or chemoradiotherapy is used in the treatment of many different types of cancer. With the development of radiolabelled cisplatin (^{195m}Pt-cisplatin) we hope to better predict therapy outcome and side-effects such as nephrotoxicity. This is a collaboration with NRG, Petten, which produces ^{195m}Pt and synthesizes ^{195m}Pt-cisplatin. In the past year animal experiments were performed to investigate imaging, efficacy, and toxicity of ^{195m}Pt-cisplatin. Currently a GMP synthesis is being developed by NRG and a clinical pilot study will be initiated in our department.

Sentinel node in breast cancer

During the last decade, indications for the sentinel lymph node procedure are extended to patients with more locally advanced breast cancer receiving neo-adjuvant chemotherapy,

multicentric/multifocal breast cancer, and patients with local breast cancer recurrence after breast conserving therapy. At present, the impact of these clinical indications and other clinicopathological characteristics on non-visualisation of sentinel lymph nodes on the pre-operative lymphoscintigram are evaluated. Furthermore, other techniques are being studied to simplify and/or improve the sentinel lymph node visualization and identification.

DEPARTMENT OF PATHOLOGY

Pathology is all about diagnosing the nature of disease processes, to guide clinical decision-making and optimize personalized and precision treatment of cancer patients. The department of pathology of NKI has the mission to provide along these lines cutting edge diagnostics for current patients visiting our institute, while at the same time focusing research efforts aimed at developing cancer diagnostics of the future, which we foresee to be very much biomarker based. Here our challenge is to generate as much relevant information from tissue, cell and DNA samples aimed at the best personalized treatment for patients today and in the future.
Important questions to be answered relate to finding, validating, and implementing prognostic and predictive biomarkers, combined with tumor classification issues. The department will sustain and extend its high level of diagnostic service and is further developing its role as a key player in translational research. Important key assets to this are Core Facility Molecular Pathology which is key to tissue biobanking as well as support of clinical and translational studies. Most staff members are actively involved in multidisciplinary research activities. The medium and long-term team efforts are briefly described below. The translational research by the Translational Gastrointestinal Oncology group, with Gerrit Meijer as principal investigator is carried out in the Division of Diagnostic Oncology and the research by Jelle Wesseling as principal investigator is carried out in the Division of Molecular Pathology. The progress of these research lines can be found in the first part of this report.

MOLECULAR PATHOLOGY OF BREAST CANCER

Jelle Wesseling, Esther Lips, Petra ter Brugge, Marlous Hoogstraat, Lotte Elshof, Sophie Bosma, Mette van Ramshorst, Emilie Groen, Mathilde Almekinders, Lindy Visser

Finding the balance between over and undertreatment of breast Ductal Carcinoma In Situ (DCIS)

A major concern in breast cancer management is the overdiagnosis and hence overtreatment of ductal carcinoma in situ (DCIS), a common breast cancer precursor. However, most DCIS lesions will never make it to fatal disease. Such lesions actually do not need treatment. To distinguish which DCIS lesions may ever turn into potentially lethal disease and which ones do not, it is first essential to estimate the magnitude of the risk of overtreatment. Therefore, we conducted epidemiological studies to evaluate the risk of subsequent ipsilateral and contralateral invasive breast cancer. To assess the prognostic role of screen detection, we studied mortality in a population-based cohort of 9,799 women

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treated for primary DCIS between 1989-2004 in the Netherlands with a median follow-up of 9.8 years, and made a comparison with the general population. The absolute breast cancer mortality rates were low and declined over time. Increased relative risk of death from breast cancer was found especially in patients 40 years at DCIS diagnosis. For women older than 50 years, the risk of breast cancer death was low and did not counterbalance the risk of lower rates found for other causes of death, indicating a healthy user effect among women older than 50 years diagnosed with DCIS. In addition, we are identifying biomarkers associated with progression of DCIS into breast cancer. Therefore, we compared DCIS samples from 200 patients developing ipsilateral breast cancer with 500 matched DCIS samples of women without invasive recurrence during a ten year follow up period. Staining for ER, PR, HER2, p16, and p53 has been performed. Gene expression profiling and mutation panel sequencing is ongoing. We are also studying, the immune infiltrate of DCIS, aiming at the detection of T-cells, B-cells, mast cells, neutrophils, macrophages, plasma cells and NK-cells. Ultimately, we aim to develop an individualized risk prediction model for DCIS patients by integrating the data to distinguish indolent from aggressive DCIS. This will eventually be essential to guide DCIS management. We hypothesize that it will be safe to offer women with innocent DCIS lesions active surveillance only. Validation of such a model can be performed in our prospective DCIS study, the Low-Risk DCIS (LORD) trial. This is a randomized controlled, phase 3, non-inferiority trial to evaluate the safety of active surveillance in 1240 women with low risk DCIS. The LORD trial is coordinated by the BOOG and EORTC. The trial is open since summer 2017 and the first patients have been randomized. Another major achievement in 2017 was the start of the PRECISION (Prevent DCIS Invasive Overtreatment Now) initiative, a Cancer Research UK Grand Challenge funded initiative, in which we strength our forces with international top experts to answer the DCIS dilemma. In this initiative we will deeply characterize three large retrospective DCIS series, in order to understand which DCIS will develop into breast cancer, and will not.

Mechanisms of response and resistance in patient-derived xenograft models of triple-negative breast cancer

We have generated patient-derived xenograft (PDX) models for BRCA1-deficient triple negative breast cancer (TNBC) and used these to test response to alkylating agents and PARP inhibitors. Initially, these models respond well to such treatments, but eventually resistance develops frequently. Resistance mechanisms include genetic rearrangements or demethylation of the BRCA1 promoter. Both mechanisms restore full length BRCA1 expression. Strikingly, response was not directly correlated to BRCA1 expression in a series of 24 TNBC PDX models treated with cisplatin (collaboration with the Curie Institute, Paris, France). In a small subset of these models, response did correlate with RAD51 focus formation. Additional analyses of candidate predictive factors are ongoing, as well as validation of the results in mice.

Development of clinically useful molecular tests to predict chemotherapy response of primary breast cancers

Within the neoadjuvant chemotherapy program, we aim to develop tests predicting response to preoperative chemotherapy. Since 2004 we collect pre-treatment biopsy

material and clinical data from all patients scheduled to receive neoadjuvant chemotherapy in the NKI-AVL, resulting now in a database and sample collection of 1700 patients. A clinical biomarker test developed in this program, the BRCA1-like MLPA assay, is now used in three clinical trials to select patients for high dose chemotherapy (in collaboration with Petra Nederlof). In close collaboration with the computational cancer biology group (Lodewyk Wessels) we identified three major tumor processes in triple negative breast cancer that allow us to stratify tumors into subtypes associated with response to chemotherapy and long-term survival. These subtypes could be validated in an adjuvantly treated cohort from the NKI-AVL. Especially tumors with a high proliferation and high expression of immunity related genes showed very high response rates in the neoadjuvant setting (79% pCR, n=28) and excellent long-term survival in the adjuvant dataset (no recurrences, n= 24). In another project we performed deep sequencing of matched samples taken before and after neoadjuvant chemotherapy of 21 patients. By comparing somatic mutations, copy number alterations and gene expression levels between 'before' and 'after' samples from the same patient, we aim to study the effect of chemotherapy on breast tumors and to identify potential resistance mechanisms. This project has yielded several potentially interesting findings that we are currently following up. In collaboration with the medical oncology department (Sjoerd Rodenhuis, Gabe Sonke) we aim to identify biomarkers for trastuzumab response (primary endpoint is pathologic complete response in the breast and lymph nodes). For this purpose we will analyze mutation data, gene expression data and protein data of the primary tumor (pretreatment) in a cohort of ~100 patients with stage II or III HER2-positive breast cancer. The data will be analyzed with a systems biology approach for studying drug response in cancer (collaboration with Lodewyk Wessels).

Defining radiotherapy sensitivity of breast cancer

To find biomarkers predictive of radiotherapy response for invasive breast cancer we performed RNA sequencing from a preoperative radiotherapy trial (PAPBI trial) (collaboration with Harry Bartelink, Marc van de Vijver and Paula Elkhuizen). 48 pretreatment biopsies and 24 post-treatment surgery specimens were analyzed to find a signature for radiotherapy response. Unsupervised hierarchical clustering did not cluster responders vs. non-responders, but most pre-and post-treatment samples clustered did. Comparison between pre-treatment biopsies and resection specimens revealed expression differences of genes involved in cell cycle, DNA repair and apoptosis. This radiotherapy response profiles will be validated in the young boost trial.

CHARACTERISTICS OF HEREDITARY NON- BRCA-MUTATED BREAST CANCER

Esther Lips, Rashmie Debipersad, Frans Hogervorst, Petra Nederlof

In our research line we try to characterize hereditary breast cancers. Since 2005 we are performing genomic profiling of those tumors, resulting now in a database with over 1000 of tumors profiled. Using these data we are currently working on the following projects: 1. We characterized a group of estrogen receptor (ER) positive BRCA1 mutation carriers, and found that on a genomic level these tumors are highly similar to ER-positive BRCA2 mutated tumors and should not be considered sporadic

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cases. This suggests that the new classes of BRCA1 deficiency targeting drugs can also be applied in ER-positive BRCA1 mutated cancers. 2. Germline mutation testing for CHEK2 has entered the clinic last year. It is considered to be a risk factor for breast cancer. We are currently analyzing genomic profiles of CHEK2 mutated tumors. This analysis could identify specific genomic aberrations associated with a higher breast cancer risk. 3. Together with MRC-Holland we develop a new assay to facilitate combined testing for a BRCA1-like and BRCA2- like genomic profile. The assay has been developed for NGS platforms, and validation is currently ongoing. 4. There are several indications that methylation patterns of genomic DNA may be different in BRCA-mutated tumors. Therefore, we performed methyl-sequencing on a genome wide level on breast cancer samples with a BRCA1 mutation, with BRCA1 promoter methylation and control samples. Results are now being analyzed.

GASTROINTESTINAL PATHOLOGY

IMMUNOTHERAPY, IMMUNE INFILTRATE AND GASTROINTESTINAL CANCER

The department of pathology actively participates in research projects within the field of gastrointestinal immunopathology. These projects are done in collaboration with many researchers and clinicians at NKI-AVL. These projects include the following: (1) Tumor-reactivity of infiltrating T cells in colorectal cancer: whether T cell infiltration in colorectal cancer is an epiphenomenon in response to an inflammatory environment or whether it is truly based on tumor antigen recognition; (2) Immune-checkpoint-inhibition associated colitis: Correlation between symptoms, endoscopic features, histological features and response to treatment; (3) The NICHE study, the PANDA study and the TARZAN study aim at establishing the role of immune checkpoint inhibitors in the treatment of colon cancer, gastric cancer and rectal cancer, respectively. We will focus on the immune response in the biopsy and resection specimens of these patients. Immune infiltrate characterization and tumor cell characteristics will be studied and quantified before and during treatment and correlated to other biomarkers and patient characteristics.

PERITONEAL METASTASES OF GASTROINTESTINAL CANCER

A substantial group of patients with gastrointestinal cancer develops peritoneal metastases. There are many ongoing research projects, also in collaboration with researchers and clinicians at AMC, UMCU and abroad, which aim at improving the treatment and outcome of this patient group. These include the following: (1) Pathology practice variability in identifying pT4 colon carcinoma; (2) Correlation between various T4 subtypes and risk of developing colorectal peritoneal metastases; how to define the pT4 variable; (3) Signet ring cell carcinomas of the colorectum and peritoneal carcinomatosis: is prognosis and therapy response correlated with signet ring cell carcinoma subtypes; (4) Histopathological and molecular classification of colorectal cancer and corresponding peritoneal metastases; (5) Prognostic markers of colorectal carcinoma metastatic to the peritoneum; (6) Clinicopathological characteristics and survival of patients with pseudomyxoma peritonei arising from the appendix.

GASTRO-ESOPHAGEAL CANCER

Esophageal adenocarcinoma (EAC) is an aggressive cancer with a variable response to neo-adjuvant therapy and poor overall prognosis. Neoadjuvant chemoradiotherapy (nCRT) according to CROSS protocol is a standard therapy for EAC in the Netherlands. Although nCRT significantly improves survival of patients compared to surgery alone, a significant proportion of patients responds moderately or poor to nCRT. Therefore, new strategies for the stratification of patients into a sub-group that will likely benefit from nCRT and a sub-group that requires a different clinical approach are needed. In collaboration with clinical and translational researchers in the NKI-AVL we perform the next project:
(1). Temporal and spatial clonal evolution in esophageal adenocarcinoma in response to neo-adjuvant chemoradiation (TRACE).
Esophageal adenocarcinomas have one of the highest mutation rates observed in human cancers, and have high levels of inter- and intra-tumoral heterogeneity. EAC is characterized by chromosomal instability and high rates of somatic copy number alterations (SCNA) of genes encoding tumor suppressors and tumor promoters. Although some efforts are made to describe the influence of chemotherapy on clonal dynamics of the EAC, the effect of nCRT on clonal evolution in EACs is largely unknown. Therefore, we will investigate the temporal and spatial clonal evolution in EAC patients in response to nCRT.
(2) We also collaborate with researchers from Academic Medical Centres in the Netherlands (AMC, Erasmus MC, VUmc) to set up a research consortium in order to build and analyze a large database with RNA seq and DNA seq data of biopsies of a cohort of patients with EAC treated with CROSS protocol.
We also participate in the research initiated by other departments at the NKI-AVL. These include the following: (3) Motion and early tumor response measurement in esophageal cancer: correlation of pathology results with imaging using fiducial markers; (4) Molecular characterization of diffuse type gastric carcinomas arising in *CDH1* mutation carriers; (5) Preoperative Image-guided Identification of Response to neoadjuvant chemoradiotherapy in Esophageal cancer (PRIDE).

NEUROENDOCRINE TUMORS (NET)

The NET research group consists of a collaboration between oncologists, surgeons, pathologists and other researchers from the NKI-AVL and UMC Utrecht. We conduct both clinical research and basic and translational research. More specifically, in 2017 we initiated a Parelsnoer project to collect biomaterials from NET patients nationwide; we hope to officially launch this project in 2018. Also we started a collaboration with the Hubrecht Institute to collect fresh tissue from NET patients to create organoids. We will generate a 'living biobank' of gastro-intestinal and pancreatic (GEP) NET organoids. The organoids will be used for genetic, epigenetic, and drug sensitivity analysis.

MOLECULAR CHARACTERIZATION OF RADIOTHERAPY AND CHEMOTHERAPY ASSOCIATED GASTROINTESTINAL NEOPLASIA IN HODGKIN LYMPHOMA SURVIVORS

Hodgkin lymphoma (HL) survivors who have been treated with infra-diaphragmatic radiotherapy and/or high dose procarbazine have an increased risk of developing colorectal cancer (CRC) compared with the general population. Within NKI-AVL, and in collaboration with researchers at Erasmus MC, a multidisciplinary team has since 2013 aimed at providing insight into the pathogenesis and clinical perspectives of gastrointestinal neoplasia in Hodgkin lymphoma survivors. We have demonstrated a higher frequency of microsatellite instability among therapy related colorectal carcinomas, which results from somatic mismatch repair gene double hits. We have also shown that therapy related gastric carcinomas are more frequently of the genomically stable subtype, which was associated with prior anticancer treatment. Collaboration with the US National Cancer Institute for molecular profiling of therapy related gastric cancer has also been established. Furthermore, through surveillance colonoscopy we have demonstrated higher prevalence of advanced colorectal neoplasia and serrated polyposis syndrome among Hodgkin lymphoma survivors. Among other projects, we aim to extend our studies to molecularly characterize therapy related small bowel carcinomas and esophageal squamous cell carcinomas.

THORACIC PATHOLOGY

LUNGSCAPE-PROJECT DESIGNED BY EUROPEAN THORACIC ONCOLOGY PLATFORM (ETOP)

Kim Monkhorst, Petra Nederlof, Paul Baas

This project aims for molecular characterization of a large European cohort (2000-2400) of stage I-IIIB resected NSCLC. NKI-AVL archival FFPE material of resection specimens of non-small cell lung carcinomas of a group of approximately 70 patients is analysed for a panel of molecular characteristics. To start with, EML4-ALK translocation was analysed by IHC and positive cases were analysed by FISH. Currently, c-MET, PTEN and PDL1 analyses were implemented as a next step in this project.

Identifying novel targets in solid malignancies: FGFR1-3 and PD-L1

Willemijn Theelen, Jeroen de Jong, Stefan Willems, Hugo Horlings, Ed Schuuring, Hans Blauwgeers, Annegien Broeks, Michel van de Heuvel

There is a strong incentive for improvement of systemic treatment of many solid malignancies. Personalized treatment, using drugs that target activating mutations have shown to improve therapy. Also novel immunotherapeutics targeting immune checkpoints have shown promising results. Often extensive molecular profiling of the tumor is required to identify the right target that predicts. FGFR3 was recently identified in our first NSCLC next generation sequencing screens to be a potential novel target. In the initial cohort two samples showed a FGFR3-TACC3 translocation. In one of these samples the FGFR3-TACC3 fusion product was already confirmed by PCR. Both samples showed to have a high FGFR3 expression as tested

by immunohistochemistry. TMA's of head and neck squamous cell carcinoma, urothelial carcinoma and NSCLC samples will be used to select positive cases which will be further investigated. PD-L1 was recently identified as a target for immunotherapy. Currently clinical trials are being performed in advanced stage NSCLC to assess the efficacy of at least six clinically active anti- PD1 and PD-L1 monoclonal antibodies. For PD-L1 a series of early stage NSCLC will be screened (300patients), but also TMA's of other thoracic malignancies, H&N, and bladder carcinoma will be screened. Data will be used to design a neo-adjuvant trial in NSCLC. If data on other solid malignancies are promising a proof of principal trial in other solid malignancies can be designed.

MOLECULAR DIAGNOSTICS PROJECTS:

Clinical characteristics and treatment outcome in a large multicenter observational cohort of PDGFRA exon 18 mutated gastrointestinal stromal tumor (GIST) patients

S Farang, Hester van Boven, Petra Nederlof, Neeltje Steeghs

PDGFRA D842V mutated GISTs are known for their insensitivity to imatinib. However, in clinical practice responses have been observed in some patients. We analyzed the natural history and treatment outcomes in a cohort of PDGFRA exon 18 mutated GIST patients. A retrospective cohort study was conducted in PDGFRA exon 18 mutation GIST patients treated in 6 expert centers in the Netherlands and the United States. Two independent radiologists assessed radiological response to imatinib according to Choi's criteria in all patients with measurable disease treated with imatinib in neo-adjuvant or palliative intent. Seventy-one patients with PDGFRA exon 18 mutation were identified of whom 48 patients (69%) had a D842V mutation. Twenty-two (45.8%) D842V-mutated GIST patients received imatinib treatment, 16 had measurable disease. Fourteen out of the 23(60.9%) patients with non-D842V mutations received imatinib treatment, 8 had measurable disease. Two out of 16 (12.5%) D842V-mutated GIST patients had partial response, 3 patients (18.8%) had stable disease and 9 patients (56.3%) had progressive disease as best response. Two patients did not have follow up CT scans to assess response. Six out of 8 (75%) patients with non-D842V exon 18 mutations had partial response and 2 (25%) had stable disease as best response. Patients with D842V-mutated GISTs can occasionally respond to imatinib. In the absence of better therapeutic options, imatinib should therefore not be universally withheld in patients with this mutation.

DATA SHARING PROJECTS:

AACR GENIE project: Powering Precision Medicine through an International Consortium

Mariska Bierkens, Jan Hudecek, Emile Voest and international collaborators

We participate in curating and sharing clinico-pathological and genomic data of routinely diagnosed cancer patients within "The AACR Project GENIE project". AACR Project (Genomics Evidence Neoplasia Information Exchange (GENIE) is an international data-sharing consortium focused on generating an evidence base for precision cancer medicine by integrating clinical-grade cancer genomic data with clinical outcome data for tens of thousands of cancer patients treated at multiple institutions worldwide. In conjunction with the first public data release from approximately 19,000 samples, we describe the goals, structure, and data standards of the consortium and report conclusions from high-level analysis of the initial phase of genomic data. We also provide examples of the clinical utility of GENIE data, such as an estimate of clinical actionability across multiple cancer types (>30%) and prediction of accrual rates to the NCI-MATCH trial that accurately reflect recently reported actual match rates. The GENIE database is expected to grow to >100,000 samples within 5 years and should serve as a powerful tool for precision cancer medicine.

BRCA1/2 RELATED PROJECTS:

Clinical significance of common Dutch BRCA1 variants

S Mogadashi, C van Asperen (LUMC), Petra Nederlof, Frans Hogervorst, Lizet van der Kolk

Clinical significance of common Dutch BRCA1 variants; application of the multifactorial likelihood model and correlation with functional data. The aim of this study is to assess pathogenicity of the most common BRCA1 variants identified following patient referral to clinical genetic centres in the Netherlands. We applied an integrated approach using multifactorial likelihood analysis, including not only assessment of variant segregation in families and breast tumour histopathological features, but also array-comparative genomic hybridization as a new component of the model.

Copy number signatures of BRCA1 and BRCA2 association across breast and ovarian cancer

P Schouten, Lodewyk Wessels, Sabine Linn, Petra Nederlof, Esther Lips

The *BRCA1* and *BRCA2* genes serve important roles in error-free DNA repair of DNA double strand breaks through homologous recombination. Germline inactivating mutations confer a large risk of developing breast and ovarian cancers that are deficient in DNA repair. Error-prone DNA repair subsequent to BRCA inactivation was found to leave traces in DNA copy number aberration (CNA) profiles of such tumors. Previously, breast cancer classifiers were trained that predicted the association with *BRCA1* and *BRCA2* mutated cancer based on the CNA profile and that proved to be predictive for benefit of high dose double strand break inducing chemotherapy due to the underlying DNA repair defect. Therefore we trained *BRCA1* and *BRCA2* classifiers on 50 *BRCA1* mutated, 10 *BRCA2* mutated and 13 non-familial ovarian cancers and investigated whether tumor type and mutation type independent classifiers could be trained.

Clustering of low and moderate risk alleles rather than a recessive high risk gene in non-BRCA1/2 sib trios affected with breast cancer

F Hilbers, P Devilee, C van Asperen (LUMC), Petra Nederlof, Frans Hogervorst

Breast cancer risk is approximately twice as high in first-degree relatives of female breast cancer cases than in women in the general population. Less than half of this risk can be attributed to the currently known genetic risk factors. Recessive risk alleles represent a relatively underexplored explanation for the remainder of familial risk. To estimate the polygenic effect of common low risk variants we analyzed non-BRCA1/2 breast

cancer families in which at least three siblings were affected, while no first-degree relatives of the previous or following generation had breast cancer. Germline DNA from one of the siblings was subjected to exome sequencing, while all affected siblings were genotyped using SNP arrays in order to assess haplotype sharing and to calculate a polygenic risk score (PRS) based on 160 low risk variants. These findings suggest that the familial aggregation is, at least in part, explained by a polygenic effect of common low risk variants and rarer intermediate risk variants, while we did not find evidence of a role for novel recessive risk alleles.

Primary Molecular Profiling in NSCLC using Plasma cfDNA from the LEMA cohort, the POPSTAR study.

Kim Monkhorst; Daan van den Broek; Michel van den Heuvel; Robert Schouten, Valesca Retel; Veerle Coupé

We want to investigate if cfDNA analysis from plasma can be used for pre-treatment comprehensive molecular profiling including EGFR in stage IV lung cancer patients, what are the associated costs of cfDNA analysis and in what scenario cfDNA analysis is cost effective. We will investigate clinical validity and cost effectiveness of plasma cfDNA NGS analysis in the diagnostic and molecular workup of patients with stage IV NSCLC, and determine how this method best can be positioned next to SOC tissue analysis. To this end we will analyze plasma cfDNA with the AVENIO platform from 200 patients that have undergone full molecular profiling by standard of care (SOC) procedures in different hospitals in the Netherlands in the LEMA project. Inclusion will be from Q1 2017 – Q2 2018.The primary aim of the proposal is to determine the optimal position of plasma NGS cfDNA analysis in the diagnostic workup in stage IV disease NSCLC. Secondary aims of the proposal are to determine the number of patients where the tissue biopsy analysis fails (no tissue, not enough DNA, low quality DNA, low tumor cell percentage). To determine the time from (liquid and tissue) biopsy to the final test results, the impact of cfDNA on the number of patients receiving targeted treatment, the cost effectiveness of cfDNA for primary molecular profiling in stage IV disease NSCLC, the performance / sensitivity of the AVENIO platform in stage IV disease, the concordance between tissue and plasma results, the concordance between ddPCR, the AVENIO platform and tissue analysis (based on the first 50 patients analyzed).

Ultra-deep next generation sequencing of plasma DNA to detect resistance mechanisms in patient treated with tyrosine kinase inhibitors

Kim Monkhorst, Daan van den Broek, Michel van den Heuvel, Karlijn Hummelink, Victor Velculescu (JHU)

Tumors with oncogenic drivers are known for a substantial clinical response to targeted therapy, such as tyrosine kinase inhibitors (TKIs). Unfortunately, most tumors develop, often multiple, resistance mechanisms against these drugs. The most common mechanism of resistance involves mutations in the kinase domain that alters the binding kinetics of the TKI. Second, amplification of the driver itself is reported as a resistance mechanism. Third, the development of a second oncogenic driver, with or without loss of the original driver can drive resistance. These different resistance mechanisms dictate different treatment strategies and are crucial in predicting therapy response. To analyze these mechanism of resistance, a tumor biopsy is needed. Unfortunately, this is an invasive procedure with a failure rate of 20-30%. Liquid biopsies are an attractive alternative and provide a bio source for tumor DNA or RNA (e.g. circulating tumor DNA (ctDNA) and platelet RNA but also urine samples showed comparable sensitivities). These minimally invasive 'liquid biopsies' are easy to repeat and are a fast way to investigate TKI resistance mechanisms. To detect resistance multiple platforms exist e.g. ddPCR, BEAMING and NanoString. Although these techniques are very sensitive they unfortunately do not allow broad panels and detection of fusion proteins and / or amplifications. Targeted ultra-deep next generation sequencing (20.000x) however will allow detection of fusion proteins (e.g. ALK1, ROS1 and RET) and amplifications). NGS therefore allows us to detect multiple resistance mechanisms with one comprehensive test

Molecular analysis using pleural fluid with ddPCR

Kim Monkhorst, Daan van den Broek, Michel van den Heuvel, Karlijn Hummelink

In NSCLC patients, pleural fluid is associated with a M1a status or stage IV disease according to the WHO classification. In this research project we want to analyze pleural fluid of stage IV NSCLC patients with ddPCR to find primary driver mutations or mutations related to TKI resistance. Usually the cell pellet is used for molecular analysis but this is hampered by low tumor cell percentage and low allele frequencies of resistance mutations that result in low sensitivity. Preliminary data shows that next to the cell pellet the fluid itself contains high concentrations of cell free DNA (cfDNA) that can be used for analysis. We hypothesize that cfDNA in pleural fluid could be a valuable tool in the diagnostic process of NSCLC patients, especially when analyzed with ddPCR. This may lead to less invasive procedures and a faster (molecular) diagnosis.

GYNECOLOGICAL PATHOLOGY

USe of Molecular biomarkers to refine the diagnosis and treatment for (metastatic) breast and ovarian cancer

Marleen Kok, Carolien Smorenburg, Gabe Sonke, Sabine Linn, Christianne Lok, Willemien van Driel, Frederic Amant, Katrien Berns, Ton Schumacher, René Bernards, Marc van de Vijver, Hugo Horlings

With the introduction of novel high throughput genomic technologies, it is possible to analyze a complete cancer genome at an affordable cost and reasonable time. Therefore, classification of malignancies based on genetic alterations is emerging. This will lead to improvement of stratification of patients for targeted and immunotherapies. The current challenge is to facilitate the implementation of screening of a patient's cancer genome for diagnostic and/or therapeutic purposes. Understanding these technologies to profile DNA, coding and noncoding RNAs and proteins, will be crucial for pathologists to provide expert support to every physician. Together with a team of excellent medical oncologists, surgeons, pathologists, molecular biologist, bioinformaticians, technicians and with support of the central facility of molecular pathology

and bio banking we aim to apply molecular biomarkers to refine the diagnosis and treatment of (metastatic) breast and ovarian cancer. The main emphasis will be on identification of genetic make-up of the tumor contributing to a poor prognosis for the patient and therapy resistance, although we also work on identification of women at high risk for ovarian cancer through somatic mutations in precursor lesions and liquid biopsies Specific aims are:

1. Identification of cancer-immune related factors that can predict clinical response to immunotherapy in metastatic breast and ovarian cancer patients

Immunotherapies are revolutionizing cancer treatment by producing durable responses in patients with metastatic disease. However, for breast and ovarian cancer the response rates presented so far are limited to 5-20%. Further knowledge on the interaction between tumor cells and the immune system will be crucial to improve immunotherapeutic for the various breast and ovarian cancer subgroups and to develop predictive tests for response. The main objectives of this research line are I) to unravel the interactions between the cancer-immune environment and genetic features in large retrospective breast and ovarian cancer patients; II) to determine the predictive power of cancer-immune related factors in metastatic breast and ovarian cancer patients treated with (neo-) adjuvant immunotherapy (TONIC and N16OPE trial).

2. Uncovering the molecular pathways that lead to resistance / exceptional response to ERBB2 directed therapies.

2.1 Exceptional response to ERBB2 directed therapies

Until the introduction of the anti-HER2 drug trastuzumab, metastatic breast cancer (MBC) was generally considered as an incurable disease with short survival. However, some patients with HER2-positive MBC treated with trastuzumab have an exceptional response and survive over ten years. We therefore aimed to retrospectively evaluate which clinical and pathological characteristics are associated with long-term survival in patients with HER2-positive MBC treated with a trastuzumab-based treatment. We included all patients with histologically proven HER2-positive MBC treated with trastuzumab-based therapy in the NKI between January 2000 to January 2015. We identified 172 patients with a median age at diagnosis of MBC of 51 years (range 27-82). Preliminary analyses were performed on 138 patients. Median follow-up since diagnosis of MBC was 9 years (range 0-13). In multivariable analyses, factors associated with long-term survival were oligo-metastases, single-organ metastases, no skin metastases, no prior trastuzumab, and achievement of radiologic complete response on treatment. Thirty patients (17%) achieved rCR. In this group, the estimated 10-year survival was 61% (95% CI 32-77%). Achieving rCR is the strongest predictor for long-term survival in patients with HER2-positive MBC. This finding advocates the strategy for administering the most effective agents as first line treatment, as is often but not always applied in clinical practice. At the moment, we have collected tumor and normal tissue from 110 primary tumors and – if available – from metastases (n=50) to analyze tumor and genetic characteristics from all NKI patients. In addition, we are collecting data from 582 patients identified in other hospitals to increase the power of our analyses and to serve as an independent validation cohort.

2.2 Resistance to ERBB2 directed therapies

Trastuzumab is currently indicated for the treatment of ERBB2 positive breast cancer in the adjuvant and metastatic setting. Therapeutic resistance poses a significant problem for the targeted treatment of patients with ERBB2 positive cancer. Understanding the molecular mechanism of anti-ERBB2 drug resistance will be instrumental to identify patients that fail to respond to the therapy upfront and help design more effective (combination) treatment strategies. Through loss-of-function shRNA genetic screens, we have previously identified several predictive markers for trastuzumab response in ERBB2 positive breast cancer (*(PTEN loss, PIK3CA mutation)*
In short, we have performed gain-of-function trastuzumab resistance screens in HER2-amplified breast cell lines and identified that GRB7 overexpression confers robust resistance. Our preliminary data indicate that GRB7 protein levels, rather than RNA levels, may serve as a predictive marker for trastuzumab response. Next, we aim to validate our findings in clinical samples from trastuzumab treated patients. We will perform GRB7 IHC on the tissue samples mentioned above (project 2.1). Clearly, this well annotated ERBB2 positive breast cancer series and TMAs that we generate in this project may provide useful resources to address other research questions relating to ERBB2 positive breast cancer.

3. Establishing a comprehensive biobank to identify predictive markers for personalized treatment in ovarian cancer patients

Prognosis of patients with epithelial ovarian cancer (EOC) is poor and survival has not changed over the past 20 years, despite extensive research on EOC. In collaboration with IKNL, 4,956 patients with EOC who underwent either primary cytoreduction or interval cytoreduction in the Netherlands were identified retrospectively. Based on the Netherlands Cancer Registry (NCR) there were 3,689 patients with high-grade serous ovarian cancer (HGSOC). For this study, a selection of HGSOC patients treated within three centers were included (600 patients). Formalin-fixed paraffin embedded (FFPE) tissue blocks are collected for analyses of the tumor microenvironment, chemotherapy response and molecular subtypes. Recently, in the NKI-AVL, an electronic biobank system was built (cBioportal), comprising clinical data, digital images, data on pathology and pathology revision, mutational analyses, available materials for research including blood, FFPE tissue and fresh frozen tissue. All data collected in the present study, will be included in cBioportal.

4. Identification of women with malignant ovarian cancer through somatic mutations in liquid biopsies

Patients with early stage ovarian cancer often present with an ovarian tumor. Differentiation malignant from benign ovarian tumors before surgery is often difficult with the currently used biomarkers. This leads to misclassification and incorrect referral to oncologic centers. Tissue biopsies from ovarian tumors could confirm malignancy preoperatively and provide guidance to referral and therapy, but these biopsies are invasive and may even cause spreading of tumor cells in the abdomen. Noninvasive sampling of "liquid" biopsies overcomes limitations of collecting tissue biopsies. Liquid biopsies contain circulating cell free tumor DNA (ctDNA in collaboration with Victor Velculescu) and tumor educated platelets (TEP in collaboration with Tom Wurdinger). So far, we have collected 80

liquid biopsies to assess genetic alterations in ctDNA and TEP using three complementary techniques: 1) deep sequencing (25,000x) of a targeted panel of 63 cancer genes in ctDNA and corresponding tumor tissue samples to assess tumor specific mutations, 2) low coverage whole genome sequencing (0,5x) of ctDNA to assess copy number alterations (NIPT in collaboration with Erik Sijstermans) and 3) mRNA profiles of TEPs. Based on power calculations, Genomic alterations will be compared between patients with a benign (n = 198) versus malignant ovarian tumors (n=66). The sensitivity of these markers will be compared to the known serum biomarkers CA-125 and HE4.

UROPATHOLOGY

Tumor characteristics in radical prostatectomy specimens to optimize focal radiotherapy

Ghazale Ghobadi, Jeroen de Jong, Uulke van der Heijde

Dose escalation and focal radiotherapy of primary prostate cancer can reduce toxicity. To optimize recognition of tumors on MR imaging – which is needed for focal therapy –, digital delineation of primary tumors and assigning Gleason scores to separate tumor foci on histopathological slides will be used as a reference.

Correlation between the location of tracer injection in the prostate and the observed lymphatic drainage pattern

Nynke van den Berg, Simon Horenblas, Jeroen de Jong, Henk van de Poel

For prostate SN procedure a hybrid tracer (ICG-99mTcnanocolloid) that is both radioactive and fluorescent, will be injected in the peripheral zone where most tumors occur. Location of the tracer injection will be correlated to tumor location examined by pathological evaluation. The goal of this study is to determine where the tracer was injected in relation to the location of the tumor and how this affected lymphatic drainage; were more often "true" tumor draining (metastasis containing) SNs identified when the tracer deposits were placed near/in the tumor compared to the intra-prostatic injection.

Integrative Androgen Receptor genomics as a read-out for recurrence risk and treatment

Suzan Stelloo, Henk van de Poel, Jeroen de Jong, Wilbert Zwart

Tumor material from prostate cancer patients will be tested for Androgen Receptor/chromatin binding profiles using ChIP-seq. In addition, other transcription factors and epigenetic histone modifications will be mapped, next to global gene expression profiles. These data will be integrated and correlated with response to treatment, to identify ADT resistance biomarkers and predictive markers for tumor recurrence. We aim to generate the most comprehensive overview of primary prostate cancer genomics. This will include Androgen Receptor/chromatin binding patterns, histone modifications and gene expression data derived from prostate tumor samples and prostate cancer cell lines. This may enable us to identify distinct predictive markers for prostate cancer recurrence and treatment resistance.

Predicting Response to Enzalutamide as a Second Line Treatment for Metastasized Castration Resistant Prostate Cancer Patients: a biomarker design study (PRESTO-study)

Suzan Stelloo, Henk van der Poel, Jeroen de Jong, Walter Prevoo, Michael Hauptmann, Ekatarina Nevedomskaya, Andre Bergman, Wilbert Zwart

Enzalutamide is a new anti-hormonal drug, which showed excellent activity as a second line treatment for patients progressing after docetaxel treatment. However, 46% of patients did not reach a 50% response on Enzalutamide and eventually all patients progressed. Biomarkers that can identify patients who will have excellent, and long-lasting responses are highly needed. In this study, we will explore the exact actions of Enzalutamide on Androgen Receptor (AR) regulation, design predictive AR/DNA binding signatures and examine the role of AR mutations and alternative growth signals in prostate cancer growth. Therefore, biopsies from bone metastases, lymph nodes or visceral metastases will be taken prior to start of Enzalutamide treatment. Possible biomarkers will be further validated in Formalin Fixed Paraffin Embedded (FFPE) primary tumor material.

Dynamics of Androgen Receptor genomics and transcriptomics after neoadjuvant androgen ablation (DARANA)

Wilbert Zwart, Suzan Stelloo, Jeroen de Jong, Andre Bergman, Henk van der Poel

To identify AR chromatin binding patterns and downstream responsive genes that hallmark distinct sensitivity to enzalutamide treatment in prostate cancer, as well as the dynamics thereof before and after treatment. The role of third generation antiandrogens in the neoadjuvant setting has not been studied. To analyze the effects of the novel antiandrogen enzalutamide on AR-responsive gene expression, tumor samples will be assessed before (biopsy) and after (resection) 6 weeks of neoadjuvant androgen ablation, and PSA and Ki-67 will be determined by immunohistochemistry. Patients will be stratified on alterations in PSA and/or KI-67 to identify alterations in AR genomic profile and downstream regulated genes that correlate with response to androgen ablation.

Core Facility Molecular Pathology & Biobanking

Annegien Broeks, Donne Majoor, Joyce Sanders, Carolien Bierman, Ingrid Hofland, Dennis Peters, Sten Cornelissen, Linde Braaf, Sanne Broersen, Wouter Kievit, Charlotte van Rooijen, Esther Holman, Jose Overwater, Astrid Vonk, Erik Hooijberg, Rianne van der Linden, Rianne van der Wiel, Dagmar Verweij

In recent years, the need for controlling the 'secondary use' of human biospecimens for research purposes at the NKI-AVL became more apparent. To ensure human material is used properly and efficiently, especially in the case of scarce, valuable samples, a facility for issue and use of NKI-AVL biospecimens according to legal issues was desired. Therefore, in 2010, the Core Facility Molecular Pathology & Biobanking (CFMPB) was founded. The CFMPB registers, coordinates, assists and facilitates research involving archived human/patient material (biospecimens), using the online Application & Request tool (ART-CFMPB, http://art.nki.nl/. This concerns all research using (secondary use) biospecimens both from the department of

Pathology (the paraffin-block archive, frozen tissue bank, fresh tissue) and the department of Clinical Chemistry (the serum and blood biobank. The facility provides professional expertise, appropriate samples and tissue based experimentation in the context of optimally controlled medical-ethical issues. Additionally ART-BAVL (http://artbavl.nki.nl/) has been released for registration and review of new Biobanks. Online links and information of both ART-CFMPB and ART-BAVL can be found on the translational Research Portal (TRP) on antonet. The CFMPB has a fully equipped and dedicated Molecular and a histology/ immunohistochemistry (IHC) lab. All routine IHC (including all diagnostic protocols) is performed using the BenchMark Ultra (Ventana, Roche) automated stainer, in close collaboration with the diagnostic pathology department. Additionally a Discovery Ultra ((Ventana, Roche) automated stainer, adaptable to a broad array of tissue testing capabilities, is available. We have the Vectra 3 scanner (Perkin Elmer) for digital pathology multi spectral imaging (coordinator Erik Hooijberg). The Vectra is a microscope enabling detection of up to six different markers in situ. Fluorescent immunohistochemistry (IF) allows for measurement of the number and position of immune cells, tumor cells, stromal cells and other components of the tumor microenvironment. A variety of multiplex IF (MPIF) antibody panels are up and running and the design of new MPIF panels can be requested Ample experience is available for the development of new antibody staining protocols. Elaboration and optimizing of staining protocols is performed in close collaboration with the requesting scientist and the involved pathologist. In 2017 90 new studies for biospecimen use were registered in ART-CFMPB, and 53 Biobank collections are registred in the NKI-AVL biobank catalogue which is also connected to the national BBMRI biobank catalogue https://catalogue.bbmri.nl/.

DEPARTMENT OF RADIOLOGY

Imaging has proven its value in personalized treatment of cancer patients. Research of the dept of Radiology is focused on multidisciplinary clinical and translational research developing and validating modern imaging technology to assess and predict treatment response. The research especially focuses on functional MRI to guide Organ preservation in rectal cancer. There are several multicenter trials in this topic running financed by the Dutch Cancer Society. Another important focus of research is multiparametric MRI. It investigates the incremental value of combining functional MR imaging biomarkers for personalised medicine. Artificial intelligence is the focus of translational research at the department of radiology. The most important of this is 'Radiomics' which entails the extraction of predictive features for treatment response from standard CT or MR image using mathematical models. An interesting imaging (in spec Radiomics) research line is in Immunotherapy. We seek for radiomics methods to better predict response to immunotherapy and aims to correlate this with molecular biomarkers. Interventional therapy plays an important role in minimal invasive cancer treatment. Critical for its success is an accurate target of the lesion. Research is focused on development of real time image fusion techniques to guide interventional treatment and navigation surgery.
The research of the department is in close collaboration with teams in NKI-AVL, Philips R&D, Medical and Technical Universities in the Netherlands, Dana Farber Cancer Institute and Harvard University, Memorial Sloan Kettering Cancer Center, Fudan University Shanghai, Karolinska University Stockholm, Catholic Universities Rome and Leuven.
The research team consists of 27 PhD students, 7 postdoc fellows and 8 postdoc staff radiologists. In 2017 the work received grants from funding organisations and has resulted in 3 dissertations.

COLORECTAL CANCER IMAGING

D Lambregts, M Maas, M Lahaye, J van Griethuysen, S Trebeschi, M vd Sande, L Min, M de Boer, M Taghavirazavizadeh, I Kurilova, M van Heeswijk, H Aerts, E Nerad, R Beckers, J Krdzalic, R Dijkhof, B Hupkens, S Assili, D Hilling, M Kusters, N Schurink, R Beets-Tan

Rectal Cancer Imaging for Organ Preservation

This research aims to develop and validate modern MR techniques for better selection and follow up of complete responders after preoperative chemoradiotherapy of rectal cancer, as well as pre-treatment prediction of response. This will allow the inclusion of a broader spectrum of patients for organ preservation (watch and wait). There are several multicenter trials all financed by the Dutch Cancer Society cancer:

- A recently completed multicenter MRI trial validating diffusion MRI.
- A recently initiated multicenter project on the development of a predictive model to predict treatment response before start of treatment
- A recently initiated 'unique high risk' project on Radiomics for treatment response prediction
- A currently running multicenter study focused on implementation of rectal organ preservation in Dutch medical centers coordinated by the NKI as the principal investigating center.
- An international prospective registry initiative (www.iwwd.org) for all 'watch and wait' patients worldwide. This project is awarded with the Bas Mulder Award from the Dutch Cancer Society.

Collaboration in rectal cancer research exists with colorectal teams in Memorial Sloan Kettering Cancer Center, Fudan University Hospital in Shanghai, Karolinska University Hospital and Catholic University Hospitals in Rome and Leuven.

Multiparametric imaging and advanced image post-processing

M. van Heeswijk completed a PhD project on the translation of these novel parametric MR techniques into practice which resulted in a dissertation in oct 2017 at Maastricht University Medical Center(MUMC). Ongoing projects include the use of advanced image postprocessing methods (texture analysis and Radiomics) and assessment of imaging biomarkers from multiparametric functional MRI including diffusion-weighted imaging, dynamic contrast-enhanced MRI and magnetization transfer imaging. Aim is to develop a robust multiparametric predictive model to predict treatment response and outcome. This research is funded by two research grants from the Dutch Cancer Society and (partly) done in collaboration with Philips R & D Best and Aachen aiming to develop software tools to support

these type of analyses and translate it into tools for clinical practice.

WHOLE-BODY IMAGING IN ONCOLOGY

D Lambregts, M Lahaye, M Maas, I van 't Sant-Jansen, M. Engbersen, L Min, J van Griethuysen, N Schurink, S Trebeschi, R Beets-Tan

Multimodality and Multiparametric Imaging

This research line includes several institutional multidisciplinary collaborative projects within the departments of Nuclear Medicine, Radiation Oncology, Medical Oncology, Surgery and Gynecology. It focuses on the combined, multimodality and multiparametric imaging assessment of different tumour types (colorectal, gynecological, breast and urogenital malignancies) in order to boost diagnostic performance for tumour staging, response evaluation / prediction and prognostication. Imaging biomarkers from MRI, CT and PET will be incorporated and combined to validate the incremental value of each imaging biomarker from a whole-body, multi-modality and multiparametric perspective. This research is a necessary preparatory step for research validating the true hybrid PET-MRI.

MRI of peritoneal carcinomatosis

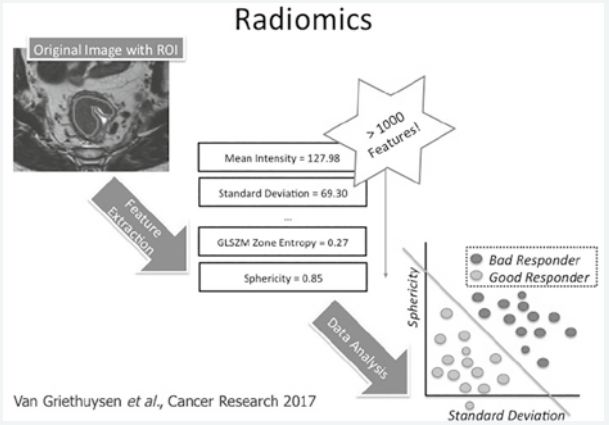
In 2016 a Peritoneal Carcinomatosis Research group was formed in NKI-AVL consisting of teams from the department of Radiology, Surgery, Gynaecology and Pathology. The department of Radiology initiated a study to determine the diagnostic performance of DWI-MRI for the detection of patients with peritoneal carcinomatosis (PC) of colorectal and ovarian carcinoma. This study demonstrated that DWI MRI was able to identify patients who may benefit from cytoreductive surgery and HIPEC with an accuracy of 94%. These promising results were the basis for a recently awarded grant from the Dutch Organisation of Science (NWO/ZonMw) which will finance a multicentre trial to study the 'Clinical impact of dedicated MR staging in ovarian cancer patients'.

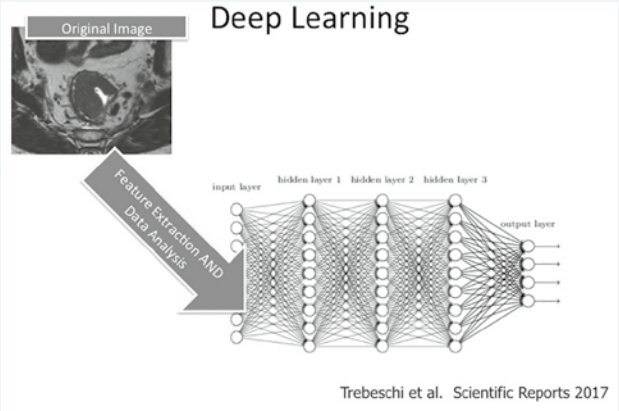
RADIOMICS AND DEEP LEARNING

J van Griethuysen, S Trebeschi, M Taghavirazavizadeh, N Schurink, P Bos, B Jasperse, D Lambregts, H Aerts, R Beets-Tan

Radiomics

Radiomics entails the extraction of quantative data from routine scans to better predict the heterogenic characteristics and prognosis of certain tumors. An important research is Radiomics in Immunotherapy. The aim is to build a more accurate noninvasive tool to predict response in metastatic melanoma and lung cancer patients treated with PD-1 blockade immunotherapy. A specific project focuses on advanced Radiomics analysis to determine whether it is possible to predict response to neoadjuvant chemoradiotherapy (CRT) using the Radiomics features extracted from the primary MRI imaging of the rectum. A pilot analysis in 142 patients was successfully completed in 2017, multicenter validation in a larger dataset will continue in 2018. Projects are running to predict primary tumour response also in breast cancer, head and neck cancer and brain tumors, melanoma and lung cancer.





Automated detection and tissue classification (deep learning)

As the amount of imaging data is exponentially increasing over time, artificial intelligence is becoming more and more important to crunch and identify patterns that humans can't. Voxel-wise detection and classification of malignancies, and classification of suspicious lesions in large, multi-parametric images are all time-consuming operations which often requires assessing the sequences in parallel. Our aim is to adopt artificial intelligence to facilitate and speed up the work of researchers and possibly clinicians at our department. We have started by implementing Convolutional Neural Network for the automatic segmentation of rectal cancer on multi-parametric MR images, with excellent classification accuracy. This will enable us to reduce the time needed to perform quantitative analysis (e.g. Radiomics) on larger datasets by months. We are planning to use these technologies from automatic detection of lesions to the classification of normal and the identification of abnormal tissues. The imaging research in Radiomics is supervised by H Aerts, dept of radiology at Dana Farber Cancer Institute, Boston, USA and in close collaboration with clinical research teams in NKI-AVL, the MR physics research team of U vd Heide at the dept of radiation oncology and the radiology dept of the University of Zurich, Suisse.

IMAGING FOR IMMUNOTHERAPY

S Trebeschi, Z Elkarghari, TDL Nguye-Kim, I Kurilova, P. Bos, B. Jasperse, H Aerts, R Beets-Tan

In 2016 an Immunotherapy imaging research line has been initiated with two main projects in close collaboration with medical and thoracic oncology and immunology. CT scans and brain MR of patients with melanoma, non-small cell lung cancer and bladder cancer treated with immunotherapy have been analysed for Radiomics modeling. Primary outcome is to build a machine learning model based on Radiomic features that would predict long term survival. Secondary outcome is the response of each metastasis to treatment. This project is in close collaboration with J Haanen, C Blank, E Smit, and M vd Heijden

ESOPHAGEAL CANCER IMAGING & ORGAN PRESERVATION

A Bartels-Rutten, S Vollenbrock, R Beets-Tan

The organ preserving treatment and imaging research of rectal cancer is extrapolated to esophageal cancer. In 2016 Bartels-Rutten started a collaboration with F. Voncken from the radiotherapy, K. Hartemink from the thoracic surgery and J. van Dieren from the gastroenterology department investigating the performance of MRI for identification of complete responders after neoadjuvant treatment with the aim to study a 'watch-and-wait'- strategy similar to the strategy used in rectal cancer patients. Collaborations also exist with UMC Groningen and UMC Utrecht. Vollenbrock and Bartels-Rutten actively participate in the N13OME study. One of the objectives is to qualitatively assess response to neoadjuvant chemoradiotherapy with, amongst other imaging methods, MRI of the esophagus. NKI-AVL participates in the SANO, a national multicenter study to investigate the safety of organ preservation for the complete responders after preoperative CRT.

BREAST CANCER IMAGING

C. Loo, G. Winter- Warnars, L Klompenhouwer, D. Schouten, E. Ioan, T van Nijnatten,RJ Schipper, R Beets-Tan

T. van Nijnatten completed the PhD project on breast MR for axillary nodal staging which resulted in a dissertation in dec 2017. Claudette Loo is PI in the research on MRI in breast cancer patients in supine instead of prone position. In the context of this study "Supine MRI-guided navigation for radioactive seed localization in breast cancer patients" Claudette Loo is co-supervising the PhD students Natasja Jansen (expected dissertation 2018) and Kleopatra Piripini (expected dissertation 2018). Our department also participates in the CTMM breast care program (the Choice project) in collaboration with UMCU (K. Gilhuijs). One of the spin offs is a PhD project initiated in October 2017. The CARP (computer aided response prediction) model will be validated and data mining in imaging (combining principal component analysis, Bayesian neural networks and binary logistic regression). In 2017 two new projects were initiated. The first project focuses on wait and see approach for breast cancer with a complete response after neoadjuvant treatment. The second project focuses on Radiomics using preoperative MRI to predict response to treatment. This project is a sub-project that is part of the DCIS project of Prof Jelle Wesseling. The breast imaging radiologists participate in several trials: The DENSE study (multicentre, coordinated from Julius centre); the Famrisk study (multicentre, coordinated from Erasmus MC); the MICRA study (AVL), PAPBI study (AVL), MaMaLoc study (AVL), BETER, and several DCIS studies which have been launched in close collaboration with the group of Wesseling, with emphasis on the correlation between imaging and pathology and the possibility of creating a prospective risk model for developing invasive cancer. Collaboration exists with the group of J. Wesseling and E. Rutgers in the LORD study, the under-estimation study with Jelle Wesseling and Gurdeep S. Mannu from the Research group of Cancer Surgery University of Oxford. Eleanor Ioan (ESOR fellow from the group of prof. Sardanelli) investigated in collaboration with the 'MICRA study group' the additional value of MRI of to predict irradical margins and LR after BCS in T3 breast cancer patients treated with neoadjuvant chemotherapy.

PROSTATE CANCER IMAGING

S. Heijmink, A. Bruining, D Schouten, N Grivas, P. de Koekkoek-Doll, I. Schoots, R Beets-Tan

MR-US guided focal organ preserving treatment

In 2016 MRI-guided biopsies that were performed at the NKI-AVL from 2014-2016 were analyzed and compared with MRI-ultrasound fusion biopsies. The large majority of cancers found through direct MRI-guided biopsy were intermediate to high grade and MR correlated well with the final aggressiveness score on histopathology in patients who underwent subsequent prostatectomy. Result of MR guided biopsies were comparable to MRI-ultrasound fusion biopsies but a learning curve exists. In collaboration with Philips and dept of Urology (H vd Poel), NKI-AVL, we will investigate the use of Ultrasound MR fusion guidance in organ preserving focal therapy.

Analysis of MR predicted seminal vesicle invasion

The preoperative prediction of seminal vesicle invasion was analyzed in a cohort of 527 patients who had undergone a

robot-assisted laparoscopic prostatectomy from 2012 to 2015. High sensitivity and specificity were obtained, particularly when reported by an experienced genito-urinary radiologist. Addition of the MR result to the clinically used nomograms provided a significantly higher prediction of seminal vesicle invasion.

MRI for prediction of functional outcomes after surgery

MR for the prediction of functional outcomes after both prostatectomy and brachytherapy is one of the PhD projects in collaboration with the dept of urology (H vd Poel). Preoperative MRI characteristics such as the width of the prostatic fascia was directly correlated with the amount of erectile dysfunction post-surgery. It was also noted that the brachy dose distribution was predictive of the erectile function after brachytherapy. Furthermore, analysis of a cohort of patients who had undergone prostate surgery, preoperative MR was found useful in for classifying patients in BPH patterns which are strongly associated with preoperative LUTS. However, BPH patterns did not predict remnant LUTS or postoperative incontinence. Postoperative continence status was only associated with preoperative LUTS and membranous urethra length as measured on the MR. Collaborative research between the depts. of radiology at Erasmus MC and NKI-AVL as well as the dept of radiation therapy at NKI-AVL is initiated by Schoots with the aim to build a predictive risk model to council patients prior to therapy.

HEAD AND NECK CANCER IMAGING

B Jasperse, P Bos, C Lange, M Maas, P de Koekkoek

MRI and Radiomics

MRI, CT and ultrasound imaging plays a key role in treatment planning, surgical planning and tumor follow-up in head and neck cancer. Genetic profiling and histopathologic features of tumors are promising predictors of tumor growth rate, treatment response and overall prognosis. In line with this, our research focuses on advanced imaging techniques and image analysis techniques (Radiomics) to detect imaging features that have similar, added or independent predictive properties relevant to treatment planning.
Pre-surgical planning is of great importance to maximize treatment success and mimize morbidity. One cause of post-surgical morbidity is nerve damage. We are currently evaluating new MR sequences to directly locate nerves in the head and neck area that can inform the surgeon on the location of nerves in relation to the tumor or lymph nodes to be resected. Conventional MRI is routinely used in post-treatment follow-up in head and neck cancers. Recurrences can be hard to detect due to small size and concurrent tissue changes due to surgery, chemotherapy and radiotherapy, allowing room for improvement. In our research we try to improve recurrence detection by applying advanced MRI techniques, including perfusion and diffusion weighted imaging. Our head and neck PhD projects are supervised by the department of head and neck oncology and radiology and in collaboration with radiotherapy, genetics and pathology at NKI-AVL.

Ultrasound fusion guided FNAC of cervical nodes

The detection of involved lymph nodes in the head and neck region remains a big challenge. We hypothesize that ultrasound fusion guided FNAC will improve the nodal staging in head and neck cancer. We are performing a prospective study comparing the diagnostic value of (Percunav) real-time ultrasound image fusion to current ultrasound-only guided lymph node fine needle aspiration in head and neck cancer patients. The patients undergoing this procedure are typically pre-imaged with four different modalities for real time ultrasound fusion: (1) MRI only; (2) CT only; (3) MR + PET/CT; (4) CT + PET/CT. For validation, the findings will be compared with the results of the histological lymph node state at neck dissection and the results of fine needle aspiration. The use of Percunav is expected to increase the sensitivity and specificity compared to US-FNAC alone.

LUNG CANCER IMAGING

S Trebeschi, F. Lalezari, A. Bartels-Rutten, H Aerts, I Kurilova, Irene v Kalleveen, R Beets-Tan

A Radiomics research line has started in lung cancer patients treated with immunotherapy as described above in the section on imaging for immunotherapy. The thoracic radiologists are involved in trials such as N14MPN, N12HYB, M09PBO, M11VOL and M14PRT. A project on the development of novel MR sequences for lung cancer imaging has been initiated in collaboration with the dept of lung surgery (H Klomp) and the dept of clinical physics (L ter Beek)

INTERVENTIONAL RADIOLOGY AND IMAGE GUIDANCE

E Klompenhouwer, M Maas, B Aarts, M de Boer, W Prevoo, I Kurilova, F Gomez Munoz, R Beets-Tan

Ultrasound fusion guided Interventional Treatment

In NKI-AVL thermal ablations are performed under CT-fluoroscopic guidance. Due to the near-real time imaging an optimal placement of the ablation antenna can be achieved. Ultrasound fusion (PercuNav) guided ablations will be investigated for more accurately targeting of lesions like small residual areas of tumours only visible with PET or multiparametric MRI by fusing these planar high-resolution images with real-time US images. At the dept of Radiology 30 patients with liver lesions and 60 with small renal tumours will be included for real-time US fusion guided thermal ablations. In some patients visualisation of organs for interventional procedures (Nefrostomy, drainage of fluid collections, PTCD and embolization of thoracic duct) can be challenging. In those patients fluoroscopy guidance could have additional value but lacks detailed real-time imaging. PercuNav guided procedures will be evaluated and compared with fluoroscopy guidance. This research in ultrasound fusion guidance is in collaboration with the group of T Ruers, surgery and with the dept. of urology (S Horenblas and A Bex).

Ultrasound fusion guided Biopsy

In the Netherlands Cancer Institute an increasing number of biopsies are performed to select the right treatment for the individual patient (personalised medicine). Furthermore consecutive biopsies are taken on a patient base to monitor the efficacy of treatment during immunotherapy. At the same time with the increased use of PET and MRI, an increased number of small equivocal lesions only visible with PET or MRI requires even more biopsies to obtain histological confirmation. Our dept

investigates the value of real-time uultrasound fusion guided biopsies as a fast, safe and cost-efficient tool to facilitate the increasing number of image guided biopsies in the institute.

Biomarkers in Interventional Treatment of CRC Liver Metastases

This PhD project investigates immunohistochemical and surrogate imaging biomarkers for the improvement of loco-regional treatment outcomes of patients with colorectal cancer liver metastases. The research analyses data from MSKCC of percutaneous ablative techniques and intra-arterial therapies performed under image-guidance of FDG-PET/CT, contrast-enhanced CT and MRI. Surrogate image biomarkers will include different metabolic, functional and anatomic parameters on FDG-PET/CT, MRI and CT. Development of these imaging biomarkers is important for the reduction of high tumor recurrence rates after ablations, which is the main limiting factor of ablative techniques. Currently there is no standardized histological confirmation of complete ablation, which could contribute to reduction of recurrence rates. Surrogate image biomarkers are important for response prediction to intra-arterial therapies as patients have a varied response to them. Thus early recognition of non-responders may help to identify patients who could benefit from extended chemotherapy or change of its regimen and avoid unnecessary treatment. In order to find optimal biomarkers BRAF, Ki67, p53, KRAS, PI3K and other gene/protein pathways will be also investigated. This research is in close collaborationand supervised by C Sofocleus, interventional radiologist at the Department of Radiology at MSKCC, NYC, USA.

Trans arterial chemoembolization in HCC

The interventional oncology group at the department of Radiology investigates the outcome of trans-arterial chemoembolization (TACE) with drug eluting beads in patients with hepatocellular carcinoma (HCC). This project is in collaboration with G Maleux, Interventional Radiologist at Catholic University Hospital Leuven. The aim of this project is to evaluate the safety and efficacy of radio-embolization (Y90) and liver transplantation in patients who previously underwent chemoembolization for HCC. And to determine if response criteria on MRI following TACE and Y90 correlate with survival and recurrence after transplantation.

Intrahepatic Mitomycin infusion for the treatment of breast cancer liver metastases

Approximately 25-40% of breast cancer will develop metastatic disease. In 50% of all breast cancer metastases, the liver is involved. For years, Mitomycin C (MMC) has been a standard chemotherapy for advanced breast cancer, mostly in combination with other drugs. Despite its efficacy, toxicities such as delayed cumulative myelosuppression and hemolytic uremic syndrome (HUS) have restricted its use. The liver is ideal for local regional therapy due to the dual blood supply via the portal vein and the hepatic artery. Selective regional administration of a chemotherapeutic agent in the hepatic artery may be used to achieve high local concentrations in the liver tumors. MMC is a good agent for intra-arterial local treatment because of the high first pass hepatic extraction. The aim of this project which is supervised and performed in collaboration with G Maleux, Interventional Radiologist at Catholic University Hospital Leuven, is to evaluate the safety and efficacy of intra-hepatic Mitomycin C (MMC) bolus infusion in the treatment of patients with liver metastasis from breast cancer and to determine if there are (pre)-treatment characteristics that may influence outcome.

Follow-up after ablation of liver metastases using modern imaging and image post processing techniques

Early detection of residual or recurrent disease after thermal ablation of liver metastases is crucial to allow for timely re-intervention and thus potentially curative treatment. This project focuses on the use of novel imaging (diffusion and perfusion MRI) and image post-processing techniques (textural analysis and Radiomics) to achieve this goal. Aim is to identify, test and validate specific (functional) imaging characteristics - from the metastatic lesions before treatment and from the ablation zone shortly after treatment - that can help predict which patients will have residual disease or are at risk to develop recurrent disease. This project is extended with a successful collaboration in research with the Interventional radiology group at the Department of Radiology at Memorial Sloan Kettering Cancer Center, MSKCC. The project investigates the value of imaging biomarkers (including PET/CT) and correlates these with molecular markers.

John Haanen

Head Division Medical Oncology

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Sofie Wilgenhof Temporary staff
Bianca Cioni PhD student
Gwen Dackus PhD student
Marnix Geukes Foppen PhD student
Dianne de Gooijer PhD student
Bart Jacobs PhD student
Rutger Koornstra PhD student
Mirte Muller PhD student
Maartje Rohaan PhD student
Annelot van Rossum PhD student
Lisette Rozeman PhD student
Izhar Salomon PhD student
Emilia Sawicki PhD student
Philip Schouten PhD student
Robert Schouten PhD student
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Joke Foekema Nurse practitioner
Emmy Harms Nurse practitioner
Peggy den Hartog-Lievaart Nurse practitioner
Jacoline van der Hek-van Essen Nurse practitioner
Marjo Holtkamp Nurse practitioner
Inge Kemper Nurse practitioner
Maria Kuiper Nurse practitioner
Elsbeth van der Laan Nurse practitioner
Judith Lijnsveld Nurse practitioner i.o.
Jana van der Sar Nurse practitioner
Lisette Saveur Nurse practitioner
Henk Mallo Nurse practitioner
Suzanne Onderwater Nurse practitioner
Saskia Pulleman Nurse practitioner i.o.
Margaret Schot Nurse practitioner
Wilma Uyterlinde PhD Nurse practitioner
Marion Zimmerman Nurse practitioner i.o.

Division of Medical Oncology

INTRODUCTION

The Division of Medical Oncology comprises a growing number of research activities with focus on translational research, early drug development and clinical research. In this report only research from the largest groups is presented. Much of the work is multidisciplinary and involves groups from different divisions or different institutions both in The Netherlands and abroad. Two of the major common themes between the different research groups within the Division are personalized medicine and immunotherapy. We expect that cancer treatment will be more and more individualized, so that patients can be offered the optimal treatment for their specific type of cancer, be it chemotherapy, targeted therapy or immunotherapy.

CLINICAL PHARMACOLOGY OF ANTICANCER DRUGS

Jan Schellens, Bastiaan Nuijen, Hilde Rosing, Henk Boot, Annemieke Cats, Jolien de Groot, Serena Marchetti, Frans Opdam, Dieta Brandsma, Neeltje Steeghs, Sabine Linn, Baukelien van Triest, Alwin Huitema, Jos Beijnen

Research activities of the department of Clinical Pharmacology, the department of Pharmacy & Pharmacology and the division of Pharmacology (group Schellens) are closely integrated. There is close collaboration with the departments of Gastro-enterology, chest oncology, neuro-oncology and radiotherapy.

Novel approaches to improve oral bioavailability

Oral docetaxel formulation: An oral docetaxel formulation (ModraDoc006/r) has been developed in the pharmacy of the NKI-AVL and MC Slotervaart. Two phase I trials with once daily and twice daily treatment schedules reported acceptable safety and favorable pharmacokinetic results in patients with advanced solid tumors. New trials with the oral docetaxel formulation in prostate cancer are still ongoing, including a multicenter trial with weekly treatment with oral docetaxel in metastatic castration-resistant prostate cancer and a phase I trial evaluating the feasibility of chemo radiation in early high-risk prostate cancer. A food-interaction trial to further optimize treatment with ModraDoc006/r is ongoing.

Oral paclitaxel formulation

In addition to docetaxel, treatment with an oral paclitaxel formulation (ModraPac005/r) in a metronomic schedule is investigated in a phase I trial and a food-interaction study was included.

Pharmacology (PK/PD, ADME, mass balance) of novel anticancer drugs

Currently, we perform 91 phase I/II, pharmacological and proof of concept studies, which number has increased compared with last year. We recruited more than 300 new patients in these studies this year. Thirty-seven of these studies are two- or multicenter studies. Representative examples are described. Here's a selection of the studies we execute.

Phase I/II studies with the combination of MEK and pan-HER inhibition

Based on preclinical work done in the lab of Rene Bernards, three clinical trials have been initiated with the combination of pan-HER and MEK inhibitors in KRAS mutant and PIK3CA wildtype non-small cell lung cancer, pancreatic cancer and colorectal cancer. So far, 88 patients have been included in four different hospitals throughout The Netherlands. These patients received escalating doses of afatinib-selumetinib, lapatinib-trametinib or dacomitinib-PD0325901. Preliminary results encourage further development of this combination strategy.

Pembrolizumab for the treatment of malignant pleural mesothelioma

In the multicenter phase Ib trial, we investigated the safety and efficacy of pembrolizumab in PDL-1 expressing mesothelioma patients after failure of standard therapy. Progression free survival was 5.4 months and the overall survival was 18 months which is a relevant improvement of the historical 10-month overall survival on standard cisplatin-pemetrexed therapy. These promising results were published in the Lancet Oncology (see figure).

Development of the oral wee1 inhibitor AZD-1775 as monotherapy or in combination treatment

The MKO study is a phase II pharmacological study with Wee-1 inhibitor AZD-1775 combined with carboplatin in patients with p53 mutated epithelial ovarian cancer who show early relapse (<3 months) or progression during standard first line treatment with carboplatin – paclitaxel combination therapy. Re-exposing patients with early relapse to carboplatin in combination with Wee1 AZD-1775 has shown promising anti-tumor effect before. Therefore, an additional safety and preliminary activity cohort was opened.

Weekly AZD-1775 with carboplatin

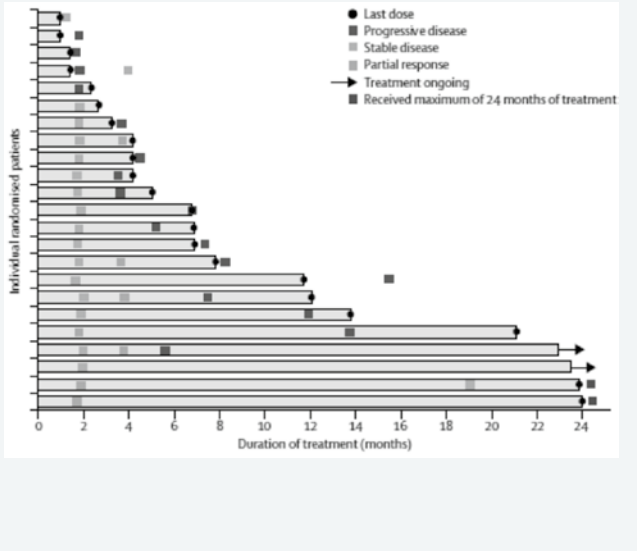
A phase I study to determine the MTD of weekly carboplatin with AZD1775 in patients with p53 solid tumors. The hypothesis is that with dose-dense administration of AZD1775 and carboplatin in a more frequent but lower dose schedule, efficacy increases with a manageable toxicity profile.

Food-effect study and continuous treatment with AZD1775 monotherapy

This is a phase I food-interaction study with AZD1775 in patients with advanced solid tumors.

Beacon crc: Safety Lead-In (SLI) and phase III study for the Combination of Binimetinib (BINI), Encorafenib (ENCO), and Cetuximab in Patients with *BRAF*^{V600E} Metastatic Colorectal Cancer (mCRC)

So far, the SLI of this multicenter study has been completed with



Treatment exposure and response duration (RECIST, investigator assessed). The length of each bar corresponds to the duration of treatment for each patient. Response symbols represent the time first reported and not best overall response. A post-baseline assessment was not available for two patients.
RECIST= Response Evaluation Criteria in Solid Tumors.

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good tolerability of the triple combination and promising efficacy results. The phase III part of this trial is ongoing.

MoTriColor: Molecularly guided trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of colorectal cancer

We initiated this multicenter study in which we screen patient for newly molecular defined subtypes and treat them with specific targeted treatments. The screening and the three clinical trials were opened in 2017.

Proof of principal study with the HDAC inhibitor vorinostat in resistant advanced *BRAF V600* melanoma

We initiated this trial in collaboration with the group of Rene Bernards and reached proof of principle in the first 6 patients. In the clinical trial emerging resistance using ctDNA clones guides therapy switch to vorinostat and later back to MEK-BRAF inhibition.

Pharmacogenomics to identify patients at risk for toxicity or undertreatment *DPYD* genotype-guided dose individualization to improve patient safety of fluoropyrimidine therapy: call for a drug label update

Although it is known that patient safety of fluoropyrimidine treatment can be significantly improved by upfront genotyping for polymorphisms resulting in dihydropyrimidine dehydrogenase (DPD) deficiency and dose reductions in variant allele carriers, this is not currently included in the drug label of fluoropyrimidine drugs. We sent a proposal to the European Medicines Agency (EMA) and the Dutch Medicines Evaluation Board (MEB) to recommend adjusting the labels, as DPD genotype-guided dose adjustment of fluoropyrimidines should be the new standard of care. After reviewing our proposal, the EMA has now asked the involved pharmaceutical companies to update the SPC of fluoropyrimidines by including information on DPD-genotyping and genotype-guided dosing.

Safety, feasibility and cost-effectiveness of genotype-directed individualized dosing of fluoropyrimidines

In 2015 we initiated a large multicenter study, to confirm whether upfront genotyping for four polymorphisms of the enzyme dihydropyrimidine dehydrogenase (DPD) can increase safety of fluoropyrimidines. Patients identified carrying polymorphisms resulting in DPD deficiency are treated with a reduced starting dose of the fluoropyrimidine. In this nationwide study, with 18 centers in the Netherlands participating, over 1160 patients have been enrolled.

Combined modality studies

The three studies employing PARPi olaparib in combination with radiation in NSCLC, breast and head and neck cancer are ongoing. The phase I study employing ModraDoc006/r plus radiation in locally advanced prostate cancer is ongoing as is the phase I study employing the DNA-PKi MS2490484A as radiosensitizer was started in patients with head and neck cancer.

CLINICAL IMMUNOTHERAPY AND TARGETED THERAPY

John Haanen, Christian Blank, Hans van Thienen, Sofie Wilgenhof, Sandra Adriaansz, Henk Mallo, Elsbeth van der Laan, Wilma Uyterlinde, Judith Lijnsveld, Loes Pronk, Marieke Groot-Obbink, Marnix Geukes Foppen, Lisette Rozeman, Maartje Rohaan, Anna Blokland, Willem Boogerd, Annette Compter, Maaike Schuur, Dieta Brandsma

Background and Objectives

The clinical immuno- and targeted therapy group is primarily involved in the treatment of melanoma and renal cell carcinoma patients. Translational immunotherapy research focuses on neo-adjuvant targeted and immunotherapies, on dissection of immunological changes upon immune checkpoint inhibition in combination with targeted agents, combination with local therapy (RFA, oncolytic viruses) and on adoptive cellular therapies, such as T-cell receptor gene therapy and treatment with tumour-infiltrating lymphocytes (TIL) for melanoma and DNA and peptide vaccination studies for HPV-related squamous cell cancers. For renal cell cancer our group implementing or participating in trials to improve the treatment with small molecule receptor tyrosine kinase inhibitors (RTKI), combinations of checkpoint inhibitors, and novel immunological approaches using combination therapy with immune checkpoint inhibition.

MELANOMA

Clinical adoptive T cell transfer program

Based promising phase 1 data gathered at our institute we have initiated a European randomized controlled phase III trial, comparing TIL therapy to ipilimumab as 1st or 2nd line treatment for patients with stage IV melanoma. This trial is a collaborative effort with a center in Copenhagen, Denmark, and for TIL production with Sanquin blood transfusion services in Amsterdam. The primary objective is improvement in PFS at 6 months. In both institutes a total 45 patients have been randomized so far. It is the first randomized TIL trial worldwide.

Between 2011 and 2017 we have enrolled 11? patients in a phase I/II trial with T cell receptor (TCR) gene therapy. HLA-*0201 positive patients with MART-1 expressing metastatic melanoma and no further treatment options are infused with genetically modified autologous peripheral blood T lymphocytes. These modified cells express a TCR specific for the melanocyte differentiation antigen MART-1, expressed in 80% of melanomas. Recently, the clinical protocol has been amended to allow treatment of patients with metastatic uveal melanoma.

Immune checkpoint inhibition in melanoma:

As of end of 2011 anti-CTLA4 (ipilimumab) has become available in the Netherlands for metastatic melanoma, originally as 2nd line therapy, but in 2013 also as 1st line therapy. As of June 2014 the anti-PD1 drug pembrolizumab became available in a named patient program for patients that have failed prior anti-CTLA4 treatment. In 2015 both nivolumab and pembrolizumab became approved for 1st line treatment of metastatic melanoma, and the combination of ipilimumab plus nivolumab in 2016.
We developed a phase I biomarker study (Opacin) for patients

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with stage IIIB/C melanoma with the combination of ipilimumab and nivolumab as neoadjuvant versus adjuvant treatment. In patients treated with 2 courses of neoadjuvant ipilimumab/nivolumab combination, deep partial and pathological complete responses were observed, and none of the responders has relapsed so far with a median follow-up of 18 months, Biomarker identifying long-term responders has been presented at ESMO 2017 and highlighted in the proffered paper session. This high efficacy comes at the cost of high toxicity rates A follow-up randomized controlled international multicenter phase II trial has been initiated under the lead of the NKI-AvL with the aim to reduce toxicity, but preserve efficacy.

Based on mouse models (see section IV, Prof Blank) in 2016 a feasibility phase I/II trial (Impembra) has been started combining anti-PD1 with short-term combination targeted therapy (dabrafenib + trametinib) in BRAF V600 mutated metastatic melanoma patients. The study has meanwhile recruited near 50% of patients needed and short-term targeted therapy and checkpoint inhibition has excellent tolerability.

Furthermore, in 2017, we published a position paper management of immune-related adverse events and an overview article on the standard therapy of melanoma and future perspectives, In addition our biomarker proposal, the Cancer Immunogram, has become has become a working model world-wide. Currently, we are analysing large cohorts of patients treated with anit-PD-1, anti-CTLA-4 or their combinations to move this concept towards a clinical decision tool.

We are participating in a biomarker study with ipilimumab and nivolumab. In addition blood samples from HLA*0201 positive patients are being analysed for changes in cellular immune responses upon pembrolizumab treatment (see Division of Immunology).
In metastatic uveal melanoma ipilimumab combined with radiofrequency ablation of a single liver metastasis has finished accrual and has been presented at ESMO 2017.
Finally, we have been successful in acquiring large grants analysing new biomarkers, inclusive the microbiome, as predictive biomarkers for the outcome upon checkpoint inhibition (POINTING and N-CIA projects).
Another project with the aim of improving patients' quality of live, we have initiated together with the department of epidemiology (section xy) a quality of life study for patients being tumor-free longer than 2 years after ipilimumab treatment. This will be the first study analysing the patients functioning after immunotherapy curation.

BRAF V600 and NRAS mutated melanoma

As of September 2012 vemurafenib and as of end 2013 dabrafenib have been approved for the treatment of BRAF V600 mutated melanoma. At the end of 2015 and in 2016 the combinations of both dabrafenib plus trametinib and vemurafenib plus cobimetinib have been approved in The Netherlands. From many of these patients, blood and tumor samples have been collected for translational research (see also Division Immunology and Division Molecular Oncology). Published results from two phase 3 RCT in which we participated proved the idea of improving PFS and OS when combining BRAF and MEK inhibition.

Based on these data we are performing currently a neoadjuvant phase II trial in unresectable stage III melanoma patients with the combination of dabrafenib + trametinib, in order to investigate the ability of this treatment to downsize these tumours to allow a R0 resection. In 2015 also the Reposit study, a multicenter phase II study was initiated that combines vemurafenib plus cobimetinib in patients with BRAF V600 mutated metastatic melanoma. The goal of this study is to find early markers of response or resistance. On treatment biopsies, blood sampling and PET (both FDG and FLT) are being done for this purpose. Finally, a multi-center trial that was setup together with Nijmegen and Zwolle (and implemented in all Dutch melanoma centers) testing the ability of upfront targeted therapy for improving the outcome of combination immunotherapy (COWBOY trial) has started finally.

Renal cell carcinoma

In the renal cell carcinoma program, we closely collaborate with Dr Axel Bex from the urology-oncology group.
In 2005 we started participation in a treatment-use program of the small molecule sunitinib, a multiple receptor tyrosine kinase inhibitor with high affinity for VEGF-R, PDGF-R, c-KIT and FLT3. Since VEGF and PDGF play prominent roles in the pathogenesis of sporadic clear cell renal cell cancer, inhibition of kinase activity of their receptors appeared to be a rational therapy in this patient population. In 2016 we also participated in a 2nd line RCC investigator-initiated phase I/II study, combining everolimus with cyclophosphamide (to reduce regulatory T cells).
This year the data of another RCT in which we participated testing 1st line treatment of ipilimumab plus nivolumab in comparision with sunitinib, demonstrated for the first time since 10 years overall survival benefit as compared to sunitinib. We further included patients in a trial testing the combination of immunotherapy (avelumab) with targeted therapy (axitinib) which has finished accrual. In addition, we also treated metastatic RCC patients in a phase I study with IFN-a plus atezolizumab.

The idea of defining the optimal timing for nephrectomy in primary metastatic RCC was tested in the SURTIME E30073 study initiated by our group and implemented as EORTC trial. The results of the trial were presented this year during the plenary session of ESMO 2017.

Currently we are moving combination checkpoint inhibition to earlier stage treatment in (neo-)adjuvant settings, with the aim of increasing response rates and subsequent patients' outcome. Similarly to melanoma, we are participating in trials testing adjuvant immunotherapy, and set-up a neo-adjuvant combination immunotherapy. We are including patients into 2 phase 3 RCT which test either atezolizumab for 1 year (Immotion 010) or nivolumab plus iplilimumab for 6 months (Checkmate 914) against placebo in patients with clear-cell RCC with a high risk of recurrence. In addition, we opened N17JAV, a phase 2 single-arm study of 3 months neoadjuvant avelumab and axitinib for patients with clinically high-risk RCC. This study has a strong translational component to investigate mechanisms of resistance.

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THORACIC ONCOLOGY

Paul Baas, Sjaak Burgers, Wieneke Buikhuisen, Maria Disselhorst, Michel van den Heuvel, Wanda de Kanter, Joop de Langen, Egbert Smit, Willemijn Theelen, Jose Belderbos, Houke Klomp, Joost Knegjens, Petra Nederlof, Kim Monkhorst, Sjaak Neefjes, Laurel Schunselaar, Annegien Broeks, Jan Schellens

The Department of Thoracic Oncology is one of the fastest growing departments of the NKI. It stands for optimal patient centered care, based on the newest preclinical, clinical developments and translational research.
In 2017 the emerging fields involved the implementation of immune therapy for non-small cell lung cancer and new developments in thymic tumors and small cell lung cancer.

Immune-Checkpoint Inhibition

Recently, many immunology studies have been initiated and finalized in non-small cell lung cancer (NSCLC) and mesothelioma. For instance, we addressed the possible impact of high-dose radiotherapy SBRT on anti-PD1 treatment in stage IV recurrent NSCLC in our investigator-initiated trial (PembroRT). Translational research on tumor biopsies focusing on predictive factors and immunological mechanisms is ongoing in collaboration with the group of Ton Schumacher. The collaboration with Free University Medical Center (Amsterdam) and Erasmus University Medical Center (Rotterdam) will foresee that patient accrual will be complete in 2018 with 74 patients randomized. Furthermore, randomized first-line studies have continued with IO inhibitors. One of our single institution studies involves the combination of ipilimumab with PDL3280.
In a collaborative effort with investigators at the VUMC we completed imaging studies using ^{18}F-PD-L1 fragments and ^{89}Zr labeled anti-PD-1 monoclonal antibodies in patients.
Many patients participate in studies to identify tumor derived genomic biomarkers, establish organoids and fluid phase biopsies to identify new biomarkers and therapies.

Malignant Pleural Mesothelioma (MPM)

We participated in two maintenance trials for MPM, contributing the majority of the patients in an international trial and still running our national investigator-initiated trial on switch-maintenance with gemcitabine (NVALT-19). One study (INITIATE) investigated the effect of anti-PD1 plus CTLA4 treatment, with a translational research endpoint, has been successfully completed and was presented at the WCLC 2017. This study was the successor of the single agent nivolumab in the same patient group in 2016. Pre- and post-immunotherapy treatment biopsies will be analyzed in corporation with the group of Ton Schumacher. A grant has been obtained to investigate the appearance of neoantigens in these patients.
In collaboration with the Division of Cell Biology the primary short-term cultures for tumor cells in pleural fluid have been continued to identify sensitivity for chemotherapy compounds in primary tumor cell cultures from pleural fluid. The group is pivotal in the set-up of the ETOP initiative called Mesoscape to collect data from Europe on diagnosis, treatment and survival. Studies are now initiated to test biomarkers and analyze genetic changes in material of > 300 patients.

Neuroendocrine Tumors

As certified ENETS Center of Excellence we focus on the diagnosis and treatment of patients with neuroendocrine tumours of the lung. Recent studies concern a phase 2 study to evaluate the efficacy and safety of PDR001, a PD-1 inhibitor in patients with low grade metastatic neuroendocrine tumours in the lung. Furthermore, a multi-center, double blind phase 3 study to evaluate the efficacy of Lanreotide Autogel/Depot 120 mg versus placebo for tumour control in well differentiated metastatic neuroendocrine tumours of the lung. Also a biomarker study in which a transcript profile of NET cells in human blood is measured to explore if sequential blood samples can identify disease status (response) during treatment of patients with low grade neuroendocrine tumours.

Non-Small Cell Lung Cancer (NSCLC)

In addition to the current standard of screening patients for activating mutations, we have expanded the panel with gene sequencing (ROS1, RET etc.). We have attracted a number of clinical studies covering the entire spectrum of targetable mutations in non-small cell lung cancer, consolidating our role as national cancer institute in the Netherlands. In collaboration with the Department of Pulmonary Diseases of VUMC we completed a study of Herceptin and paclitaxel in patients with HER2 amplification and expression as a resistance mechanism to EGFR TKI's. Follow up studies in this field targeting HER2 are in progress. Also, investigator-initiated studies in the field of rare activating EGFR mutations are initiated.
Within the European Thoracic Oncology Platform (ETOP) we initiated several studies. The prevalence of ALK translocations has been analyzed retrospectively in a large European cohort of 2,300 patients who underwent surgical treatment. Another study addresses the effect of adjuvant checkpoint-inhibition treatment in patients treated in stage III with concurrent chemo radiation.

Small-Cell Lung Cancer (SCLC)

Phase III studies with novel agents such as lurbinectedin (a tubulin inhibiting agent) and PD-L1/CTLA4 blockade in first line treatments were started. Efforts to establish organoids in collaboration with the Hubrecht Institute are ongoing.

Smoking Cessation

Active involvement of the department of Thoracic Oncology has led to implementation of smoking-cessation programs in the Netherlands Cancer Institute. Members of our group are leading in national and international (IASLC) committees, allowing influence on a political level for example to compel politicians not to interact with tobacco lobbyists. A criminal lawsuit has been initiated in The Netherlands against the tobacco companies.

Thymic Epithelial Tumours

Last year we have updated our institutional database, joined an international database of the ETOP (ThymoScape) and have made the first plans for two investigator-initiated studies (EORTC study and acombination study of pemetrexed with bevacizumab).

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BREAST CANCER THERAPY AND RESPONSE PREDICTION

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Background and objectives

The objective of this program is to develop and improve potentially curative therapy for patients with locoregional or oligometastatic breast cancer and to improve treatment options in metastatic breast cancer. Close collaborations are maintained with the Dutch Breast Cancer Research Group (BOOG), the EORTC Breast Cancer Group, the Breast International Group (BIG), and Cancer Core Europe. In 2017, some 60 patients were entered in fifteen clinical studies.

Preoperative chemotherapy

The preoperative chemotherapy program is the core of a multidisciplinary research effort to optimize response prediction. It currently consists of separate multicenter studies for ER+/HER2- breast cancer (AFTER; NCT00738777)), triple negative tumors (SUBITO; NCT02810743) and HER2+ tumors (TRAIN-3 in preparation). The TRAIN-2 study (NCT01996267) was selected for oral presentation at the 2017 ASCO annual meeting. TRAIN-2 randomized 438 HER2-positive breast cancer patients to receive three cycles of 5-fluoruoracil-epirubicin-cyclophosphamide followed by six cycles of paclitaxel-carboplatin or to receive nine cycles of paclitaxel-carboplatin. Patients in both arms received trastuzumab and pertuzumab concurrently with all chemotherapy cycles. The pCR rate (ypT0/is,ypN0) in both arms were 67% and 68% respectively (p=0.75). Significantly higher pCR rates were seen in ER negative tumors (84-89%) than in ER-positive tumors (51-55%), but no differential treatment effect according to ER-status was found. Febrile neutropenia and cardiac dysfunction were more frequent in the anthracycline-containing arm. Follow-up is required to confirm these results with regard to long-term survival. The TRAIN-3 study will build on the results of TRAIN-2 as well as on recently published analyses showing good correlation between radiologic and pathologic complete remission during chemotherapy. In the study, the number of pre-operative chemotherapy cycles will be limited if an early radiologic complete remission is confirmed in the resection specimen.

Metastatic breast cancer

The OLIGO study (NCT01646034) randomizes patients with oligometastatic disease (1-3 distant metastases amenable for radical local treatment) whose tumor harbors homologous recombination deficiency between conventional chemotherapy and intensified alkylating treatment. The aim of the study is to provide randomized evidence to support an aggressive oligometastatic approach in a BRCA(-like) population. Whether BRCA1-like status in triple negative breast cancer predicts for increased PFS after 1st line carboplatin/cyclophosphamide ± atezolizumab versus paclitaxel ± atezolizumab will be addressed

in the amended Triple B-study (NCT01898117), after safety of the carboplatin/cyclophosphamide + atezolizumab combination had been demonstrated in the PROLOG study.
The NKI led international phase Ib/II POSEIDON trial (NCT02285179) evaluates safety and efficacy of tamoxifen + the isoform selective PI3K inhibitor taselisib versus tamoxifen plus placebo in ER+/HER2- metastatic breast cancer patients with prior exposure to endocrine treatment. The randomized phase 2 part is currently accruing patients. The SONIA study (NCT03155997) investigates the optimal use of CDK4/6 inhibitors added to first or second line endocrine therapy in advanced ER+/HER2- breast cancer. Primary endpoint is progression-free survival after two protocol-defined lines of treatment, with overall survival, quality of life and cost-effectiveness as key secondary endpoints. ZonMW and the collective Dutch health insurance companies fund this nationwide study. The TONIC trial (NCT02499367) is a single center phase II trial in metastatic triple negative breast cancer, which we initiated to determine the activity of anti-PD1 (nivolumab) after four different immune response induction treatments in TNBC patients with metastatic disease. We hypothesize that short-term induction treatment with low dose doxorubicin, metronomic cyclophosphamide, cisplatin, or radiation induces an anticancer immune response resulting in increased activity of nivolumab as compared to single agent nivolumab in the unprimed tumors. The GELATO (NCT03147040) study is a multicenter phase 2 trial recently initiated for invasive lobular breast cancer (ILC) patients with metastatic disease. Based on preclinical data we hypothesize 1) synergy between platinum and checkpoint blockade and 2) that there is a subgroup within ILC that will have benefit from this combination regimen. In the GELATO study, the toxicity and efficacy of weekly low dose carboplatin in combination with anti-PDL1 (atezolizumab) will be evaluated.

GASTROENTEROLOGY

Henk Boot, Annemieke Cats, Myriam Chalabi, Jolanda van Dieren, Cecile Grootscholten, Monique van Leerdam, Margot Tesselaar, Wieke Verbeek, Linda Henricks, Linda van Veenendaal, Elvira Nuijten, Lisanne Rigter, Esther Toes, Arthur Kooyker

Background and objectives

The department of Gastroenterology is involved in different phases of research, with emphasis on early detection and prevention of and innovative multimodality treatments for GI cancers including neuro-endocrine tumours (NET) and hereditary GI-cancer syndromes.

Upper GI cancer

For esophageal cancer several imaging studies are being performed including the evaluation of fiducials, MRI and 4DPET. The first studies have been submitted.
We are reference center for hereditary diffuse gastric cancer (HDGC) families. Endoscopic characteristics and results of prophylactic gastrectomies of 25 CDH1 mutation carriers (2008-2015) are described. The results of surveillance gastroscopies (2005-2015) in non- CDH1 mutation carriers are described in a second cohort study.

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In 2015, all intended 788 patients with primary resectable gastric cancer were enrolled in the international, randomized, phase III CRITICS study. First results are presented at ASCO 2016 and the manuscript is now submitted.
For patients with advanced cancer of the stomach or the GE-junction we determined the safety and preliminary activity of docetaxel, oxaliplatin and capecitabine in a phase 1a/1b study. The overall response rate was comparable to other reports. Toxicity was relatively mild. The main results have been published.
In gastric cancer patients with limited peritoneal carcinomatosis a dose-finding study of cytoreductive surgery with HIPEC, using oxaliplatin and increasing doses of docetaxel is started.

Lower GI cancer

In collaboration with the Erasmus MC, Rotterdam, we are responsible for the monitoring and evaluation of the Dutch population-based CRC screening program (www.rivm.nlwww.rivm.nl). The first results are published, new data will be submitted soon.
Furthermore, we are a Dutch NFU expert center for hereditary GI cancer syndromes. Several research projects are going on in high-risk groups including patients with hereditary CRC syndromes, serrated polyposis syndrome and Hodgkin Lymphoma survivors (MLDS grant).
Several studies are focusing on DPD activity. Genotype-guided dosing resulted in adequate systemic drug exposure and improved safety and was cost-effective. An internal collaboration resulted in a meta-analyse of 7365 patients treated with fluoropyrimidines of which DPYD genotypes were determined retrospectively.
We are involved in translational and clinical studies with targeted and immunotherapy for CRC.

NET

In close collaboration with the UMCU Utrecht, we are a ENETs center of excellence and a Dutch NFU GEP-NET expertise center. As from March 2016, with the start of PRRT we now have all techniques to diagnose and treat patients with a GEP-NET. Several research projects are going such as exploring new blood biomarkers in patients with metastatic NET as well as GEP-NEC.

UROLOGIC ONCOLOGY

André Bergman, Martijn Kerst, Michiel van der Heijden, Elsbeth van der Laan, Anoesjka Lechner, Helga Schrijver, Helga Hoogenhout, Rebecca Louhanepessy, Sushil Badrising, Nick van Dijk

Background and objectives

The urologic oncology group is dedicated to the treatment of prostate, bladder, testicular and penile cancer. This subdivision of the division of Medical Oncology aims to contribute to international trials and to play a leading role in initiation of national trials and translational research. The Dutch Uro-oncology Studygroup (DUOS) is a national platform of 23 hospitals in which our subdivision participates. Andre Bergman chairs the DUOS metastasized prostate cancer workgroup

and Michiel van der Heijden the DUOS invasive bladder cancer workgroup.

Prostate cancer

A randomized, open label, Phase IIB trial of Optimal Sequencing of Treatment Options for Poor Risk Metastasized Castration Resistant Prostate Cancer Previously Treated with Docetaxel (OSTRICh trial)

The OSTRICh study is a multicenter, national trial in patients with poor prognostic features, previously treated with docetaxel. Patients are randomized between cabazitaxel and enzalutmide or abiraterone. The primary endpoint is the establishment of the Clinical Benefit Rate (CBR). CBR is an PSA independent endpoint, which is recommended for trials comparing the efficacy of drugs with different modes of action. Formal comparison of the CBRs in both arms is a secondary endpoint. Biomarker studies include serum levels of cytokines involved in neutrophil homeostasis and analysis of cfDNA.

Predicting Response to Enzalutamide: a biomarker design study (PRESTO-study)

In this single center study, biopsies of metastatic sites of castration resistant prostate cancer are taken prior to enzalutamide treatment. In the biopsies, binding profiles of the androgen receptor to the chromatin are assessed, which may hold biomarker properties as a predictor of response to enzalutamide.

Registry of Treatment Outcomes of Patients Treated with Radium-223 (ROTOR-registry)

Radium-223 is the newest life-prolonging therapy for metastasized prostate cancer patients. This national study aims to assess the course of pain of patients treated with radium-223, the positioning of this treatment among other treatment options in a non-study population and identification of bone metabolism specific biomarkers for response. This year, the study was completed after including the 300th patient. Biomarker studies include serum levels of indicators of osteoblasts and osteoclasts activity, levels of osteoclasts precursors and chemical markers of bone metabolism and inflammation

Industry sponsored studies include: Phase IIIb Study of the Efficacy and Safety of Continuing Enzalutamide during docetaxel treatment (PRESIDE). DNA damage as a result of taxanes treatment is under control of the androgen receptor. In this international trial, patients with chemotherapy naïve castration resistant prostate cancer are treated with enzalutamide. At the time of disease progression patients are all treated with docetaxel and randomized between simultaneous treatment with enzalutamide or placebo. Phase II study of pembrolizumab patients with metastatic castration-resistant prostate cancer previously treated with chemotherapy (MK3475-199). In this international trial patients with measurable metastatic disease not previously treated with docetaxel and progressive during enzalutamide treatment after an initial response are treated with a combination of enzalutamide and pembrolizumab. A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib (Lynparza TM) Versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with

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a New Hormonal Agent and Have Homologous Recombination repair Gene Mutations (PROfound). In this trial patients with documented mutations in key genes in HR DNA repair are randomized between olaparib and abiraterone or enzalutamide.

Bladder cancer

Activity of checkpoint inhibitors in urothelial cancer

After encouraging findings with MPDL3280A in a phase I study in platinum-refractory advanced urothelial cancer, a large multicentre phase II study was initiated in the same patient group (*IMvigor 210*). A separate cohort enrolled first-line patients who are platinum-ineligible. Thirteen patients were included at the NKI, 3 of these patients are still alive, which is remarkable given the poor prognosis in this group of patients. The platinum-refractory cohort was published in the Lancet in February 2016; a manuscript reporting results of the cisplatin-ineligible first-line cohort was published in the Lancet January 2017. A follow-up phase 3 trial was opened in 2015 (*IMvigor 211*). Patients were randomized between MPDL3280A and standard chemotherapy (vinflunine or taxane). The NKI enrolled 34 patients in this trial. Atezolizumab did not show a statistically significant overall survival (OS) improvement in the PDL1+ population, the primary endpoint of this study. Although formal statistical testing was not possible due to the statistical design of the study, explorative analyses showed an OS benefit in the ITT population.

Clinical trials with immunotherapy are now moving to the frontline setting, the first example was the *DANUBE* trial: chemotherapy vs durvalumab vs tremelimumab + durvalumab as first line treatment in advanced bladder cancer (24 patients included in the NKI). In 2017, the *CA209-901* (ipilimumab/ nivolumab vs standard of care chemotherapy) was initiated in the AVL. Fourteen patients have been randomized so far in the AVL. In addition, an adjuvant trial (*IMvigor 010*) comparing atezolizumab to observation is enrolling high-risk bladder cancer patients after cystectomy.

Separate from the various immunotherapy trials, the *RANGE* trial, comparing Docetaxel +/- Ramucirumab for second-line urothelial cancer patients, was analyzed for the first primary endpoint: progression-free survival. A statistically significant difference was noted; results were published in the Lancet, September 2017.

Other bladder cancer clinical trials active in 2017 were:
Study 10: Tremelimumab + Durvalumab expansion cohort of a phase 1 trial for 2d/3d-line urothelial cancer patients
KAMELEON: Trastuzumab-emtansine for HER2-positive platinum-refractory urothelial cancer patients.
ABACUS: Atezolizumab as pre-operative treatment in urothelial bladder cancer.

Molecular characterization of urothelial cancer in the neo-adjuvant setting.

In collaboration with Bas Van Rhijn (Surgical Oncology), a large cohort of bladder cancers treated with pre-operative platinum-based chemotherapy is molecularly analyzed. Previously we found an unexpected association between *ERBB2* mutations and response to chemotherapy. Our group participated in a large international cohort, led by the University of British Columbia, to

test the association between molecular subtypes, chemotherapy response and prognosis in muscle-invasive bladder cancer. Results showed that luminal tumors had the best OS with and without NAC. Claudin-low tumors were associated with poor OS irrespective of treatment regimen. Basal tumors showed the most improvement in OS with neo-adjuvant chemotherapy compared with surgery alone.
Small amounts of cell-free tumor DNA (cfDNA) can be found in peripheral fluids, such as plasma. Due to its proximity to the tumor, the urine is a particularly rich source of cfDNA for bladder cancers. In collaboration with investigators in Cambridge, we analyzed pre-operative plasma and urine samples from bladder cancer patients. Clearance of cfDNA, especially in urine, was associated with improved outcome.
These studies are starting to form a foundation for personalized treatment in the neo-adjuvant setting, based on molecular characteristics of the tumor. Future studies by our group will focus on how to use this knowledge in clinical practice, for example by selecting certain patients for chemotherapy, and others for immunotherapy.

Testicular cancer

Our department continued its role as a reference center for testicular cancer, covering the treatment of all subtypes and all clinical stages, including relapse treatment using high dose chemotherapy and autologous stem cell transplantation.

E1407 TIGER study

This is an international trans-Atlantic prospective randomized trial for patients relapsing after BEP chemotherapy, in which Conventional Dose Therapy (TIP) is compared with sequential High Dose Therapy (TICE).

M16FPV study

Vascular fingerprint to identify patients at risk for arterial cardiovascular events within the first year after start of cisplatin-based chemotherapy for testicular cancer: a validation study.

M14 LET study

The TACKLE study, a national study to identify risk factors for development of cardiovascular disease after treatment is currently recruiting patients.

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Division of Pharmacy and Biometrics

BIOMETRICS DEPARTMENT

In 2016 the new division Pharmacy and Biometrics was born. It encompasses the Department of Pharmacy & Pharmacology and the Department of Biometrics. Both departments typically act as service providers for clinical research. The Department of Pharmacy & Pharmacology provides pharmaceutical services and the Department of Biometrics bio-statistical support, data collection-processing, documentation etc. Quality systems are pivotal for our work. The Department of Pharmacy & Pharmacology has governmental GMP (Good Manufacturing Practice), GLP (Good Laboratory Practice) and GDP (Good Distribution Practices; ISO) licenses. The Department of Biometrics operates according to GCP (Good Clinical Practice).

The Biometrics Department serves as the medical data center of the institute and provides the infrastructure for clinical research through biostatistical support, centralized patient data collection and documentation, data processing and coordinated administration and monitoring of clinical trials. The statisticians and data managers collaborate in clinical research projects both within the institute and in national and international multicenter studies. Working procedures follow Good Clinical Practice and reporting and data sharing are in compliance with National and International laws and guidelines.

Tumor registries

The tumor registry is responsible for completing and maintaining three important registries for the Institute. Since 1977, the department maintains an electronic Tumor Register containing information on patients visiting the hospital with benign tumors, pre-malignant, and malignant tumors. Depending on the clinical involvement at the hospital with respect to the diagnosis and therapy of the tumor, the number of items collected ranges from minimal to very extended. From July 2016 until July 2017 about 9546 tumors have been added to the full register. This database is a valuable source for research and contains now almost 250.000 records. A selection of cases of about 3500 tumors, who have been diagnosed and treated primarily in the Netherlands Cancer Institute, is sent to the National Cancer Registry at regular intervals.
A second series of registries belong to the category of quality registers. Most of these registries are developed by the Dutch Institute for Clinical Auditing (DICA). DICA aims at creating valid monitoring systems for quality in healthcare by collecting a fixed set of items of interest per area over time. The system is set up to continuously auditing quality of care through online benchmarking taking patient- and disease characteristics into account. Currently, the tumor registration group participates in audits for breast cancer (NBCA), colorectal cancer (DSCA), upper gastro-intestinal cancer (DUCA), lung surgery (DLSA) and lung radiotherapy (DLRA), melanoma treatment (DMTR),

gynecologic cancer (DGOA), liver cancer (DHBA) and head and neck cancer (DHNA), an implant registry (DBIR) and a prostate cancer registry (ProZib). In July 2016- June 2017 more than 2100 patients were registered for this purpose and the demand continues to increase.
A third registry, starting from July 2015 is the 'Landelijke Basisregistratie Ziekenhuiszorg (LBZ)'. This is a registry of medical, administrative and financial data of patients at the outpatient clinic, the day care department or who have been hospitalized. Key aspects are the use of ICD-10, an international coding system for diagnosis, and a standardized list of medical activities.
Last year the department has started processes to efficiently link with the Electronic Hospital Information System (EZIS) and integrating other available sources (e.g. PALGA) into the Data Warehouse (DW) of the institute. In collaboration with the department of `Informatievoorziening, Financiën en Control (IFC)', a major project is initiated to make full use of the DW to allow the registrations to take place as automated as possible. The efficiency will not only allow providing better overviews to the clinicians, but will also serve more efficiently data exchange initiatives and end-users with standardized clinical data.

Clinical studies and services

The Biometrics Department provides support for clinical trials performed in and by the Institute. Clinical Project Managers or Clinical Research Associates facilitate the development of protocols and submission to Medical Research-Ethics Committee (MREC) and coordinate the project management. Local data managers facilitate the initiation of studies and perform the registration of pre-screening, screening and entry of patients into clinical trials. They perform drug resupplies and are the source of information with regard to clinical trials in general. Central data management designs the Case Record Forms and takes care of the quality of the central data bases of investigator initiated studies and monitors ensure that the clinical trials are conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirement(s). The number of studies – approved according to the Medical Research Involving Human Subjects Act (WMO) – activated in 2017 (almost one hundred) was almost similar to that of the previous year, while the number of patients registered increased even slightly compared to 2016 (expected about 2800 patients). Currently about 250 WMO-studies are open for patient accrual. About one in every 5 patients who receives treatment in the AVL participates in WMO-studies.

Collaborations within the NKI

During the 'compassionate use' program of the novel immunotherapy agent Nivolumab, roughly 300 patients in the Netherlands Cancer Institute were treated after progressing on first line treatment. In responders, the duration of response and overall survival are a spectacular improvement over what was commonly seen in this patient group before the introduction of immune therapy, but unfortunately the percentage of responders is merely 20%. Hence, here in the NKI and elsewhere in the world researchers are trying to find biomarkers that in an early phase of treatment would tell the difference between patients who are going to respond and patients who will not respond to Nivolumab and might be better off with

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Publications Pharmacy

Bartelink IH, Prideaux B, Krings G, Wilmes L, Lee PRE, Bo P, Hann B, Coppé JP, Heditsian D, Swigart-Brown L, Jones EF, Magnitsky S, Keizer RJ, de Vries N, Rosing H, Pawlowska N, Thomas S, Dhawan M, Aggarwal R, Munster PN, Esserman LJ, Ruan W, Wu AHB, Yee D, Dartois V, Savic RM, Wolf DM, van 't Veer L. Heterogeneous drug penetrance of veliparib and carboplatin measured in triple negative breast tumors. Breast Cancer Res. 2017;19:107

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chemotherapy instead. The WA is involved in various projects of this kind, trying to find biomarkers based on thrombocytes (in cooperation with VUmc), based on gases measurable in the patients' breath using an 'electronic nose' (in cooperation with AMC), based on PET scans of the tumor and based on tumor markers measurable in blood such as NSE, Cyfra, CA125, etc which were already measured in all patients as part of the standard of care. The latter project is interesting for reasons beyond the application to Nivolumab. In a cooperation between the AKL (Huub van Rossum, Tiny Korse), Lung Physicians (Mirthe Muller, Michel van de Heuvel), I & A (Ruben Moritz, Jelle Wesseling) and WA (Tony van de Velde, Vincent van der Noort) we are creating a digital infrastructure that relates the blood marker data measured routinely by the AKL to clinical outcome parameters (response, progression, survival etc) and presents these relations in a user friendly and visually attractive way. The user interface displays the percentages of patients receiving the outcome of interest as a function of the relative increase in a biomarker to be chosen by the user between two time points to be specified by the user. The combination of flexible input and easy to read output serves several goals. It helps researchers trying to create composite biomarkers to quickly get a feel for the data and see what are the relative strength of the individual markers and times of measurement. Also it helps clinicians to help interpret measurements of an individual patient by providing context from past patients. Overarching goal hereby is to make it easier and more attractive for both clinicians and researchers to make more use of the lab data already available. An important strength in this last aspect is that the underlying lab data are updated automatically from Glimps so that the predictive power of the system increases with time without much extra effort.

In addition to developing a useful prediction model for Nivolumab response the near-term future objectives of the projects are on one hand to integrate this model with the digital environment in a 'self-learning' manner so that it automatically improves as more patients enter the database and predictions for individual new patients are easy to extract and on the other to make the underlying infrastructure available NKI-wide to link lab data to clinical outcomes in many different patient cohorts, thus enabling in a user friendly way the creation or exploration of biomarkers for various tumor types outside the study setting and preventing the 'going to waste' of lab data already collected.

This year final analyses of several phase III trials were completed. One example is the CRITICS trial, in which almost 800 patients with gastric cancer were randomized to preoperative chemotherapy, surgery and postoperative chemotherapy or preoperative chemotherapy, surgery and postoperative chemoradiotherapy. The primary endpoint was overall survival. No superiority of the postoperative chemoradiotherapy was found. In the CRITICS randomization was done before neo-adjuvant chemotherapy, which prevented selection bias, but resulted in several methodological consequences. Responsibility of our group was to assure a proper inference of this trial and to communicate it with the clinicians.

In the field of immunotherapy many `pick-the-winner` phase II designs are being set up. Most commonly those trials are designed according to the two-stage Simon's design. A disadvantage of this design is the necessity to put the trial on hold for a couple of weeks/months during the interim analysis. This causes logistical consequences and it is it generally

considered undesirable by the investigators. Therefore, when possible, we are shifting towards Bayesian equivalence of the Simon's design, which allow us to run trials more smoothly keeping its desirable safety. In 2018 a PhD student will start a project in collaboration with the Julius Center in Utrecht in which efficient designs and methods of analysis of – in particular – biomarker-driven research questions will be studied.

Collaborations with the Princess Maxima Center

In 2015, the department was asked to extend their data center and in particular statistical services to the area of Innovative Therapies for Children with Cancer (ICTT) of the Princes Maxima Medical Center (PMC). The PMC (Prof. CM Zwaan) is leading in a few international phase I/II studies with novel drugs such as Bosutinib in pediatric patients with chronic myeloid leukemia who are resistant or intolerant to at least one prior tyrosine kinase inhibitor therapy and Inotuzumab Ozogamicin as a single agent and in combination with chemotherapy for pediatric CD22-positive relapsed/refractory acute lymphoblastic leukemia (each with 5 patients currently recruited) and Crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies (in the startup phase). Other projects performed in the setting of ITCC include the study of Azacitidine (Vidaza®) in pediatric patients with relapsed high-grade pediatric MDS or JMML (currently 8 patients recruited) or a feasibility and phase II study of Bortezomib (Velcade®) in childhood relapsed acute lymphoblastic leukemia (manuscript submitted). Additional projects include the collaboration in a chapter about clinical and drug research in an upcoming Handbook of Pediatric Oncology edited by G. Kaspers (existing app currently in test version).

In the context of the longstanding service provided to the international collaborative group (co-chair Prof. M.M. van den Heuvel-Eibrink) on Wilms' tumors (SIOP-RTSG), a number of analysis were performed. These studies were based on a database of children with nephroblastoma from 261 centres in 28 countries in Europe and elsewhere, centrally collected and maintained at our department. The risk of biopsies at diagnosis with respect to outcome was studied in 2971 patients, the prognostic value of age was modeled in 5341 patients and the optimum surveillance schedules and methods for detecting tumor relapse post therapy was studied in 4271 eligible patients. All manuscripts have been submitted. A new protocol and therapy guide for Wilms' tumors is currently in the process of being evaluated by national MRECs and will be initiated in 2018. The protocol contains the most up-to-date guidelines for diagnosing and treating Wilms' tumors and recommendations for non-Wilms' renal tumors. Over time research proposals will be developed and integrated into the protocol. One of the areas of interest will be new therapies in stage IV patients. For the first time data will now be centrally collected in an electronic data capturing system with case record forms developed at the Biometrics department in ALEA.

Collaborations with national study tumor groups

One of the collaborations of the department with the national breast cancer research group (BOOG) is the Stop&Go study. This open randomized phase III non-inferiority study comparing 8 continuous cycles of chemotherapy with 8 cycles of intermittent (2 times 4 cycles) chemotherapy in first line treatment, in combination with bevacizumab, and second line treatment

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of patients with HER2/neu negative, incurable, metastatic or unresectable locally advanced breast cancer. An oral presentation of results from first line treatment was given at the ESMO 2017 Congress in Madrid. A manuscript is currently being finalized and is expected to be submitted before the end of the year.

The collaboration of the with the Dutch Colorectal Cancer Group (DCCG) has already brought about several large randomized phase III studies. This year the results of the SALTO study were published. In this study, 161 patients from 27 hospitals in the Netherlands were treated either with capecitabine or S-1. S-1 is an oral fluoropyrimidine which has an efficacy comparable to capecitabine in gastrointestinal cancers, but which is associated with a lower incidence of hand-foot syndrome (HFS) in Asian patients. The SALTO study investigated whether giving S-1 instead of capecitabine as first-line treatment could reduce the incidence of HFS for colorectal-cancer patients from Western countries too.

The cumulative incidence of grade 2/3 HFS was calculated by using statistical methods from the field of survival analysis (figure 1). Patients without HFS were censored at the last day of treatment except if treatment was stopped because of disease progression, which was considered as a competing risk in this analysis. By doing so, the calculation could take into account that treatments which were given without toxicity until progression, should be counted as a success. This prevents the bias that would have arisen if the Kaplan-Meier estimator would have been used. On the other hand however, the method also takes into account that patients without HFS but who stopped early for other reasons, provide only information about the incidence during the time they were actually on treatment.
Therefore, this analysis gives a more reliable comparison of the two treatments than a simple 2x2-table.

The most extensive collaboration in terms of services is with the Dutch Chest Physician Association (NVALT). Since 1999 the department is involved in the planning, designing, running, monitoring, handling administration of adverse events, and analyzing the clinical trials of this group in lung cancer and mesothelioma. In 2015 the support has been extended with a clinical trial coordinator and a legal expert taking care of all the contracts and legal issues. More than 40 hospitals in the Netherlands participate in these clinical trials. Funding has been obtained from the KWF and pharmaceutical company grants.

The NVALT 8, a randomized phase II study of adjuvant chemotherapy with or without low-molecular weight heparin in completely resected non-small-cell lung cancer patients was written down in a manuscript and is submitted to the JCO.

The NVALT11 evaluated the value of prophylactic cranial irradiation (PCI) versus observation is studied in radically treated patients with stage III non-small cell lung cancer. The results were presented at the ASCO, 2017 and also submitted to the JCO. In addition, a collaboration has been initiated with the meta-analysis study group of the Institute Gustav-Roussy (dr. JP Pignon) in Paris to perform an individual patient data meta-analysis on this subject.

The NVALT18, a randomized phase II study of docetaxel versus intercalated erlotinib docetaxel combination therapy in patients with relapsed EGFR wild type, ALK negative non squamous cell carcinoma, the NVALT 22 a phase III comparing cisplatin-pemetrexed with carboplatin-paclitaxel-bevacizumab as first line chemotherapy in KRAS mutated non-small cell lung cancer patients and the NVALT24, randomized, placebo-controlled trial of the human monoclonal antibody directed against programmed cell death ligand 1 (PD-L1) MEDI4736 in completely resected primary stage IB (> 4cm), II and IIIA non-small cell lung cancer patients, the latter by invitation of the National Cancer Institute of Canada are all currently accruing patients.

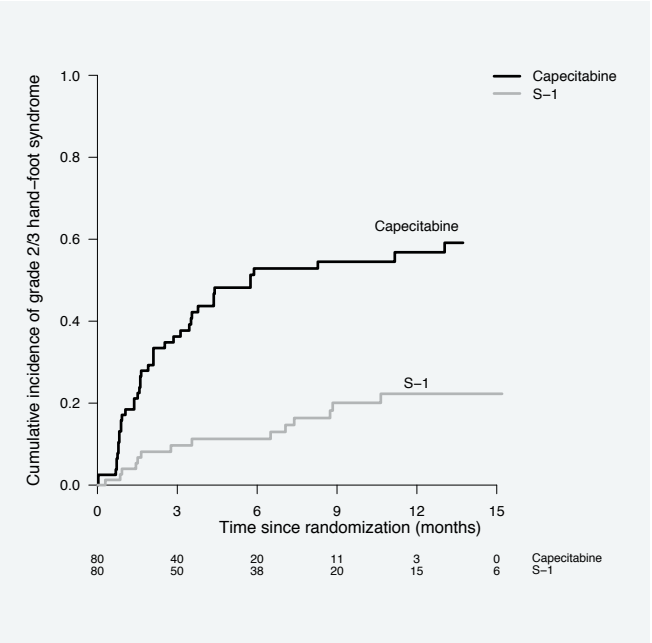
Finally, in 2016 the department was asked to setup a national register for immune modulating treatment in lung cancer. Currently 2444 patients have been registered and the registry will be extended to include all expensive drugs applied in lung cancer. Recently a Data Access Board has been installed and a first manuscript about the data is drafted. In 2018 a WMO-translational research study will be starting, linked with the registry, exploring and validating resistance mechanisms in thoracic oncology patients treated with immune modulating or targeted therapy.

The statisticians have collaborated with many departments of the institute and other, academic and non-academic institutes in a variety of studies. All these collaborations resulted in co-authorships of more than 35 peer-reviewed publications in 2017 (see reference list).

PHARMACY DEPARTMENT

Drug manufacturing

We supported >20 mono- and (international) multi-center clinical trials (*e.g.* DRUP, POSEIDON, REPOSIT) with drug manufacturing, packaging and distribution. Novel pharmaceutical formulations have been designed and tested in clinical studies in-house. An example is PazSol001, an alternative formulation of pazopanib (Votrient®) which showed a significant increase in solubility and bioavailability as compared to the marketed formulation. Development and manufacture of vorinostat, a histone deacetylase inhibitor, enabled a clinical study with the compound in advanced resistant BRAF V600 melanoma. Furthermore, clinical studies with the in-house developed and manufactured oral solid dispersion formulations of docetaxel (ModraDoc006) and paclitaxel (ModraPac005) are ongoing.
The Biotherapeutics Unit (BTU) is a biotech facility within our department. Here, we develop and manufacture ATMPs (Advanced Therapeutic Medicinal Products) for clinical trials. Currently, Tumor Infiltrating Lymphocytes (TIL) infusions are produced for melanoma patients participating in a multi-center phase III trial with TIL therapy which is the first and only in the world. In 2015, this treatment was selected to receive temporary re-imbursement by the ministry of health. At this time (November 2017), 45 patients have been treated with TIL *or* ipilimumab therapy in this trial. BTU also manufactures MART-1 T cell receptor modified T cells. We observed powerful on-target reactivity of these cells in cutaneous and uveal melanoma patients and then decided to treat other patients with



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an adjusted cell number and milder chemotherapy to reduce toxicity. In 2017, 5 patients have been treated in this manner. Future clinical trials with TCR modified T cells and innovative T cell therapies directed against patient specific neo-antigens are now prepared. Besides T cell products, DNA vaccines have been manufactured for HPV induced malignancies, in the context of the FP7 RAIDs program. The second clinical trial in this consortium will test plasmids encoding the onco-proteins E6 and E7 cloned in a minimal helper cassette containing subcellular localization sequences. The first patients in this trial are enrolled by the Gynecology department (prof. G. Kenter). We perform immune monitoring for this trial. BTU is also partner in the FP7 TargetAMD consortium for which clinical grade pDNA for the *ex vivo* transfection of retina cells, is produced. In 2017, the first clinical batch, containing a mixture of transposon / transposase pDNA in electroporation buffer, has been produced and successfully quality controlled and released.
The radiopharmaceutical ^{177}Lutetium-PSMA for imaging and treatment of prostate cancer is under development.

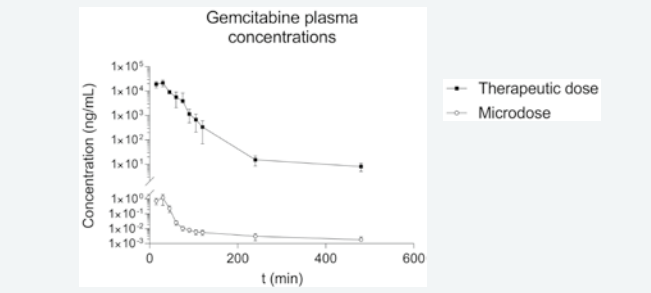
Bioanalytical method development + implementation in pharmacokinetic studies

Our therapeutic drug monitoring (TDM) service for the optimization of drug treatment, particularly with the new tyrosine kinase inhibitors (TKIs), has been extended past year and now includes more than 30 agents. The number of samples grows annually: we have started this service in 2010 with around 100 samples and this year we expect to receive 3500 samples for analysis. To handle this big increase of samples we have developed liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods where we quantify more than 10 different oral drugs in a single run. We have also set up a specific assay for Δ(4)-abiraterone, a newly discovered active metabolite of the androgen receptor inhibitor abiraterone. In general, our extensive data sets combining laboratory values (drug concentrations in plasma) and clinical observations (antitumor activity / toxicity) greatly aids to define and to advise the right drug dose for each patient and which can be considered as an ultimate form of personalized medicine. Lurbinectedin (PM01183) is a synthetic analogue of the marine derived drug trabectedin (Yondelis®) and is currently investigated in clinical trials. A mass balance study is performed to investigate the routes and the time course of excretion of lurbinectedin. Moreover, a metabolite profiling study is executed to identify and to quantify metabolites formed in treated patients. In this clinical trial, six patients receive an intravenous dose of 5 mg of ^{14}C-PM01183 (100 µCi), after which plasma, urine and feces samples are collected. Validated LC-MS/MS assays were developed to quantify lurbinectedin in plasma and in urine. Furthermore, total radioactivity analyses are executed on all samples to measure the amount of radioactivity. So far, four patients have been included in the trial. Recovery of radioactivity was nearly complete, with a mean (±SD) total cumulative recovery of 96.9 (±9.9)%. Feces is clearly the main route of excretion with a mean total recovery of 91.4 (±11.9)%. The identities of the metabolites still remain to be elucidated. Another mass balance study is currently carried out with SGI-110, also known as guadecitabine. SGI-110 is a prodrug of decitabine, which acts as DNA methyltransferase inhibitor. Preliminary results of the mass balance trial show that SGI-110 is rapidly metabolized and excreted, with the renal pathway

as a major route of elimination. Further research is ongoing to elucidate the metabolic pathway of SGI-110 as well as its intracellular mechanism of action.
Micro dose studies are exploratory investigational new drug (eIND) trials which can provide valuable information on the pharmacokinetics of the investigated compound. The aim of such trials is to accelerate drug development by early selection of promising candidates with a minimal drug exposure to study participants. We conducted a proof-of-concept trial, in which a gemcitabine micro dose, being >10,000 fold lower than the therapeutic dose, was administered in order to determine drug pharmacokinetics. We were able to measure plasma concentrations in the low picogram per mL range with our ultrasensitive LC-MS/MS (API 6500) platform. The included figure 2 shows concentration-time curves of gemcitabine after administration of a micro dose (100 µg) and after administration of a therapeutic dose (1,000 – 1,250 mg/m^2) in five study patients.
Routine analysis to support trials within and outside the Institute concerned paclitaxel, docetaxel, capecitabine and its metabolites, vorinostat, olaparib and platinum (originating from cisplatin, carboplatin and oxaliplatin). To screen for dihydropyrimidine dehydrogenase (DPD) deficient patients, we analyse the DPD substrates uracil (U) and dihydrouracil (UH_2) in plasma to prevent the increased risk of developing severe fluoropyrimidine-related toxicity.

Pharmacokinetic and Pharmacodynamics (PK/PD) modelling and simulation

Research on population PK/PD modelling and simulation was focused on the optimization of trials with novel agents and improved use of approved agents. Our group is one of the partners in the recently initiated Research High Performance Computing facility within the Institute. Previously, the feasibility and safety of individualized dosing of pazopanib based on therapeutic drug monitoring was shown. We performed a retrospective assessment of the relationship between pazopanib blood trough concentrations and efficacy in a real world clinical setting and confirmed the threshold of 20 mg/L from clinical trial data as a relevant target for efficacy of pazopanib in both renal cell cancer as soft tissue sarcoma. As pazopanib has a dose dependent bio availability, plasma exposure may also be increased by splitting the dose instead of a dose increase. For this, simulation studies were conducted using a previously developed PK/PD model showing this increase when switching form 800 mg once daily to 400 mg twice daily. Based on these results, a clinical trial is ongoing in patients with low pazopanib exposure.
The relationship between left ventricular ejection fraction (LVEF), trastuzumab and anthracylin exposure was evaluated using population PK/PD modeling. From this analysis it was concluded that high troponin T levels after anthracyclin treatment and before trastuzumab treatment are predictive for the larger decreased in LVEF. This model will be used to further improve the monitoring and management of trastuzumab treatment.
Previously, a relationship between the active tamoxifen metabolite endoxifen plasma concentration and treatment outcome in breast cancer has been established. We studied the contribution of other endoxifen metabolites to overall anti-estrogenic activity and outcome using the same dataset.



Plasma concentration-time curves of gemcitabine after i.v. administration of a microdose (100 µg) (○) and a therapeutic dose (1,000 – 1,250 mg / m2) (■)

For this, the anti-estrogenic activity of tamoxifen and three metabolites was evaluated in vitro. The in vitro activity was subsequently used to calculate an overall anti-estrogenic activity score by dividing the concentration of the metabolite by its relative activity. This anti-estrogenic activity score proved to be a slightly better predictor for treatment outcome than only endoxifen albeit that endoxifen accounted for most anti-estrogenic activity.
We are currently involved in various clinical trials taking place in East Africa, Colombia, and South Asia on the neglected tropical parasitic disease leishmaniasis, mainly focusing on the repurposed anticancer PI3K/Akt inhibitor miltefosine. For the first time we have identified a relationship between disease relapse and miltefosine exposure and in various studies the past year we demonstrated that children were underexposed and require a higher drug dose. Based on our population PK models we developed an optimized allometric dosing regimen for pediatric patients, which is currently being evaluated in a clinical trial in Kenya and Uganda. Current research will focus on integrated modelling of parasitic and immunological biomarkers in relation to treatment response and drug exposure. Our group is partner in the recently awarded H2020 consortium Afri-KA-Dia, which will investigate efficacy and PK/PD of combination therapies for leishmaniasis in East Africa.

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Division of Radiation Oncology

In 2017, the department continued to invest in its two main research themes: image-guided adaptive radiotherapy (IGART) and targeted radiosensitization.

By combining geometric, biological and functional imaging information before, during and/or after irradiation, we are able to update the treatment plan if necessary. This adaptive strategy, in combination with 3-dimensional in vivo dosimetric verification, contributes to the ultimate ambition of state-of-the-art radiotherapy: individualized, highly precise and safe treatment delivery.

As member of the international MRI-Linac Consortium, we conduct tumor site-specific studies on MRI-guided treatment planning and delivery, and prepare the introduction of this new imaging/treatment machine in our clinic. In 2017, we started a clinical study on MRI-sequence optimization and workflow development for treatment guidance, using the integrated MRI scanner of the MRI-Linac system.

Our lab research aims to translate targeted radiosensitizers from bench to bedside and vice versa. Several of these "bio(chemo)radiotherapy" strategies are already part of our expanding clinical program, including DNA-PK inhibition, DNA repair interference, immunomodulation and anti-angiogenesis.

At the ESTRO meeting in May in Vienna, Paul Essers, postdoc in the Verheij/Vens group, received the prestigious Donal Hollywood Award for his research on prediction of DNA repair defects in head and neck cancer.

On August 1st, Dr. Ir. Jan-Jakob Sonke was appointed professor in Adaptive Radiotherapy at the University of Amsterdam.

In December, the department held its 6th Radiotherapy Retreat on bridging strategies between our clinic and research.

In December, we introduced the Papillon technique, together with our surgeons and gastro-enterologists as the first clinic in The Netherlands. This modernized image-guided contact therapy device delivers high local superficial doses of radiation and is used for the treatment of small (primary, residual or recurrent) rectal tumors.

In 2017 five (MD)PhD students successfully defended their theses:
- Femke van der Leij: Optimizing Treatment of Low Risk Breast Cancer Patients
- Simon van Kranen: Geometric Uncertainties and Mitigation Strategies in Radiotherapy of Head and Neck cancer
- Roel Rozendaal: Large Scale In Vivo EPID Dosimetry
- Heike Peulen: Optimization of Lung SBRT
- Monique de Jong: Predicting Radioresistance in Head and Neck Cancer

PRE-TREATMENT IMAGING AND IMAGE PROCESSING

Cuong Dinh, Catarina Dinis Fernandes, Petra van Houdt, Rick Keesman, Ernst Kooreman, Edzo Klawer, Marcel van Schie, Rita Simoes, Uulke van der Heide

With in-room imaging devices such as cone-beam CT and the MR-linear accelerator, we can deposit intricate dose distributions to target heterogeneous tumors accurately. This requires automated processing of images, for example for contouring of target volumes and organs at risk. This also creates an opportunity to adjust the radiation dose to the local radiation sensitivity. Our research focuses on automated image processing and the development and validation of quantitative imaging methods that allow tumor characterization for radiotherapy dose painting. Strategies to integrate anatomical and quantitative MRI and PET in the radiotherapy workflow are designed and applied to a range of tumor sites. We also investigate the potential of these techniques as imaging biomarkers to predict outcome after radiotherapy.

TREATMENT PLANNING

Geert Wortel, Erik van der Bijl, Emmy Lamers, Angela Tijhuis, Dave Eekhout, Amber Duijn, Johan Trinks, Rob Harmsen, Agnieszka Olszewska, Guus Retèl, Tomas Janssen, Eugène Damen

Single-click automated treatment planning

Labour-intensive procedures, such as adaptive radiotherapy and complex treatment plans, result in an increased workload in the treatment planning department. We therefore started the FAST-planning project, a Framework for Automatic Segmentation and Treatment planning. The purpose of this project is to produce single-click automated treatment planning for the majority of tumor sites.

In FAST planning, the patient id, dicom identifiers and the selected planning protocol are combined, and an Autoplan document (XML) is composed. In the framework, each module accepts Autoplan documents and coordinates actions accordingly; e.g. automatic localization of the patient record, import of DICOM objects with delineated target volumes, auto-segmentation of OARs, creation of additional ROIs, creation of advanced beam-setups (VMAT, IMRT), optimization and finally the creation of a report (optionally uploaded to R&V MOSAIQ). The software is written in Python and makes use of Pinnacle3 scripting and transfer protocols DICOM and XML over HTTP. The following workflow is automated: after the physician delineated the target, a single mouse-click initiates RT plan generation on our remote treatment planning system Pinnacle3. Subsequently a preview report of the generated plan is send to R&V system MOSAIQ. The created RT plan is fully optimized and ready for inspection by the RTT. As of December 2017, FAST-planning has been implemented into our clinic for Breast, Prostate, Head and Neck, rectum, 'simple planning'.

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Publications

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Apart from the FAST framework, we have extensively worked on the implementation of Pinnacle Autoplanning (AP) in daily clinical practice. Where FAST is an automation of the workflow, AP is an automation of the actual planning activity. We have now implemented AP for rectum, prostate, head and neck (elective fields only) and simple planning. For all these techniques, we have shown that the plans generated using AP are at least similar (and sometimes better) in quality, compared to manual plans.
This, combined with our in-house developed automatic planning module for breast cancer patients, results in a fully automated workflow for all these sites.
The automation of these treatment sites has reduced the RTT's planning time considerably (up to 2 hours per RT plan), while maintaining the same plan quality. The workflow automation currently covers approx. 25% of our patient throughput, i.e. 1500 RT planning sessions/year.

Robust Mamma VMAT treatment planning

In order to deliver a conformal dose distribution to breast cancer patients, physicians more and more tend to prefer modern techniques like VMAT over the conventional irradiation technique using two tangential fields. However, due to the large amount of geometric uncertainties and deformations in the breast, it is not obvious that such a technique delivers the dose in a robust manner.
In order to deal with this issue, we developed a VMAT technique that is robust to anatomical variations. We do this by artificially expanding the breast tissue during a first round of beam aperture optimization and subsequently optimize only the aperture weights of the plan without the artificial expansion, leaving the beam appertures untouched. In this way, one ensures that the beam appertures cover a possible expansion of the breast tissue, while not overcompensating in the nominal situation.
Using both simulation as clinical conebeam data we have validated both the lack of robustness of a conventional VMAT approach for breast cancer, as the robustness of our approach. Moreover, we have shown that the technique can be safely combined with deep-inspiration breathhold. The technique is currently in clinical use at our department.

Quality assurance of prostate autoplanning

Treatment planning for our prostate cancer patients is performed fully automatic using FAST and the Pinnacle Autoplanning (AP).
In collaboration with Erasmus MC we have studied the quality of these plans using a machine learning approach to planning QA. In this approach, the anatomy of the individual patient is related to the resulting dose distribution. Therefore, if the model is properly trained, one can use it to predict the achievable dose distribution for a given patient. We used this approach to check whether AP results in the optimal expected dose distributions. For this we used a database of 100 clinical AP patients, split in a testing and training set (50/50). The resulting analysis found 6 outlier plans that all could indeed be potentially improved. Apart from these outliers, predictions where accurate with the mean difference well within one standard deviation. Pinnacle AP created acceptable treatment plans for the far majority of patients, but suboptimal plans did occur. Therefore, in clinical practice we recommend the use of independent treatment plan QA in combination with Pinnacle AP.

EPID DOSIMETRY

Igor Olaciregui-Ruiz, Iban Torres-Xirau, Brent Huisman, Kees Landheer, Aldemar Torres Valderrama, René van Oers, Ben Mijnheer, Anton Mans

DVH-based evaluation criteria

Currently, g evaluation is the commonly applied method for comparison of two (multi-dimensional) dose distributions. This method, however, has some disadvantages: results cannot directly clinically meaningful, it does not distinguish between under- and overdosage and systematic differences may go undetected. Our 3D in vivo dosimetry method allows for another comparison method: DVH (dose-volume histogram) analysis. We investigated the correlation between g and DVH parameters for three pelvic treatment sites. Strong correlations between mean g and g pass rate and difference in PTV ΔD50 were observed for all sites. DVH- and g-based alerts agreed on >80% of the fractions for the majority of the investigated alert thresholds and methods. In conclusion, the comparison of multi-parametric alert strategies showed clinical equivalence for g and DVH-based methods.

Virtual patient 3D dose reconstruction

At our institute, a back-projection algorithm is used to reconstruct *in vivo* patient and pre-treatment in phantom 3D dose distributions using EPID measurements behind a patient or polystyrene slab phantom, respectively. In order to eliminate the need for phantom positioning and re-planning, an extension to the back-projection algorithm was developed whereby in air EPID measurements are used in combination with patient planning CT data to reconstruct virtual patient 3D dose distributions. The new method was verified against the transit algorithm with measurements made behind a slab phantom, against dose measurements made with an ionization chamber (IC), as well as against dose calculations performed with our clinically used treatment planning system (TPS). Virtual and *in vivo* patient dose verification results are also compared. Virtual dose reconstructions agree within 1% with IC results. The average g pass rate values in 3D dose comparison with IC array and TPS patient data are 98.5 ± 1.9% (1SD) and 97.1 ± 2.9% (1SD), respectively. The new method makes pre-treatment verification based on deviation of DVH parameters feasible and eliminates the need for phantom positioning and re-planning.

Portal dosimetry for the MR-Linac

Last year, we have demonstrated the feasibility of applying a back-projection method in the presence of a strong attenuating medium. This year, we took the method a step further, and performed a characterization of the MR-Linac for portal dosimetry. The magnetic (B) field at the position of the panel was very low (< 10 mT). Experiments with and without B field show that the impact of the B field on the detector is negligible. IC and EPID measurements show that the beam attenuation by the housing and the couch is gantry angle dependent. Furthermore, excellent repeatability of portal dose was demonstrated. These results give us confidence that back-projection portal dosimetry for the MR-Linac is feasible (figure 1).

Towards template-based commissioning

Currently, an elaborate series of measurements is performed to calibrate an EPID for dosimetric use. However, as the panels used on different linacs are of identical type, and linac beams

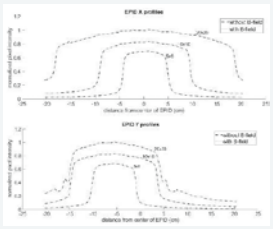

Figure 1. X(top) and Y (bottom) EPID lateral profiles of square fields of 5x5, 10x10 and 20x20 cm^2 irradiated to a 20 cm slab phantom are shown for images acquired with (dotted-grey) the magnetic field, and without (dashed-black). Note the shift of the Y profiles due to the non-centered position of the EPID, and also the strong attenuation because of coils affecting the 10x10 cm^2 curve in the penumbra, and more clearly the 20x20 cm^2 field, creating also oscillations due to heterogeneities in the cryostat, and the ring.

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are commissioned to be equivalent, it is expected that the parameters of a commissioning model shouldn't vary too much between EPIDs and linacs. Therefore, we investigated the use of template commissioning models, and compared results from phantom and patient verifications between full and template-based commissioning models. All results show differences smaller than 1.1%, demonstrating the clinical applicability of the template-based approach.

IMAGE GUIDED ADAPTIVE RADIATION THERAPY

Casper Carbaat, Heike Peulen, Iban Torres-Xirau, Ingrid Valkering, Jose Belderbos, Maddalena Rossi, Martin Fast, Monique Bloemers, Nelly Kager, Olga Hamming-Vrieze, Peter Remeijer, Rob de Graaf, Rose Koopman, Shaheen Ali, Simon van Kranen, Stijn van de Schoot, Tessa van de Lindt, Uulke van der Heide and Jan-Jakob Sonke

Decision rule for adaptive plan modification for radiotherapy of head-and-neck cancer patients based on accumulated dose

The delivered dose in head-and-neck cancer radiotherapy may deviate from the planned dose due to systematic and progressive anatomical changes. The purpose of this work was to develop a decision rule for adaptive radiotherapy that selects patients with the largest dosimetric discrepancies. To that end, for 89 patients treated with a simultaneously-integrated-boost to 70 Gy in 35 fractions, dose was recalculated on daily cone-beam CTs and accumulated on the planning CT. Relevant DVH-parameters were extracted for various organs-at-risk (OARs) and targets. Given the first f fractions, regression analysis was applied to estimate the final accumulated DDVH-parameters (accumulated – planned) and the corresponding prediction-interval at uncertainty level a. Patients for which the prediction-interval was below\above (for target or OAR respectively) the c% highest\lowest final DDVH-parameter distribution were marked as candidates for adaptive intervention. Receiver-Operator-Curves were constructed by varying the uncertainty level a, simultaneously evaluating all OARs and CTVs for fractions 5-20. The accumulated mean dose for the parotid glands (PGs), constrictor muscle and oral cavity differed from planned with respectively: 0.6±1.2 Gy, 0.2±0.6 Gy, 0.2±1.1 Gy, the D99% for the primary and elective CTVs, with -0.5±0.8 Gy and -0.4±0.5 Gy. With c =95%/85%/75% for each OAR\CTV, 16/32/50 patients were regarded as candidates for adaptive intervention. DVH-parameter prediction was capable of modeling the progressive changes to PGs and other VOIs. Patients could be identified with an area under the curve ranging from 0.55 (fraction 5), 0.80 (fraction 12) to 0.95 (fraction 20), more or less independent of c. In conclusion, a decision rule based on daily dose accumulation was successfully developed to predict predefined deviations in DVH-parameters early in treatment with high accuracy. The clinical workload can be balanced with tolerance to dose discrepancies.

Tumor trailing for liver SBRT

Tumor trailing is a delivery technique which continuously adjusts the shape of the beam aperture according to the time-averaged (mid) position of the target. Unlike MLC tracking, trailing only

compensates the low-frequency components of motion, thus easing the requirements on image frequency and system latencies. This study investigates whether tumor trailing can improve target coverage in liver SBRT treatments in the case of substantial baseline drifts. To that end, liver SBRT treatment plans were created and treatment delivery was simulated using in-house developed software. Target motion was modelled as cos^4 trajectory (amplitudes from 4dCT, 4 sec period) centered around the mid-position, with 1 cm/20 min and 5 mm/20 min baseline drifts added in cranial and posterior direction respectively. The trailing delivery was based on the mid-position of the target, calculated from three previous respiratory cycles. The average peak-to-peak respiratory motion was 8.6 mm in superior-inferior and mean delivery time was 19.8 min. The average increase in GTV D100% of the trailing delivery compared to a conventional delivery without active motion mitigation was 3.0 Gy per fraction (figure 2). In conclusion, tumor trailing improves target dose in liver SBRT in cases of large baseline drifts.

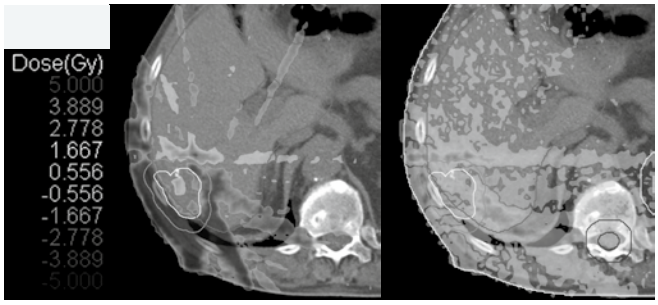

Figure 2. (left) Conventional delivery minus original plan. (right) Trailing delivery minus original plan. Note that dose from a single 20 Gy fraction delivery is tripled in this representation.

Library of plans and CTV-PTV margins for VMAT irradiation of cervical cancer

The purpose of this study was to evaluate possible margin reduction following clinical introduction of a library of plans (LoP) correction strategy for cervical cancer radiotherapy. To that end, for each patient intermediate CTV structures were constructed from manual CTV delineations of the cervix-uterus on a full and empty bladder pCT in combination with an algorithm that utilizes Robust Point Matching for interpolation. Intermediate CTV structures were generated with a maximum distance of 1 cm between CTV structures. The number of CTV structures within the library thus depends on the maximum distance between the manual CTV delineations of the cervix-uterus on the full and empty bladder pCT. Two CTV-PTV margins were applied: A) 1 cm left-right and 1.5 cm in other directions, B) 1 cm isotropic. Subsequently, three observers selected the most appropriate CTV out of the library for each CBCT of each patient. The observers verified for each CBCT if the uterus and cervix were in the PTV of the selected LOP for margin A and B. For margin A, the top of the uterus was outside the PTV in 8% and 16% of the pre- and post-treatment CBCTs respectively. For margin B, this was the case in 15% and 26% of the pre- and post-treatment CBCTs. For margin A, the cervix was always inside the PTV while for margin B, the cervical markers were outside of the PTV in 1-2% of the pretreatment and 2-3% of the post treatment CBCTs. In conclusion, the clinically used CTV-PTV margin of 1 cm left-right and 2 cm in other directions that is used for VMAT irradiation of cervical cancer could be reduced with the use of LoP, provided that the geometry of cervix-uterus with respect to the PTV is carefully monitored.

Geometric validation of a 4D-MRI guided correction strategy on the MR-Linac

Respiratory motion in upper-abdominal targets remains a challenge for accurate radiotherapy delivery. The introduction of an integrated MRI and linear accelerator (MR-Linac) allows for daily target visualization in upper abdominal tumors. Therefore, the aim of this study was to develop and validate a 4D-MRI guided mid-position (midP) correction strategy on an MR-Linac. Experiments were performed on an MR-Linac (ATL1, Elekta AB, Sweden), using the CIRS MRI-LINAC Dynamic Phantom (CIRS Inc., USA). The moving cylinder was filled with anisotropic MRI

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contrasts and a Perspex spherical target. Motion was performed in CC direction using a Lujan 4 motion pattern with a 20mm amplitude and 4s period. Cranial-caudal baseline shifts of 5, 10, 15 and 20mm were applied to the phantom motion. For every shift, a retrospective self-sorted 4D-MRI was acquired (axial single-shot TSE, 2x2x5mm3, TE/TR=60/400ms, 30dyn) and each phase was registered to the midP reference image to calculate the time average displacement. The plan was adapted accordingly, performing a virtual couch shift using aperture morphing. All plans were delivered while electronic portal imaging device (EPID) cine images were acquired. The time average displacement of the target was calculated from the EPID images and geometric accuracy of the workflow was quantified as the distance of the average position of the target to the field edges in the EPID images. The geometric accuracy of the 4D-MRI guided workflow was 0.3±0.4mm in CC, which includes the 4D-MRI registration accuracy. In conclusion, 4D-MRI guidance on an MR-Linac was shown to be feasible and had sub-millimeter accuracy. Such a correction strategy has great potential for moving targets that are difficult to visualize on alternative image guidance modalities.

A simplified IGRT protocol for SBRT of central lung lesions

IGRT protocols for SBRT of pulmonary lesions often consists of a pre-correction CBCT to determine the couch shift that aligns the tumor and a post correction (PCorr) scan for verification of the applied shift. The purpose of this study was to evaluate the potential to omit a Pcorr scan for SBRT with 8 fractions. To that end, 16 patients treated with 8x7.5Gy without a Pcorr scan were compared with fifty patients treated with 3x18Gy following a PCorr scan. Patient characteristics were compared and intra-fraction tumor position variability in Left/Right(LR), Cranial/Caudal(CC) and Anterior/Superior AP) were calculated in terms of Group Mean(GM), systematic (Σ) and random(σ) variations. No significant difference in patient characteristics between the groups was observed; Intra-fraction tumor position variability in both groups was small in all directions. The GM and random error were not significantly different between the 2 groups whereas the systematic error was significantly smaller for the 8x7.5Gy group in the AP direction. In conclusion, a setup correction validation scan could be safely omitted for patients with central tumors treated with a 8x7.5Gy dose regimen.

BREAST CANCER

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PAPBI trials (Preoperative Partial Breast Irradiation)

In 2017 the Image guided Preoperative Accelerated Partial Breast Irradiation (PAPBI)-has closed. This trial was directed at implementing pre-operatively given image guided accelerated partial breast irradiation without compromising local control in early breast cancer patients. By assessing tumor response to radiotherapy, the goal of the study is to develop a gene expression profile that predicts the breast cancer radiosensitivity. This gene signature of breast radiosensitivity would further design optimal treatment strategies for individual breast cancer patients treated with BCT.

To qualify for the trial, patients must be 60 years or older, and have a unifocal cT1-2 (≤3 cm) pN0 M0 breast cancer; sentinel node procedure before irradiation. 78 patients were treated by PAPBI consisting of delivering 10x4 Gy over 12 days. The radiation schedule has changed to 5x6 Gy in a 1 week schedule, to reduce the overall treatment time, this shorter schedule is commonly used in post-operative radiation partial breast irradiation. Six weeks after PAPBI, a wide local excision is performed. As the tumor remains 'in situ' during irradiation, accurate tumor delineation and control of accurate radiation dose delivery to the tumor becomes possible by treating these patients with a cone beam CT linear accelerator.

To identify a subgroup of breast cancer radiosensitivity, biological studies performed are gene expression profiling from RNA and DNA isolated from biopsies taken of the tumor before radiotherapy and at time of surgery. The mRNA gene expression profiles, the miRNA expression profiles and the DNA copy number changes will be correlated with response to radiotherapy, defined as pathologic response at the time of the lumpectomy (i.e. 6 weeks after the completion of the PAPBI). Response of the tumor will be evaluated by MRI scan and PET (before radiotherapy and before surgery) and classical pathology. In total 140 patients are needed.

At this time, 139 patients are included in the study (NKI n=73; IGR n=39; Karolinska n=10; UMCU n=17). The first 70 patients (all treated with 10x4 Gy) were analyzed. Post-operative complications were noted in 11 of 70 patients (16%) The overall postoperative infection rate was 11%. The majority of patients had no or mild fibrosis and fibrosis improved over time. At 1, 2 and 3 years of follow-up respectively 90%, 98% and 100% of patients had no or mild fibrosis. Fibrosis was only found in a small volume of the breast. The global cosmetic outcome, scored by the physician, was good to excellent in 77% at 6 months to 100% at 3 years. The majority of the Dutch patients was satisfied to very satisfied with the cosmetic result; 81%, 86%,

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80% and 79% after respectively 0.5, 1, 2 and 3 years. Three patients developed a local recurrence.
Other important aspects of this study are collections of fresh frozen tumor tissue (i) to assess the radio-induced genetic alterations on the surgical post-radiation specimen compared to the tumor response 6 weeks after the end of radiotherapy; (ii) to study the early changes in gene-profiling and (iii) to evaluate the early functional imaging modifications. In 2018 the results will be updated. In the meantime, the promising results of the PAPBI trial, led to an international, multicenter phase III study (PAPBI-2) comparing pre- and postoperative partial breast irradiation (schedules 5x5.7 Gy). This study focusses on cosmetic outcome and late side effects. Inclusion started in September 2016.

Breast cancer clinical trials consortia and collaborations

Within the BOOG network and the EORTC, the department takes part in a number of clinical trials and studies of breast cancer. These include the IRMA trial of post-operative external beam 3D conformal accelerated partial breast irradiation (43 patients included), the BOOG 201308 trial of omission of the sentinel node procedure in patients undergoing breast conservation therapy, and the BOOG male breast cancer study (prospective registration study, 8 patients included). Trials that have finished accrual and are in active follow-up include the EORTC / BIG SUPREMO trial of post mastectomy chest wall irradiation in intermediate risk breast cancer, to which we have contributed 47 patients of the 1680 total inclusion (Co-chief PI: Russell), and the EORTC DCIS boost- no boost trial.

Shared decision making

Within a Dutch Cancer Society project (MAC 2014-7024: "The challenge of implementing Shared Decision Making to personalize choices for loco-regional treatment and its follow-up of breast cancer patients") we are currently developing a personalized decision aid for choices related to addition or omission of radiotherapy in certain preference sensitive situations, such as low-grade DCIS, or post mastectomy radiotherapy.
2017 saw the start of a multi-centre BOOG trial: Implementing a decision aid for breast cancer and DCIS patients deciding on their radiation treatment: A pre- and post-intervention study. pre- and post-intervention trial (BRASA). 164 patients will be included before the introduction of the decision aid, and 164 patients after the introduction of the decision aid. The decision aid will be a personalized decision aid based on the individual tumor and patient characteristics to help patients estimate their risks of tumor recurrence and toxicity of treatment. The primary endpoint of the trial is decisional conflict at three months after the decision about adjuvant radiotherapy has been made. Secondary end-points include: the perceived level of shared decision making, patient knowledge, and decisional conflict one year after the decision has been made.

MR Linac

Within the Elekta MR Linac consortium, the NKI-AVL is an active participant in the Tumour Site Group (TSG) breast cancers. Current initiatives are focusing on delineation of breast tumors in situ for pre-operative partial breast irradiation, and delineation of lymph nodes in the axilla and peri-claviculair region for boost treatments of residual lymph nodes. Scan protocols for use in supine position on the MR linac are being optimized. Currently

patients in the PAPBI -2 trial randomized to pre-operatieve irradiation are being included in the MR Linac Umbrella protocol with MR scans on the MR linac (beam off) during the week of radiotherapy treatment on the conventional linac.

COMBINATION OF RADIOTHERAPY AND CHEMOTHERAPY/BIOLOGICALS

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Several clinical trials during the last decades clearly show that (concurrent) delivery of both chemotherapy and radiotherapy (chemoradiotherapy; CRT) significantly improves local control in a variety of advanced solid tumors. Major further improvement can be expected from the combination of radiotherapy and/or chemotherapy with biological agents that specifically target deregulated pathways in tumor cells (bio-chemo/radiotherapy). The following section describes our activities in this field for different tumor sites.

Head and neck

In September 2012, the ARTFORCE trial started. The original design of this randomized international phase II study was a 2x2 randomization between CRT with cisplatin or cetuximab and between adaptive dose redistribution or standard radiotherapy (268 patients with locally advanced oropharynx, oral cavity or hypopharynx squamous cell cancer). In May 2014, after inclusion of 24 patients, an amendment for this trial was accepted excluding the cetuximab treatment arms. Randomization between adaptive dose redistribution or standard radiotherapy is identical allowing analysis of all patients for the primary endpoints loco-regional control and toxicity. Furthermore, a new imaging modality, the HX4-labeled-PET scan, will be performed for all patients included in the study in the Netherlands to evaluate its predictive value for treatment outcome. To date, 181 patients have been included of which 43 were treated at NKI.
In October 2014, we started an olaparib dose escalation study in combination with radiation in patients with HPV-negative oropharyngeal or laryngeal squamous cell carcinoma. Olaparib inhibits PARP, an enzyme that is involved in the repair of DNA single strand breaks. Preclinical work shows that the inhibition of PARP by olaparib leads to radiosensitization. The main objective of this trial is to establish the maximum tolerated dose (MTD) of olaparib in combination with high dose radiotherapy. The accrual is ongoing. To date, 11 patients have been included and 8 of them were treated with olaparib in combination with radiotherapy. We observed late toxicity at 6 months after treatment in two patients treated at the first dose level. Therefore, we continued at a lower dose level. In the four patients included in this lower dose level we did not encounter any severe toxicity so far.
In addition, a new phase I study employing the DNA-PKi MS2490484A as radiosensitizer was started. In this trial patients with an indication for palliative treatment in the head and neck area are treated with the combination of RT and the DNA-PKi. Two patients have been entered in the trial. No severe normal toxicity was experienced. Both patients had a good remission of the lymph node metastases after treatment. The inclusion criteria have been extended to all patients with lymph nodes in the head and neck and thorax region, independent from the primary tumor origin.

Breast

In 2013 we started with an olaparib dose escalation study and radiation treatment in patients with inoperable, metastatic or inflammatory breast cancer. The primary endpoint of this study is to establish the MTD of the treatment of the breast and regional lymph nodes. Secondary endpoints are safety and pharmacodynamic endpoints in blood- and tumor samples. Patients are stratified for with or without skin sparing treatment. Four patients without and three patients with skin sparing treatment have been treated with respectively 50 mg BID and 25 mg BID. So far, no toxicity due to the addition of olaparib has been encountered in these patients. In three patients, a very good response on the post-treatment MRI was seen. Inclusion has been extended to a separate cohort of patients with high risk factors for local recurrence after breast sparing treatment or mastectomy.
A further study in breast cancer is the use of radiotherapy as a primer for immunotherapy. The single centre TONIC trial NL53438.031.15 (PI: M Kok) explores the activity of PD-1 blockade with nivolumab after four different immune response induction treatments in patients with triple negative metastatic breast cancer. We hypothesize that short-term induction treatment induces an anti-cancer immune response resulting in increased activity of nivolumab as compared to unprimed, single agent nivolumab. Radiotherapy is given to one of the metastatic sites (but not the site for biopsies is given) to a dose of 24 Gy in 3 fractions over 10 days. So far 70 patients have been included, 15 of whom received radiotherapy.

Gastroenterology - Esophageal cancer

The prognosis of patients with resectable esophageal cancer has improved since the introduction of neoadjuvant CRT (nCRT), but further improvement of treatment is expected by:

1. Optimizing radiotherapy in both setup, delineation and image acquisition.
2. Improvement of treatment selection by identifying both the complete responding patient as well as the poor prognostic patient after CRT.

We are currently accruing patients for a single center prospective observational study to evaluate organ motion and early tumor response measurement during nCRT for esophageal cancer. The primary aim of this study is to quantify motion-based variation of the target volume over the course of CRT in esophageal cancer patient, and to use this information to calculate appropriate PTV margins. The first 26 patients on this trial have been analyzed for tumor motion and exploration of possible setup surrogates for IGRT was performed. Substantial and anisotropic position variability was observed. Before firm conclusions can be drawn, the sample size will be enlarged. Currently, 68 patients have been included of whom at least 10 were not evaluable for this analysis.
As a secondary objective of this study we aim to optimize imaging of the esophageal tumor by assessing the functionality of 4D-PET-CT and MRI and to evaluate these modalities for staging, for early response assessment during CRT and for response monitoring after completion of treatment. These secondary endpoints will be analyzed in a multi-institutional setting, in collaboration with University Medical Center Utrecht (UMCU) and University Medical Center Groningen (UMCG). A KWF grant was awarded on this project.
Currently, we are analyzing the qualitative response after nCRT on diffusion weighted (DWI)-MR in 60 esophageal cancer patients with complete datasets (37 NKI and 23 UMCU). The response will be scored by 3 independent readers and correlated with tumor regression grade on the surgical specimen. Furthermore, we are evaluating the results of a pilot study to explore the clinical value of four-dimensional imaging of PET-CT in esophageal cancer patients.
Currently, we are finalizing a paper on a prospective multicenter delineation study that aims to: (1) study the possible additional value of PET to CT for GTV delineation; (2) study institutional differences in GTV delineation; (3) study the possibility to delineate GTV on MR with DWI in comparison to PET-CT. All Dutch institutes have participated in the parts of the study relating to aims 1 and 2. The MRI delineation will be performed in the MR dedicated institutes only, i.e. NKI and UMCU. Substantial differences in interobserver variability were observed. Delineation on MRI resulted in an interobserver variation comparable to the variation observed in current clinical practice (using CT and PET). Furthermore, we are exploring the next step toward MR based delineation for the MR-linac.
In order to better select patients who will benefit from surgery after nCRT, we analyzed the correlation of elevated tumor markers (CEA and CA19-9) at diagnosis and early treatment failure; metastases or death within one year after completion of CRT. Patient with elevation of both CEA and CA19-9 at diagnosis was associated with early treatment failure and decreased overall survival. The benefits of surgery might not outweigh the downsides when both markers are elevated at baseline, suggesting the need for adjuvant/additional treatment options.
Finally, we are accruing patients into the national multicenter randomized trial of dose escalation in definitive CRT for patients with esophageal cancer (ART DECO) and accrual has been reached for a multicenter phase I trial evaluating the safety and efficacy of the addition of Trastuzumab to neoadjuvant CRT (CROSS regimen) for Her2+ esophageal cancer patients, results are expected in the near future.

Gastroenterology – Gastric cancer

Both postoperative CRT and perioperative chemotherapy are evidence-based strategies to improve outcome in operable gastric cancer. The international phase III CRITICS study randomized 788 patients with resectable gastric cancer to receive preoperative chemotherapy, surgery and postoperative chemotherapy, or preoperative chemotherapy, surgery and postoperative CRT. Final analysis demonstrated equivalent outcome in both treatment arms; subgroup analyses are ongoing. Based on the observations that preoperative chemo(radio)therapy is associated with better patient compliance as compared to postoperative regimens and preoperative treatment results in a high chance of obtaining disease downsizing/downstaging and microscopically radical resections, we designed the CRITICS-II trial to identify the optimal preoperative regimen in operable gastric cancer. In November, this study was opened for accrual at NKI.
Gastric cancer is an attractive entity for MRI-guided radiotherapy. Therefore, we started a feasibility study evaluating the role of MR-imaging in radiotherapy for gastric cancer (N16GMR). Initial data indicate that MRI-based target volume delineation in gastric cancer is feasible in the pre- and post-operative setting. The axial T2w TSE MRI sequence with navigator triggering in exhale was identified as the optimal imaging quality to delineate the CTV and provided sufficient details to also delineate the GTV for the majority of the patient (figure 3). This could enable boosting strategies in the future.

Gastroenterology – Rectal cancer

MRI-based functional imaging and response monitoring are now major subjects of interest for research in rectal cancer. More information on (differential) tumor and nodal movement is needed for practice changing treatment on the MR-linac. For patients with rectal cancer this new treatment option is very promising, hopefully leading to more organ sparing treatment and less toxicity. The N13RMI study (weekly multiparametric MRI) resulted in a publication on tumor changes during treatment time of 5 weeks (Lambregts et al.). This information is of importance for adaptive strategies on the MR-linac and for more precise response prediction of patients treated with CRT. In the end, we expect to be able to better select patient with poor response for a boost treatment. More information is needed on anatomical variation (position, shape, size) of the GTV. With this information margin reduction can be performed based on daily imaging.
The Library of Plan (LoP) strategy is now part of our daily practice. On a standard planning CT-scan we delineate the GTV and the CTV for the tumor and lymph nodes. Then, a LoP is created with a total of 5 plans, two larger than the standard plan and two smaller.
In the international consortium, we are working towards clinical implementation of the MR-linac. Within this collaboration we are preparing MR-based guidelines for rectal cancer and a clinical treatment protocol for feasibility testing of the MR-linac for rectal cancer treatment.

Lung - NSCLC

In the N11ORL phase I study that started accrual in 2012 our standard concurrent CRT (CCRT) regimen for locally advanced NSCLC is combined with dose escalation of the PARP inhibitor olaparib. The aim of the N11ORL study is to define

the recommended dose of olaparib when combined with CCRT for locally advanced NSCLC. Since the opening of the trial in May 2012, ten patients entered the CCRT arm of the trial. Four patients entered the first dose level, olaparib 25 mg BID. New dose constraints for the Dmax of the esophagus were applied because of severe late esophagus toxicity. We switched to a TITE-CRM design. TITE-CRM has several advantages above the normally used 3x3 dose escalation design, as late toxicity can be included as a dose limiting toxicity and TITE-CRM allows continuous patient accrual. The third adaptation we made in the N11ORL was dose-de-escalation of olaparib of the CCRT treatment arm. Altogether, the lowest dose level of olaparib 25 mg QD in combination with CCRT was considered to be above the maximum tolerated dose. The CCRT arm of this trial was therefore closed.

As we know that concurrent chemotherapy (cisplatin) substantially increases the risk of esophageal toxicity and olaparib sensitizes both cisplatin and radiation, we opened a second treatment arm in the N11ORL study for NSCLC patients treated with sequential CRT. In this arm, patients are first treated with chemotherapy and if they have a favorable response they are treated in the study with radiation and olaparib (without concurrent chemotherapy). We included five patients at the dose level of olaparib 25mg QD without having seen any severe toxicity. Therefore, the dose was escalated to olaparib 25mg BID. In this dose level 7 patients have been treated so far. Unfortunately, also this dose level was considered to be above the maximum tolerated dose level due to pneumonitis and late esophageal toxicity. We therefore de-escalated the olaparib again to 25mg QD and included 5 more patients. So far, one patient out of ten treated patients at this dose level did experience severe toxicity (pneumonitis). Further follow-up of the current patients and inclusion of two additional patients with more strict radiotherapy dose constraints for the healthy lung dose will determine whether this dose level is considered to be tolerable.

In 2017 a total of 75 patients have been treated with CCRT (66 Gy to the primary tumor and 58.08 Gy to the involved lymph nodes in 24 fractions using IMRT, with daily cisplatin administration 1-2 hours before the irradiation).

In the multicenter phase II PET-Boost trial (M09PBO) dose-escalation is executed by boosting the radiation dose within the primary tumor based on biological activity on pre-treatment FDG-PET/CT. Patients are randomized to receive the standard 66 Gy in 24 fractions with a dose-escalation to the primary tumor as a whole (minimum dose 3 Gy/fraction up to 72 Gy in 24 fractions) or to the volume with ≥50% SUVmax within the primary tumor. In both treatment arms, patients are irradiated to the same Mean Lung Dose to the lung and may receive concurrent or sequential chemotherapy. The contributing European sites are Manchester, Leuven, Copenhagen, Maastricht, Amsterdam (AMC) and Eindhoven. Seven patients were randomized this year (total 107 randomizations).

In the N12LPR trial protocol weekly FDG PET/CT scanning in NSCLC patients during CCRT is investigated. The goal of this study is to correlate early FDG-PET/CT responses during CCRT with treatment outcome. A total of 40 patients have been included since 2013. In 2017 five patients were included. The trial ended 31 October 2017, and analyses are ongoing.

The FDG-PET/CT metrics on response scans of locally advanced NSCLC patients treated with CCRT in the randomized phase

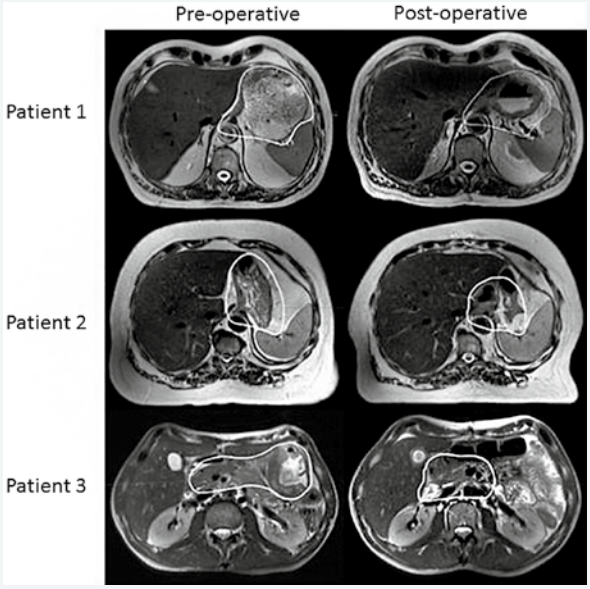

Figure 3. Pre- and post-operative CTV delineated on the axial T2w TSE navigator triggered in exhale in 3 patients with gastric cancer.

II RADITUX trial were analyzed. The RADITUX trial was a multicenter randomized phase II (NTR2230) that assessed the effect of additional Cetuximab to CCRT (102 randomized patients between February 2009 and May 2011, revealed no benefit of additional Cetuximab). The median OS for these patients was exceptionally high with 31.5 months and the 5-yr OS was 37.3%. The purpose of the current analysis was to investigate whether FDG-PET metrics have prognostic value in relation to local, regional and distant failure. In 72 patients a response FDG-PET-scan after a median of 4.2 weeks (range, 1.6-10.1 weeks) was made. After excluding the patients who had an additional resection, 47 patients were included in the analysis. The following pre- and post-treatment PET metrics were calculated of the primary tumor as well as the combined involved lymph nodes: SUV_{max}, total lesion glycolysis and metabolic tumor volume. The response ratio between the pre- and post-treatment values was calculated as well. Preliminary results show that the response SUV_{max} of the primary tumor and the post-treatment SUV_{max} of the lymph nodes were significant prognostic factors for regional failure in patients with locally advanced NSCLC treated with hypofractionated CCRT.

Lung - SCLC

Small cell lung cancer accounts for approximately 15% of lung carcinomas. At the time of diagnosis, approximately 30% of patients with SCLC will have limited-stage disease (LS), i.e. tumors confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes. Patients with tumors that have spread beyond these areas are staged as extensive-stage disease (ES).
For LS-SCLC, the combination of chemotherapy and thoracic radiotherapy is the standard treatment. Two meta-analyses have shown that thoracic radiotherapy given concurrently with chemotherapy improves both local control and survival. Nevertheless, several important questions including the optimal total radiation dose and radiation fractionation remain unanswered. In 2009 the EORTC started an international, multicenter randomized phase III trial comparing twice daily (BD) radiotherapy with high dose radiation delivered once daily (OD), both given concurrently with standard cisplatin and etoposide chemotherapy (CONVERT trial). In July 2013, the target of 532 patients (4 patients from NKI) was reached and recruitment was closed. The results of this largest study ever completed in LS-SCLC were published in Lancet Oncology in August this year. After a median follow-up of 45 months there were no significant differences regarding outcome between the two treatment schedules. Toxicities were comparable except for significantly more grade 3/4 neutropenia (74% BD vs 65% OD, p=0.03). There was no statistical difference in grade 3/4 oesophagitis and grade 3/4 radiation pneumonitis. Survival was higher than previously reported in other trials and radiation toxicities were lower than expected, likely due to the use of modern techniques. These inconclusive results suggest that either schedule can be used in this setting. The ongoing randomized trial CALGB 30610, a trial comparing three different radiation therapy regimens, should shed more light on this issue.

In collaboration with the division of Psychosocial Research and Epidemiology we continued accrual in the Hippocampal Avoidance-Prophylactic Cranial Irradiation (HA-PCI) trial. In this international phase III trial (NCT01780675) (NKI 2013-6096), that NKI initiated patients with limited and extensive stages of SCLC are randomized to receive PCI with or without hippocampal sparing with the aim to reduce neurocognitive decline. In both treatment arms the patients have repeat MRI's and a set of neurocognitive tests at baseline and at 4, 8 and 12 months. The radiation therapy oncology group (RTOG) published a phase II hippocampal avoidance (HA) study to investigate the feasibility of this approach. In this small non-randomized phase II RTOG 0933 trial memory preservation was associated with hippocampal sparing in patients treated with whole brain radiation therapy for brain metastases compared to a historical group. Using VMAT-IMRT the mean radiation dose to the neural stem cells of the hippocampus can be significantly reduced while adequate coverage and dose homogeneity for the remaining whole brain is maintained. An inter-observer hippocampus delineation analysis was performed and the influence of the delineation variability on dose to the hippocampus was studied. Even though substantial inter-observer delineation variation was observed, for the hippocampi the required dose constraints (Dmean) $\leq$8.5Gy, which correlates to a mean biological dose (Dmean biological) of $\leq$6.2Gy (α/β=2Gy) was met for all observers' delineations.
The trial is accruing in the Netherlands in Amsterdam (NKI and AMC), Eindhoven, Groningen, Rotterdam, Tilburg, and in Belgium in Leuven, Antwerp and Ghent. In 2017, 50 patients have been randomized (total 164 of 168 required). A planned interim analysis was performed that revealed that the hippocampus sparing policy did not increase the incidence of brain metastases. The trial will complete accrual end of December 2017. After analyzing the primary endpoint in 2018 we discussed in an investigator's meeting a possible new trial design: the best treatment arm with or without a neuroprotector.

Urology - Penile cancer

Treatment outcome of loco-regionally advanced penile cancer (LRAPC) was unacceptable. Survival and control rates were poor while the treatment regimen (neoadjuvant chemotherapy, surgery and adjuvant radiotherapy) is quite toxic. Given the more favorable outcome of CRT for the other genital cancers (anal and vulvar cancer), this seems a better treatment option also for LRAPC. As a consequence, the multidisciplinary tumor board of the NKI now considers CRT as the new standard treatment for LRAPC. We therefore initiated a prospective observational study to evaluate the efficacy of CRT for LRAPC (N15PEN). Currently, 19 out of the 33 patients have been included and the study is expected to be completed by the end of 2018. Furthermore, there are initiatives to explore radio-immunotherapy also for penile cancer.

Urology - Prostate cancer

This year we initiated a phase I dose-escalation trial in high-risk early stage prostate cancer patients with positive lymph nodes. In this study weekly ModraDoc/r is given in combination with hormonal treatment and high-dose IMRT (N15DOP). ModraDoc is an oral docetaxel compound and used as a radiosensitizer. Currently, 6 out of 30 patients have been included. The first cohort of 4 patients has been evaluated. No major toxicities have been encountered. The combination of ModraDoc/r and radiation treatment for prostate cancer is safe and feasible. We are now treating patients in a dose level with the ModraDoc/r twice daily in combination with full dose radiotherapy (77 Gy).

Gynaecology - Cervical and Endometrial cancer

In locally advanced cervical cancer, the treatment of choice is a combination of external beam CRT for 5 weeks followed by (chemo) brachytherapy. Since 2012 patients in our institute are treated with Image-Guided Adaptive Radiotherapy with library of plan (LoP) VMAT irradiation and MRI based adaptive brachytherapy for the treatment of cervical cancer. We evaluated the clinical use and early outcome of this adaptive treatment and concluded that imaged guided adaptive LoP protocol for cervical cancer based on daily CBCT is feasible with similar early clinical outcome as the non-LoP treated patients. Furthermore, we investigate to what extent the CTV-PTV margin with VMAT irradiation of cervical cancer could be reduced with the use of LoP. We found that the clinically used CTV-PTV margin of 1 cm left-right and 2 cm in other directions that is used for VMAT irradiation of cervical cancer could be reduced with the use of LoP, provided that the geometry of cervix-uterus with respect to the PTV is carefully monitored. We clinically introduced a CTV-PTV margin to a uniform 1 cm, a combination of a LoP strategy and a traffic light protocol to monitor outliers. We succeeded to reach a D90 of the HR-CTV >90 Gy EQD2 for most patients, a prerequisite for our participation in the international EMBRACE 2 study. We analyzed the clinical use of needles and examined the feasibility to meet the planning criteria in three fractions of cervical cancer brachytherapy and investigated whether the needles with the largest discrepancy between application and loading are essential to treatment planning.

In 2017, we clinically introduced the Venezia applicator. With this advanced gynaecological applicator we are able to easily reach the cervix, parametrium and vaginal extensions in stage IIIA and IIIB tumors. This area has been difficult to reach with current brachytherapy techniques.

Together with Aarhus and Leuven we finalized a repetitive MRI-based functional imaging and response monitoring study in locally advanced cervical cancer. This M13IMA study evaluates the sensitivity and specificity of DWI-MRI to identify patients who will develop local failure after cisplatin-based CRT of cervix cancer. The data are currently being analyzed and will give us tools for predicting local tumor control after CRT.

Currently, we are in the designing phase for MR linac studies.

Patients with endometrial and cervical vaginal recurrences are often treated with a combination of (chemo) radiation and brachytherapy using the multichannel vaginal cylinder (MVC). We evaluated our first experience with the MVC. Since the clinical introduction of image guided adaptive MRI based brachytherapy using a MVC, 25 patients with vaginal recurrence were treated with curative intent in our department. The clinical treatment protocol accounts for the uncertainty in rotation of the cylinder with respect to the target area. By means of an imaging study, we have found the magnitude of the interfraction rotation to be 6 degrees (1 SD). We performed a simulation study to assess the impact of rotations on the main plan parameters (target D90 and OAR D2cc). Results show that the impact of the rotations is limited.

We are participating in the Portec 4 study, an international randomized phase III trial of molecular profile-based versus standard recommendations for adjuvant radiotherapy in women with early stage endometrial cancer. The goal of this study is to establish vaginal recurrence and recurrence free survival in patients with high intermediate risk endometrial carcinoma, treated after surgery with standard vaginal brachytherapy (21 Gy in 3 fractions), in comparison with molecular risk profile based recommendations for no additional treatment (55%), vaginal brachytherapy (40%) or external beam radiotherapy (5%).

Gynaecology - Vulvar cancer

Patients with locally advanced squamous cell cancer of the vulva are not curable with surgery unless extensive reconstructive surgery or a colostomy or urostomy is performed. For these patients, a multicenter phase II study of definitive CRT is open in this institute. The primary endpoint is loco-regional control rate defined as clinically or pathologically proven absence of tumor in the vulvar and groin area 12 weeks after the last CRT and after groin dissection in cN1-2 patients. Patients are treated with EBRT combined with capecitabine BID on days 1-14, 22-35 and 43-49. Secondary endpoints are treatment related toxicity, the incidence of fecal and/or urinary continence and/or reconstructive surgery performed and 2-years loco-regional recurrence rate.

An interim analysis in 50 patients showed a good local control of clinical Complete Response of 66% at 12 weeks after treatment, 12% of patients were in need of a stoma (compared to 100% in patients with extensive surgery). Major toxicity is dermatitis and pain, but this is manageable in a multidisciplinary team. We can conclude that high dose radiotherapy (64.8 Gy) in combination with capecitabine is feasible. An amendment is written to the protocol to de-escalate the capecitabine dose and to continue the trial as a national registry study.

Soft tissue sarcoma

In 2012 we started a multicenter phase I study in sarcomas of the extremities and head and neck, evaluating the safety and feasibility of standard preoperative radiotherapy combined with dose-escalated pazopanib, a small molecule inhibitor of VEGFR. The rationale behind this combined modality treatment is multifactorial: VEGF targeted therapy results in normalization of tumor vasculature which might improve the oxygenation of the tumor and greater efficacy of radiation; both radiation and VEGF-blocking agents target tumor-associated endothelial cells to induce apoptosis; radiation induced upregulation of VEGF is counteracted by VEGF-targeted therapy. By including the last patient in the highest dose level, the study was successfully completed in 2014.

Early 2016 a 35 patient confirmatory prospective phase II study has been opened with the aim to expand the highest dose level of once-daily 800 mg pazopanib concurrent with 25x2 Gy radiotherapy. Primary endpoint will be the induction of a pathological response. As side studies repeat DWI-MRI and repeat biopsies will be performed during treatment. Currently, the Royal Marsden Hospital, London, UK is also accruing patients and the LUMC, Leiden, will follow soon. Next aim, after proven efficacy in this phase II study, is another phase II study investigating the same pazopanib dose of once-daily 800 mg, concurrent with a lower radiation dose of 18 x 2 Gy.

Myxoid liposarcomas are known for their radiation sensitivity on preoperative radiotherapy to 50 Gy in 5 weeks. Based on these clinical observations a multicenter prospective phase II clinical trial is opened to investigate the feasibility of lowering the neoadjuvant radiotherapy dose to 36 Gy. Due to the rarity of the disease the study is accruing slowly but steadily. As of

autumn 2014, high-volume international sarcoma hospitals are activated as participating centers (London, the entire Scandinavian Sarcoma Study Group and Boston); other European and US centers are considering participation as well (including PMH Toronto, Canada, the MDACC, (Houston, Texas) and the Mayo Clinics, (Rochester, Minnesota), and the Universities of Mannheim, Germany and Leuven, Belgium).
In parallel to this clinical study, basic radiobiological investigations are being performed into radiation sensitivity of several cell lines, including but not exclusively of myxoid liposarcomas. Subsequently, these cell lines are propagated in mice, to investigate *in vivo* radiation sensitivity, both after conventional- and after hypofractionation. Finally, a platform of patient derived xenografts (PDX) is in development with the same aim of testing radiation sensitivity. The donated fresh sarcoma tumor material will also be used for 2D/3D cell cultures. This project is being performed in close colaboartion with the department of Biological Stress Response and the Animal Laboratory Facility.
Within the European Organization for Research and Treatment of Cancer a randomized phase III clinical trial called "STRASS", has been opened to investigate the role of neoadjuvant radiotherapy in retroperitoneal sarcomas. The study was opened in the beginning of 2013 and is accruing is now complete.

OUTCOME MODELING

Barbara Stam, Berthe Aleman, Floris Pos, Francine Voncken, Gilles Defraene, Jose Belderbos, Margriet Kwint, Marnix Witte, Matthew la Fontaine, Simon van Kranen, Wilma Heemsbergen and Jan-Jakob Sonke

SBRT for central tumors in early stage NSCLC patients

For NSCLC patients treated with SBRT, we investigated if proximity to the proximal bronchial tree is associated with non-cancer death. 769 patients with single early stage NSCLC tumor treated with SBRT in 5 institutes were selected. Treatment plans were collected, and the main and lobar bronchi were automatically delineated using atlas based segmentation. For each patient, the shortest distance from the edge of the GTV to the proximal bronchial tree (PBT) was determined. Patients were stratified into 3 groups; GTV≥2 cm from the PBT (peripheral (A); RTOG 0236), GTV ≥1 cm and < 2 cm from the PBT (B), and GTV <1 cm from the PBT (C). Actuarial non-cancer survival at 1y, 2y and 5y were determined (i.e., death from cancer was censored). Association between the stratified distance of the GTV to the PBT and non-cancer death were evaluated using univariate Cox regression (at the $p<0.05$ level), and compared to the association with cause specific survival to test for competing mortality risk. The median Biologically Equivalent Dose (α/β=10Gy) was 126 Gy, 180 Gy and 227 Gy for group C, B and A respectively, with 33, 71 and 665 patients per group. Median GTV diameter was 4.1 cm (1.1-7.0), 2.7 cm (0.9-5.7) and 2.2 cm (0.7-6.5). Survival rates were lower for patients in group C with a Hazard ratio (HR) of 2.91 ($p<0.001$). Patients in group B had a lower, non-significant HR of 0.87 (p=0.554). The association with cause specific survival showed a significantly higher HR (2.45, p=0.036) for patients in group C with respect to A, but not B. In a multivariate Cox analysis, the stratified distance from the GTV to PBT was significantly associated with non-cancer death (group C: $p<0.001$, HR=3.56, group B: p=0.319, HR=0.79), as well as age (p=0.001, HR=1.03), performance status ($p<0.001$, HR=0.30) and lung-function FEV1 (p=0.004, HR=0.99). In conclusion, patients with a tumor < 1 cm from the proximal bronchial tree had 3.56 fold higher risk of non-cancer death than patients with a peripheral tumor.

Definitive chemoradiotherapy for esophageal cancer: the impact of histological subtypes on survival

Esophageal adenocarcinoma subtypes (according to the Lauren classification) have shown different pathological response rates after neoadjuvant chemoradiotherapy. The aim of this study was to investigate long-term outcomes of esophageal cancer patients after treatment with definitive chemoradiotherapy (dCRT) according to the histological subtype. A cohort of 117 esophageal cancer patients treated with dCRT was retrospectively analyzed. Treatment consisted of 50Gy/25 fractions with concurrent fluorouracil/cisplatin, or 50.4Gy/28 fractions with concurrent carboplatin/paclitaxel. Patients who refused surgery after completion of neoadjuvant CRT, i.e. 41.4Gy-50.4Gy/23-28 fractions, were also included in the analysis. Patients were grouped by the histological subtype found in the endoscopic biopsy at diagnosis. Biopsies were classified as squamous cell carcinoma (SCC), adenocarcinomas of the intestinal subtype (AC-I) or of the diffuse/ mixed subtypes (AC-D+M). Overall survival (OS), disease-free survival (DFS) and isolated loco-regional recurrence (LRR) free interval were compared between patient groups with different histological subtypes. The impact of the histological subtype on OS was evaluated using a Cox regression model. With a median follow up of 56 months, median OS was 21 months and not significantly different between patients with SCC (20 [95% CI 15-25] months; n=73), AC-I (24 [95% CI 21-27] months; n=34) or AC-D+M (15 [95% CI 7-23] months; n=10). Median DFS was 19 months and, for SCC, AC-I and AC-D+M, DFS was 18 (95% CI 10-30), 21 (95% CI 21-27) and 15 (95% CI 7-23) months, respectively (p=0.29). Median time to isolated LRR was 64 months; for SCC, AC-I and AC-D+M, this was 64 (95% CI 0-129), 47 (95% CI 1-93) and 18 (95% CI 5-31) months, respectively (p=0.61). Age and failure to complete radiotherapy were significantly associated with overall survival in multivariable analysis. As compared to SCC, overall survival was similar for AC-I; HR 1.22 (95% CI 0.72-2.1) and AC-D+M; HR 1.93 (95% CI 0.9-4.0). In conclusion, in our cohort no significant relationship was found between the histological subtype and long-term outcomes following dCRT for esophageal cancer, although, AC-D+M showed a trend towards poorer outcomes. Not only for SCC, but also for intestinal type adenocarcinomas of the esophagus, dCRT can be considered.

Patient-reported outcome in the prostate HYPRO trial: gastrointestinal toxicity

The phase 3 HYPRO trial randomized to 19x3.4 Gy hypofractionation (HF) or 39x2 Gy standard fractionation (SF). The aim of this analysis was to compare dose parameters and patient-reported late GI symptoms between SF and HF.
Patients with localized prostate cancer treated with Image-Guided IMRT with ≥1 follow-up symptom questionnaire were eligible (n=578; 284 SF, 294 HF). Protocol dose constraints were:

mean dose anal canal <58 Gy and rectal volume <50% receiving ≥65 Gy, using a 0 mm margin towards rectum for the boost. Incidences of GI symptoms for the period 0.5y-5y post-RT were compared between treatment arms. Anorectal dose parameters (EQD2) were calculated with α/β=3 Gy. Mean anorectal dose and surface > 70 Gy (S70) were 29.0 Gy vs 29.5 Gy (p=0.4) and 14.2% vs 12.6% (p<0.01), for HF and SF, respectively. Patient-reported GI symptoms of blood loss (p<0.001) and use of pads (p<0.01) were significantly higher in the HF group (figure 4); pain with stools, abdominal cramps, and diarrhea were not increased and mucus loss was non-significantly increased (p=0.07). In conclusion, the HF schedule was associated with slightly larger rectal high-dose volumes assuming an α/β of 3 Gy, and a significantly higher risk of rectal bleeding and use of pads.

Low dose volume effect is associated with radiation-induced lung damage risk

Severe normal lung tissue damage after radiotherapy, presenting as fibrotic changes, often coincides with clinical symptoms. The aim of this study was to quantify and explain lung tissue density increase assessed by CT scans as a surrogate of lung damage in a dataset in which unusually large prescription doses resulted in a wide range of lung tissue doses. 75 stage II-III non-small cell lung cancer patients treated in a randomized phase II study (NCT01024829) were included. The randomization arms were a dose escalation to the primary tumor (Arm A) and an integrated boost to the 50% FDG PET SUVmax subregion (Arm B). When dose constraints prevented escalation, standard treatment of 66 Gy in 24 fractions was delivered (Arm 0). The planning CT (CT0), follow-up CT (CTfup) ±3 months post RT and dose maps corrected to equivalent doses in 2 Gy fractions (EQD2, α/β=3Gy) were collected. A deformable registration mapped CTfup to CT0. The median density change in Hounsfield Units (ΔHU) within the 'lungs minus GTV' contour was then extracted per dose bin of 5 Gy. The average density change response curve per study arm is depicted in figure IX.5. A saturation was observed above 60 Gy in arm A. The higher response in arm 0 above 40 Gy suggested that local dose is not the only driver of local ΔHU risk. The dosimetric prognostic factors lung V5 and MHD could explain the higher ΔHU in arm 0. In conclusion, a low dose volume effect seems more critical for the induction of severe lung infiltrations than high doses to a small lung volume, suggesting a mechanism of decreased repair capacity in the lung volume.

MR LINAC

Marlies Nowee, Tomas Jansen, Marco van den Berg, Frank van den Berg, Anja Betgen, Jacqueline van der Geest, Jochem Kaas, Abrahim Al-Mamgani, Anton Mans, Rogier van Noord, Agnieszka Olszewska, Vivian van Pelt, Thijs Perik, Peter Remeijer, Stijn van der Schoot, Jan-Jakob Sonke, Baukelien van Triest, Tineke Vijlbrief, Marcel Verheij, Frits Wittkamper, Uulke van der Heide

In 2016, the MRI-linear accelerator (MR-Linac) was installed at NKI. This device is an integration of a 1.5T MRI scanner with a linear accelerator. It creates the possibility to acquire high-quality MRI images just prior to irradiation. Based on these images, the treatment can be adapted to the anatomical geometry of the day. Imaging continues while the irradiation is ongoing, allowing monitoring of tumor motion. Intervening if a target moves out of the irradiated volume will increase treatment accuracy.

To prepare for clinical start of the MR-linear accelerator (MR-Linac), an implementation group was started, where physicians, physicists and RTTs work together. Several working groups collaborate with colleagues in the MR-Linac consortium of 7 institutes in the Netherlands, UK, US anAd Canada. After the summer, the team of RTTs that will carry out the treatments, has been recruited and training of all disciplines has started.

Next to clinical implementation, research projects are ongoing on the development of 4D MRI techniques for cancers in the abdomen, such as liver metastases and methods for trailing/tracking the tumor during motion. As treatment plans will be adapted on a daily basis, on-line quality assurance is essential. For this purpose, electronic portal imaging dosimetry, applied routinely in clinical practice, is now further developed for use at the MR-linear accelerator. The Umbrella trial started. This is an imaging trial of patients who receive MRI exams on the MR-linac to optimize imaging protocols and explore the potential of the device. Programs for clinical research after the clinical release of the MR-Linac are developed in close collaboration with the MR-linac consortium. Our group leads the effort on rectal cancer, and further focuses on gastric cancer and the treatment of oligometastases.

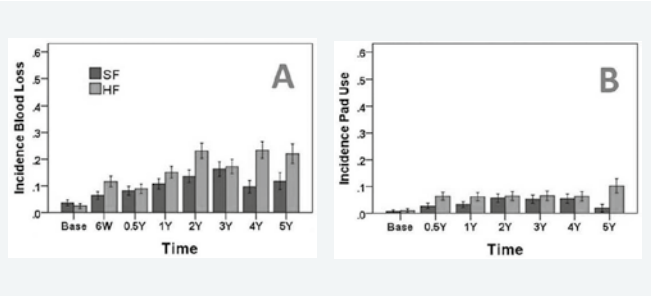

Figure 4. Incidences per treatment group (1SE)

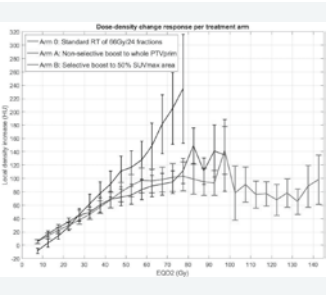

Figure 5. Population dose response curves for local density change of lung tissue 3 months post RT in arm 0 (15 patients), arm A (28 patients) and arm B (32 patients). Average and standard error of mean (SEM) per 5 Gy dose bin.

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IMAGE GUIDED SURGERY

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This research line aims to optimize surgical procedures by better surgical guidance during operative procedures. To this end new imaging technologies are developed and tested to improve tumor mapping and staging pre and intra-operative. These imaging and surgical guidance procedures should lead to more radical resections while sparing normal tissue and organ function. The research line is a strong collaboration between the NKI-AVL, Technical University Twente and industrial partners. For the moment 3 project lines are running.

In the first project we are developing a tool for optical guidance during surgery by means of spectroscopy and fluorescence techniques. To this end, an optical needle was developed together with industry. In vivo tissue measurements in breast cancer, liver metastases and lung tumors show an accuracy of over 90%. Presently, we concentrate to incorporate the developed technology into surgical tools and the surgical work flow. A STW project will start in 2018 to further develop this technology in combination with ultrasound.

In a second project we aim to bring navigation technology into the surgical work flow. In order to improve the balance between radical surgery and preventing morbidity in extensive surgery, we propose an innovative solution by using navigation equipment in the OR. Surgical navigation will guide the surgeon to the right dissection plane by supplying a sophisticated 3D road map based on pre-operative high-resolution anatomical images. Surgical navigation enables the surgeon to view the tumour and the vital surrounding structures real-time during surgery, as well as the surgical instruments by tracking and superimposing their positions on detailed pre-operative anatomical images used in an augmented reality setting during surgery. In 2015 we introduced this first in world electromagnetic navigation system for abdominal and pelvic surgery into clinical practice. Over 100 patients have been operated this way with great success and enthusiasm amongst the surgeons working with the system. The project team was able to obtain funding from the KWF/Alp d'HuZes and the Vriendenloterij and won the Venture Challenge 2016 of Health Holland (the Dutch Life science competition).

Currently several randomized trials are running on image guided surgery within the field of GI surgery, urology and head and neck tumours. In addition, a project was started in 2017, funded by the Vriendenloterij, to bring the developed technology to other hospitals.

A third project line concentrates on the introduction of hyperspectral imaging for cancer surgery. This project is funded by the European project Astonish and received a grant in 2017 from the Dutch Cancer Society (KWF). We aim that in the near future all tumor resection samples can be analyzed almost real time within the OR enabling additional resection when necessary. The research performed in the present projects leads to strong synergy with the new innovative minimal invasive operating theatre complex. The board of directors decided to support image guided surgery with extra funding for 4 years. This funding is used to further implement image guided surgery within a wide variety of disciplines within the HOD.

SURGICAL ONCOLOGY

BREAST CANCER

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DCIS

In close collaboration with the pathology division work, the LORD trial started recruiting patients to evaluate the safety of active surveillance in women with LOw-Risk DCIS, based on the results of the fundamental research line within the DCIS research group.

Choosing Wisely

Patients who need to undergo surgery and are eligible for breast reconstruction are included in the TANGO trial, investigating an internet-based tool to guide decisions on reconstructive options.

De-escalation of local regional treatment after neoadjuvant systemic therapy

As result of a retrospective analysis on the value of post chemo SN in patients with cN0 clinical practice was changed to omit SN in a subgroup of patients. In patients with cN+ disease a protocol was implemented based on PET- CT staging before NST and MARI procedure after NST to tailor axillary treatment. The 5 yr FU results of this approach are expected in 2019.
The surgical margins and local regional control after BCS in cT3 patients with a good response on NST were evaluated, and the MICRA study was initiated to prevent local surgical overtreatment. In close collaboration with the radiology department the aim is an optimal selection of patients with a pCR by use of modern MRI imaging techniques including radiomics. In patients with an excellent radiologic response, pathology results of biopsies and surgical specimen are compared, to determine if biopsies can reliably assess the presence or absence of residual tumor. This study is now expanding to a multicenter trial.

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Image guided surgery

In close collaboration with the research group of Theo Ruers computer navigated techniques are investigated to further optimize surgical tumor excision as well as the use of spectroscopy for tumor diagnosis and guidance of minimal invasive procedures.

Breast Cancer Audit

Since 2011 all patients with breast cancer in the Netherlands are registered in the NABON Breast Cancer Audit (NBCA). The objective is to assure quality of patient treatment. MJ Vrancken-Peeters is co-founder and current president of the NBCA board and supervises 2 PhD students on this quality assurance project.

MELANOMA AND MERKEL CELL CARCINOMA

Alexander van Akkooi, Jos van der Hage, Winan van Houdt, Michel Wouters, Viola Franke, Eva Huis in 't Veld, Max Madu, Linde van Veenendaal

Research is divided into tumor stage. The overarching research strategy is to develop (neo-)adjuvant combination treatment strategies for high-risk melanoma. This is supported by the construction and maintenance of clinical databases, which link to biobank material, consisting of tissue and blood for proteomics (N16MEL). This material is analyzed to determine prognostic biomarkers for prognosis and more importantly predictive biomarkers for response to treatment. For this purpose, there is also a strong collaboration with the NKI for Translational Research together with both the Daniel Peeper and Ton Schumacher labs. In parallel, the group is reporting on important clinical topics.

Specific Studies:

- EORTC 18081 study (adjuvant PEG-IFN vs. OBS in pT2-4bN0 melanoma)
- MSLT-2 study (CLND vs. OBS after Positive SN) will report first results in 2016-2017
- EORTC 1208 Minitub registry for minimal SN Tumor Burden, Alexander van Akkooi is the world-wide PI
- EORTC 1325 – Keynote 054 (Adjuvant Pembrolizumab versus placebo after CLND for stage IIIA (→1 mm), IIIB/C melanoma); accrual rate NKI-AVL highest world-wide
- OpACIN study (neo-adjuvant combination IPI+NIVO versus adjuvant IPI+NIVO for palpable groin/axilla metastases): first results presented ESMO 2016
- OpACIN-neo (neo-adjuvant combination IPI+NIVO in different schedules to maintain the efficacy, but reduce toxicity)
- Reductor study (8 weeks of Dabrafenib & Trametinib for irresectable stage IIIB/C)
- N16MEL (biobank)
- Masterkey 265 study: a phase 3 study of Pembrolizumab + Placebo versus Pembrolizumab + T-VEC in patients with injectable metastases

In-transit metastases

As 1 of the 3 National Isolated Limb Perfusion centers, many patients with this condition are treated. NKI-AVL has successfully applied for reimbursement of a, new in class, drug as add-on: intralesional injection of Talimogene Laherparapvec (T-VEC), an oncolytic immunotherapy. Since the approval and reimbursement of this drug in December 2016, AVL has become a leading (inter)national institute on intralesional and viral

treatments. This is also illustrated by an awarded grant to develop a database on this topic.

Dutch Melanoma Registry

All stage IIIC/IV patients in the Netherlands are registered in the Dutch Melanoma Treatment Registry. The objective is to assure quality of patient selection and treatment and to provide real world data for the (cost)effectiveness. Michel Wouters is co-founder and board member and supervises 3 PhD students on this quality assurance project. Currently there are contacts with Danish and German databases to combine the three databases.

COLORECTAL LIVER METASTASES – IMAGE GUIDED TREATMENT

Theo Ruers, Koert Kuhlmann, Niels Kok, Esther Kok

Research is focused on imaging and local tumor destruction and treatment.

Local tumor destruction

The EORTC CLOCC study, investigating the use of RFA in patients with unresectable colorectal liver metastases, showed a significant improvement of OS for RFA treatment. This result had a practice changing consequence worldwide for the treatment of patients with unresectable colorectal liver metastases. On the basis of this study the re-imbursement policy in The Netherlands has changed. Following these results, a multicenter European study was initiated to investigate the immunomodulatory effect of RFA in combination with immunotherapy.

The SILENT trial, a randomized trial investigating accelerated growth of synchronous colorectal liver metastases and the effects of neo-adjuvant therapy, has been finished and data is currently being analyzed

Together with the Department of Radiation Oncology another study investigates the use of stereotactic radiotherapy for local tumor destruction of liver metastases.

Together with Erasmus medical center in Rotterdam and Memorial Sloan Kettering Cancer Center in New York a study is started on the use of intra-hepatic chemotherapy adjuvant to liver resection (PUMP trial).

A nationwide study of patients with rectal cancer and synchronous liver metastases who are treated according to the "M1-schedule" (short course radiotherapy followed by systemic treatment and surgery) was initiated.

A retrospective study is performed on the longterm results of peroperative ablation and focusses on the differences between Radiofrequent ablation (RFA) and microwave ablation (MWA).

Imaging

In collaboration with the University Twente and industry 3D segmentation models are developed for visualizing colorectal liver metastases during surgery. This software is now routinely used and re-imbursed during liver surgery. Currently, the focus is on superimposing detailed pre-operative anatomical images and tumor positions on real time video screens during liver surgery creating an augmented reality setting during surgery.

Navigation

A liver navigation program for intra-operative liver surgery based on electromagnetic tracking was initiated. It shows the safety and feasibility of the approach, reaching an accuracy of 5 mm. With regard to the work-flow still an intra-operative cone

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beam CT scan has to be used. Together with the research group of SINTEF (Trondheim) a navigation system is developed based on US only which will further facilitate the work-flow.

Registry

In collaboration with the Dutch Association of Interventional Radiologists (NVIR) and a grant from SKMS (Stichting Kwaliteitsgelden Medisch Specialisten) AVL founded a nationwide registry for local treatment of liver tumours including percutaneous ablation.

In collaboration with industrial partners the use of spectroscopy for tumor diagnosis and guidance of minimal invasive procedures is investigated.
The research line is funded by, KWF, STW, University Twente, EORTC and industrial partners.

COLORECTAL SURGERY AND HIPEC

Arend Aalbers, Geerard Beets, Niels Kok, Koert Kuhlmann, Theo Ruers, Hanneke van Eden, Marit van der Sande, Maxime van der Valk, Britt Hupkens, Denise Hilling

In rectal cancer there is a large ongoing project on organ preservation, with a KWF funded multicenter implementation study, patient-centered outcome studies, a KWF funded project with the department of radiology on multiparametric imaging and prediction of response, an international registry of organ preservation (IWWD.org), and cooperative projects with LUMC, MUMC+, Sao Paulo, Lisbon and MSKCC. Through these studies and projects, NKI-AVL has become a world leader in organ preservation in rectal cancer. A contact radiotherapy machine has become operational in 2017 and will further expand the program. In cooperation with the Departments of Gastroenterology and Medical Oncology an exploratory immunotherapy trial in colonic cancer has started (Niche study) and another trial on rectal cancer will start in 2018. The COLOPEC study, a multicenter randomized prophylactic HIPEC study for patients with T4 colon carcinoma, completed accrual in 2016, and results are expected in 2018. A new imaging study on peritoneal metastases with diffusion MRI was initiated in cooperation with the Department of Radiology. The ongoing translational research concerns chemoresistance and sensitivity studies on 3D organoid cultures from tumor cells derived from resection specimens.

OESOPHAGEAL AND GASTRIC CANCER

Johanna van Sandick, Koen Hartemink, Xander Veenhof, Frits van Coevorden, Rosa van der Kaaij, Willem Koemans

An important strategy to improve the results of oesophagogastric cancer treatment is to study the outcomes of different subgroups of patients in order to identify those who might benefit from other or additional treatment regimens.

The predictive and prognostic significance of histological subtyping was studied in a cohort of 160 patients with oesophageal adenocarcinoma treated with potentially curative intent. Diffuse type tumours had a significantly worse overall survival, and were less responsive to neoadjuvant chemoradiotherapy, highlighting the need for a more differentiated treatment. In addition, epidemiological differences between histological subtypes are studied in a nationwide database of the National Cancer Registry in combination with the national pathological registry (PALGA) from 1989 onwards.

Ongoing research focusses on the genetics of oesophageal and gastric cancer, using untreated endoscopic tumour biopsies collected in the Upper GI cancer biobank since 2008. Currently, the copy number variation profiles of 110 oesophageal tumours are processed, and will be correlated to histological subtype, treatment response, and patients' survival - potentially paving the way to a more personalized treatment approach.

As yet, palliative systemic chemotherapy is the standard treatment for gastric cancer patients with peritoneal carcinomatosis. The role of hyperthermic intraperitoneal chemotherapy (HIPEC) is unknown, and the safety of cytoreductive surgery with a gastric resection and HIPEC containing oxaliplatin (in a fixed dose) and docetaxel (in escalating doses) was investigated in a feasibility study (PERISCOPE I). In October 2017, this study was closed after enrollment of 37 patients of whom 25 patients underwent the complete study protocol (CRS, gastric resection, and HIPEC). The maximum tolerated dose of intraperitoneal docetaxel in combination with 460 mg/m^2 oxaliplatin had been reached; i.e., 50 mg/m^2 docetaxel. Thereafter, a multicenter randomized trial was opened. The aim of this study (PERISCOPE II) is to compare standard palliative chemotherapy to CRS, gastrectomy and HIPEC in terms of survival, toxicity and costs in gastric cancer patients with peritoneal dissemination.

THORACIC SURGERY

Koen Hartemink, Houke Klomp, Xander Veenhof, Michel Wouters, Chris Dickhoff, Matthijs van Gool

Clinical innovations in surgical treatment for NSCLC include minimally invasive surgical techniques such as 3D-video assisted thoracoscopic surgery (VATS) and robotic surgery. Scientific research includes activities related to changes in clinical approach, multimodality treatment, including chemoradiation followed by surgery and the role of neoadjuvant and adjuvant immunotherapy and targeted therapies. Several studies are done focusing on response evaluation after chemoradiotherapy and immunotherapy as part of multimodality treatment.

SOFT TISSUE SARCOMAS

Frits van Coevorden, Jos van der Hage, Houke Klomp, Alexander van Akkooi, Winan van Houdt

At the national level, NKI-AVL actively participated and initiated the setup of a national GIST registry and has been actively involved in the design and analysis of the data from that registry, as well as the co-design and implementation of new national GIST studies focusing on serum levels in TKI treatment of GIST and the detection of circulating tumor cells in progressive GIST (Gallop study).
AVL participated in the design of a national study on the "wait and see" policy for the borderline soft tissue tumor aggressive fibromatosis.
Phase 1 studies on the neoadjuvant treatment with reduced radiotherapy dose in myxoid liposarcomas and the combination of pazopanib with concurrent radiotherapy were performed with focus on efficacy of the treatment on local control and on reduction of wound healing problems. These early studies are now followed by phase 2 and 3 studies.

On the international level NKI-AVL participates in a global network of sarcoma physicians collaborating on the development of a

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consensus in treatment guidelines and improving the outcome of retroperitoneal sarcomas; this includes a multicenter prospective study comparing surgery alone versus preoperative radiotherapy followed by surgery; and in the creation of a global database on these tumors with focus on the problem of local recurrence, identifying the most important prognostic factors.

QUALITY ASSURANCE

Michel Wouters, Johanna van Sandick, Arend Aalbers, Koen Hartemink, Marie-Jeanne Vrancken-Peeters, Alexander van Akkooi, Niels Kok, Ludi Smeele, Willemien van Driel

Several medical specialists from NKI-AVL are involved with the nation-wide clinical audits of the Dutch Institute for Clinical Auditing (DICA), which was founded in 2011. DICA facilitates 21 nation-wide clinical audits, in which colorectal, breast, lung, esophageal, gastric, hepatic, pancreatic, gynaecologic cancers as well as melanoma treatments in the Netherlands are evaluated. The audits are based on a webbased data-collection program that generates continuous and benchmarked feedback to the medical teams in Dutch hospitals.
The multidisciplinary experts in the scientific committees evaluate the results of the audit periodically, develop sets of quality indicators, initiate and supervise analyses of the data with the aim to monitor and improve quality of cancer care on a national, regional and individual hospital level. Substantial improvements in guideline adherence and patient outcome have been demonstrated after initiation of the audits. The results are published in peer-reviewed scientific journals on a regular basis. Especially, the detailed population-based clinical data and methodological aspects of quality measurement make an important contribution to medical literature. In the last year the multidisciplinary Head and Neck cancer audit has joined the DICA platform, in which several medical specialists from the NCI are involved. Also, important initiatives to add information on Patient Reported Outcomes (PRO's) are ongoing and our institute is participating in the collection of PRO's for melanoma, gynaeco-oncology and breast cancer treatments

HEAD AND NECK SURGERY AND ONCOLOGY

Michiel van den Brekel, Fons Balm, Frans Hilgers, Baris Karakullukcu, Martin Klop, Peter Lohuis, Ludi Smeele, Pim Schreuder, Bing Tan, Lilly-Ann van der Velden, Charlotte Zuur

The department is a national referral center and one of the larger clinical departments in this field treating around 500 new patients annually. The department is active in clinical and translational research. Currently, 11 staff members are working in the department, most of them with part-time appointments at the Department of Oral and Maxillofacial Surgery of the Academic Medical Center (University of Amsterdam). Being a multidisciplinary discipline, there are many clinical and research connections within the institute and internationally.

In 2017, 5 PhD theses (Renee Clapham, Monique de Jong, Mischa de Ridder, Sharon Stoker and Merijn Eskes) and 50 peer reviewed articles were published.

Personalized Medicine and Immunotherapy

In 2017 the head and neck department was involved in several translational research projects. Together with the group of Conchita Vens, next generation sequencing was further explored to study DNA repair defects and response to chemoradiation. This multi-institutional project is financially supported by the KWF lead by VUmc. A clinical phase 2 trial, using PARP inhibitors in combination with radiotherapy, was conducted. In an international study (ARTFORCE), funded by the European Community and led by Olga Hamming, adaptive radiotherapy techniques in combination with cisplatin and several translational side-studies were performed. Together with Jacques Neefjes, Huib Ovaa and Xiaohang Qiao, Charlotte Zuur explored the efficacy of a new ATM inhibitor in mice. Tumor micro-environment and immune response studies have been initiated for both HPV positive and negative tumors. Infiltration of Macrophage, gammadelta T-cells, and the role in tumor response were evaluated. Immunotherapy studies both neoadjuvant in surgery (IMCISION trial) and radiotherapy (Bioimmunoradiotherapy) were pursued in collaboration with Jan Paul de Boer, John Haanen and Ton Schumacher.

Survivorship

Rehabilitation research has been a focus of the department for many years. Prevention and treatment of swallowing and communication problems in patients treated with chemoradiation and surgery for advanced head and neck cancer is the major focus. Research on postlaryngectomy vocal and pulmonary rehabilitation, in cooperation with both the University Twente and Atos Medical in Sweden, has resulted in several new applications and devices. A project on cost effectiveness of this rehabilitation with Valesca Retèl and Wim van Harten is being conducted. Together with the Amsterdam Centre for Language and Communication (ACLC) and the Ghent University and University of Antwerp, automatic speech analysis tools were further explored. A project on prediction of voice after total laryngectomy is being carried out. The department has obtained a Horizon 2020 project in this field. Also, with the ACLC a project on physician-patient communication is being pursued.

Image guided Surgery

Sentinel node detection studies in melanoma and oral cancer, using modern image guided surgery techniques and fluorescence are continued together with Fijs van Leeuwen (LUMC). New projects on interstitial PDT guidance, mandibular reconstruction and maxillectomy reconstruction using image guidance have been initiated. A 3D lab, with external private funding by Verwelius, has been established. Development of virtual tools to predict the functional outcome after surgery as well as radiotherapy within the frame work of the Virtual Therapy project was conducted in close cooperation with the University Twente and Academic Medical Center.

Clinical research

Clinical research is diverse. Fields of interest are epidemiology and outcome as well as patient counselling and quality of care. Together with the MAASTRO clinic a decision aid tool has been developed and is currently tested. We continued our studies on waiting times for treatment and organization of optimal patient care as well as clinical audit studies on the quality of care conducted. Together with Regina Beets-Tan a radiomics project has been started. Research on ototoxicity after chemoradiation and prevention by injection of Thiosulphate in the middle ear was extended.

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UROLOGY

Simon Horenblas, Axel Bex, Henk van de Poel, Bas van Rhijn, Esther Wit, Kees Hendricksen, Pim van Leeuwen, Maaike van der Kamp, Roderick de Bruin, Kurdo Bawari, Sarah Ottenhof, Charlotte Voskuilen

Research in urologic oncology has been focused on the following themes: improved staging of urologic tumors, organ, function sparing and quality of life, fundamental research in prostate, kidney, bladder and penis cancer.

Improved staging of urologic tumours

In all urological tumors, apart from kidney cancer, sentinel node biopsy has proven to be extremely useful. In collaboration with the Department of Nuclear Medicine at the NKI-AVL and the Department of Clinical Imaging in the LUMC, fruitful clinical trials have been done assessing the use of SPECT/CT scans, intra-operative imaging with a mobile gamma camera (Sentinella®) and especially the use of hybrid tracers. The sentinel node strategy together with the Sentinella was effective in localizing sentinel nodes in patients with prostate cancer in a variety of anatomical locations, otherwise not removed during standard lymph node dissection. The rationale of patent blue, ICG and ICG with technetium is assessed and compared in various clinical trials. With the "firefly" system fluorescence imaging is integrated into the robot camera system and is extremely useful in surgery of prostate cancer, bladder cancer and kidney cancer. A new camera combining a gamma-detector and fluorescence camera is being tested within the framework of clinical studies (N16NFC). Moreover, a dropin gamma probe for robot-radioguided surgery was developed in collaboration with the LUMC.
A sentinel node program in bladder cancer (M14HSN) has been opened. In collaboration with the Department of Nuclear Medicine and Urology of the Utrecht Medical Center. Also, a clinical trial on the value of SN in testicular cancer has been launched. In the N16LND study we investigate the use of the surgical TOMTOM for treatment of nodal recurrent prostate cancer. Final data from a sentinel node study in kidney cancer (N08SNR) were analyzed and published this year.

Organ, function sparing and quality of life

In line with the wish to decrease the morbidity of the surgery and improve quality of life, robotic assisted cystectomy with intracorporeal formation of the urinary deviation has become part of the standard care. Bladder sparing within the chemo-radiation bladder preservation trial (N10BPA) is closed for recruitment and is being analyzed. A new treatment strategy for bladder preservation in non-muscle invading bladder cancer was added recently to our armamentarium: instillations with hyperthermic Mitomycine-C (HIVEC). Also, for penis cancer chemo-radiation is being used as a tissue sparing modality in advanced cases. In non-metastatic kidney cancer an increasing number of small renal masses is treated by nephron sparing strategies such as robot assisted partial nephrectomy, thermal ablation and active surveillance. Cryotherapy, as another kidney sparing modality, will be introduced next year. A new treatment strategy for upper urinary tract tumors is the endoscopic treatment with new flexible ureterorenoscopies and laser ablation with the Ho:YAG-laser, in selected patients. Coping with prostate cancer and the various choices of treatment has been

studied in more than 400 prostate cancer patients within a national study (Prokeus). With a response of more than 90% of the patients the data reveal very useful information.

Organ specific translational research

Kidney cancer

Pretreatment of clear cell renal carcinoma with VEGFR-tyrosine kinase inhibitors reduces myeloid derived suppressor cells, a mechanism which we further investigate in a neoadjuvant phase 2 trial using a combination with immune checkpoint blockade, avelumab plus axitinib (N17JAV). In addition, we cooperate with the international PREDICT consortium and the Crick Institute, London, analyzing tissue from the EORTC E30073 study for molecular signatures of response and progression. E30073 was an international phase 3 study investigating the sequence of cytoreductive nephrectomy and systemic therapy, and we presented the final data at ESMO this year. Two adjuvant phase 3 trials for high risk renal cancer after nephrectomy using the checkpoint inhibitors atezolizumab or nivolumab plus ipilimumab were started and enroll patients.

Bladder cancer

Fundamental research in characteristics of urachal cancer was recently finished by a grant from the European Association of Urology (EAU). Immunotherapy with check-point inhibitors is extensively assessed in collaboration with colleagues from the medical oncology department. The role of neo-adjuvant and induction chemotherapy in the Netherlands was assessed. In collaboration with other international centers subgrading of non-muscle invasive bladder cancer was analyzed.

Prostate cancer

MRI prediction models for functional outcome are being developed to counsel men that opt for prostatectomy. Several intraoperative surgical reconstruction techniques are being evaluated prospectively to improve continence outcome after prostatectomy. The role of MRI and targeted biopsies is studied for selection and follow-up of men to opt for active surveillance management for low risk prostate cancer in close collaboration with the department of radiology.

Penis cancer

A research project in collaboration with the Department of Gynaecologic Oncology and Department of Immunotherapy to assess the role of the micro-environment in primary tumors and draining lymph nodes, provided data on the role of inhibitors of PD-1 and PD-L1. More basic insight is gained in the immunological processes.

Improved quality control of treatment results

Using prospective data collection, almost all urological surgery at the NKI-AVL can be analyzed almost real time with the aim of further improving the quality of care.

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GYNAECOLOGY

Gemma Kenter, Frederic Amant, Marc van Beurden, Willemien van Driel, Monique Brood, Christianne Lok, Hans Trum, Henry Zijlmans, Mignon van Gent, Nienke van Trommel

GENERAL

Research in the field of gynaecologic oncology takes place in close cooperation with the other centers from the Center for Gynaecologic Oncology Amsterdam (CGOA) i.e. AMC and VUmc. The department participates in several nationwide studies within the Dutch GOG and in the EORTC. Close International cooperation exists with Institut Curie and University of Leuven as well as all partners in the RAID-EU project. The following projects are running:
The department focuses on four topics:

1. Biomarkers in ovarian cancer

Christianne Lok, Willemien van Driel, Frederic Amant, Gabe Sonke, Stef Coffelt, Karin Berns, Koen van de Vijver, Hugo Horlings, Katja Jordanova, Tiny Korse, Daan van den Broek

Several biomarkers in ovarian cancer are being studied to analyze their capacity as discriminative or prognostic tool. This involves not only HE4, but also microvesicles collected from body fluids in patients with gynaecological malignancies TIP and NIPT (Lok, Stiekema, Korse, Kenter).

The underlying immunological, molecular, genetic and epigenetic mechanisms that influence growth and invasion of peritoneal metastases of high grade serous ovarian carcinoma are virtually unknown. We investigate the ultrastructure of the different layers of the peritoneum such as the peritoneal elastic lamina (PEL) by means of several technics. Studies are running optimizing the function of tumor infiltrating lymphocytes in high grade serous carcinoma. (C. Lok, W. van Driel, F Amant, G. Sonke, S. Coffelt, K. Berns, K. van de Vijver, H. Horlings, E. Jordanova, C. Korse, D. van den Broek, J. Haanen, J. van den Berg, P. Kvistborg).

Studies are running optimizing the function of tumor infiltrating lymphocytes in high grade serous carcinoma. (C. Lok, W. van Driel, F. Amant, G. Sonke, S. Coffelt, K. Berns, K. van de Vijver, H. Horlings, E. Jordanova, C. Korse, D. van den Broek, J. Haanen, J. van den Berg, P. Kvistborg).

2. Immunosurveillance and immunotherapy for HPV related (pre)malignant neoplasms

Gemma Kenter, Sanne Samuels, Marijne Heeren, Katja Jordanova, John Haanen, Tom Schumacher, Pia Kvistborg, Lot Zuur, Simon Horenblas, Tanja de Gruijl, Helene van Meir, Willemien van Driel, Henry Zijlmans, Jan Paul de Boer, Joost van de Berg, Nienke van Trommel, Christianne Lok, Maaike Bleeker, Danielle van de Heijde, Renske Steenbergen

The role of the micro-environment in primary tumours and draining lymph nodes in cancer of the cervix as well as cancer of the vulva is being studied by collecting tumortissue, bloodsamples and lymph node scrapings during surgery (KWF 2013-6015)

A phase I trial with a DNA HPV 16 E7 vaccination in patients with HPV+ VIN lesion was finalized. The immunological responses were analyzed and the results published. No safety problems were seen, however clinical and immunological responses were not strong enough to continue with this vaccine. This trial is now followed by a phase I/ II vaccination trial in VIN patients with an improved vaccine. In case of successful responses, the trial will be followed by vaccination in HPV 16+ advanced cervical carcinoma and in HPV+ squamous cell carcinomas of the anogenital or head & neck region. This trial is part of a European project to study the molecular pathways and potentials for innovative drugs in advanced cervical carcinoma. (RAID, EU7). The role of methylation markers in HPV related tumours in screening or in selection for treatment is the subject for several new projects. In cooperation with the TU-Enschede we work on the development of a nanochip in order to analyze urine samples from patients with gynaecological tumours on the existence of methylation markers.

3. Cancer in pregnancy

Vera Wolters, Mathilda van Gerwen, Charlotte Maggen, Jorien de Haan, Christianne Lok, Frederic Amant

Our hospital is embedded in the International Network on Cancer Infertility and Pregnancy (INCIP). We register Dutch patients in a multicentre European database allowing us to collect information on pregnancy and neonatal outcome. An interim analysis in more than 1100 pregnancies will become available by the end of 2017. In addition, we follow the general health, cognitive outcome and cardiac function in children who antenatally have been exposed to cancer treatment; in 2015 we reported that these children perform as children from the same age. Now, we look into older children while expanding the 3 year old cohort. This research is financed by FWO Flanders, EU (CRADLE) and KWF.

4. Interventions to improve outcome and quality of life for patients with gynaecologic malignancies

In a randomized multicenter phase III clinical trial for stage III ovarian carcinoma the effect of secondary debulking surgery with or without hyperthermic intraperitoneal cisplatinum is being studied. This trial runs in 7 centers in The Netherlands and Belgium and is coordinated by the NKI-AVL (W. van Driel). Patient inclusion is completed, data are being analyzed and publication is in preparation.

The beneficial effect of a laparoscopy in order to predict the operability in high stage ovarian carcinoma is being studied in a multicenter randomized trial coordinated by the CGOA. Patients inclusion is completed, data have been analyzed and published. (Buist, Rutten, van Meurs, de Vrie, Mol, Kenter)

A phase II study is undertaken evaluating pembroluzimab in the treatment of stage IV ovarian cancer patients (G. Sonke, W. van Driel)

A multicenter trial is running to study the safety and immunogenicity of combined chemo-immunotherapy in high stage or recurrent carcinoma of the cervix (Cervisa). (Kees Melief, Henry Zijlmans, Gemma Kenter)
Making use of the large database from AVL, AMC and VUmc a prognostic model is being developed in order to individualize prognosis in patients with early stage cervical cancer.

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Furthermore, a combined database between CGOA, LUMC and UMCG is being analyzed for validation of this prognostic model and for analyzing several modalities of radical hysterectomy (van de Velde, van Lonkhuizen, Derks, Kenter)

The effect of hormonal replacement therapy on menopausal complaints related to biochemical changes in surgically and naturally postmenopausal women is investigated in a prospective observational comparative study. (Vermeulen, van Beurden, Korse)
Together with the LUMC we studied the need for assessment of sexual complaints after treatment for cervical cancer. (ter Kuijle, Kenter, Stiggelbout)
Geriatric screening in women >70 years with ovarian cancer (GERSOC study), aims to investigate whether geriatric screening can select patients either fit for standard therapy or in need of a comprehensive geriatric assessment (CGA) to guide further tailored treatment. The GERSOC study is a national prospective multicentre multicenter cluster randomized trial coordinated by the CGOA-AVI. (Trum, Smorenburg, van de Pol, van Soolingen)
We study the role of Physical activity and dietary intervention during treatment for ovarian cancer in a randomized trial. (van de Buffart, Hoedjes, Kenter)
Patients with cancer of the vulva can participate in a multicenter multinational trial to investigate the safety of de sentinel node procedure without complete lymphadenectomy.
The role of adjuvant radiotherapy in endometrial cancer is investigated in a multicenter randomized trial.
The radicality of resection of the parametrium in low stage cervical carcinoma is investigated in a randomized multinational multicenter trial.
We study the use of the Sentinal node in cancer of the cervix and the safety to abandone the complete lymphadenectomy in a multinational multicenter trial.

PLASTIC AND RECONSTRUCTIVE SURGERY

Marieke van den Berg, Brigitte Drost, Mahyar Foumani, J. Joris Hage, Marije Hoornweg, Martine van Huizum, Leonie Woerdeman

Our research is focused on innovative reconstructive techniques after ablative surgery by other specialists. Additionally, multi-disciplinary research is being executed in collaboration with the oncologic breast task force of the Erasmus University - Daniel den Hoed Clinic in Rotterdam, the Netherlands.
Breast-conserving therapy is defined as a breast-conserving wide local excision of a mammary tumour combined with postoperative radiotherapy. An oncoplastic approach to the wide local excision is gaining popularity to prevent breast malformation. Such an approach combines the excision by the surgical oncologist with immediate restoration of the mammary shape by use of breast reduction techniques (volume displacement) or tissue replacement techniques (volume replacement) by the plastic surgeon. Use of the internal mammary artery perforator (IMAP) flap has been suggested for immediate volume replacement. To date, however, such use has not reportedly been evaluated.

We applied this flap in 12 women (mean age, 56.1 years) after WLE (mean specimen weight, 46.5 g) of the medial aspect of the breast. Over a median follow-up of 35.3 months (standard deviation, 1.2 months), 4 women needed repeated surgery for dog-ear correction of the donor site. We conclude that, in our hands, the use of an IMAP flap is a reliable technique with good cosmetic outcomes of the oncoplastic approach. Donor site revision often proved necessary initially, but we showed that this may easily be prevented.

Women who have previously undergone radiotherapy for Hodgkin run a higher risk of developing breast cancer. These women may be treated by breast amputation and immediate or postponed breast reconstruction. Prior radiotherapy, however, is a generally accepted risk factors for unfavourable outcome of breast reconstruction.
Research with the oncologic breast task force of the Erasmus University - Daniel den Hoed Clinic in Rotterdam is focussing on the outcome of breast reconstruction following unilateral or bilateral, therapeutic or prophylactic breast amputation in 43 women who previously underwent mantle field irradiation for Hodgkin disease. This outcome is compared to the outcome in a matched control group of non-irradiated women who underwent unilateral or bilateral, therapeutic or prophylactic breast amputation and reconstruction in the same period.

DERMATOLOGY

The prevalence and cumulative risk of skin tumors in patients with Lynch syndrome or Li-Fraumeni syndrome, consequences for dermatological surveillance

Fieke Adan, W. Zandstra, S. Nieuwenburg, Marianne Crijns, Monique van Leerdam

Lynch syndrome and Li-Fraumeni syndrome are both autosomal-dominant inherited cancer syndromes, characterized by an early onset of various types of tumors. For Lynch syndrome these tumors include specific skin tumors, namely sebaceous tumors and kerato-acanthomas. However, data about the prevalence and cumulative risks of (other) skin tumors in patients with Lynch syndrome and Li-Fraumeni syndrome is lacking. Due to this lack of evidence there is no advice regarding dermatological surveillance in patients with one of these syndromes. We evaluated the prevalence and cumulative risks of different benign and (pre-)malignant skin tumors in patients with Lynch syndrome or Li-Fraumeni syndrome. The Lynch syndrome study was conducted both at the NKI-AVL and the AMC, Amsterdam. The Li-Fraumeni study was performed at the NKI-AVL. The skin tumors that were particularly analyzed were melanoma, basal cell carcinoma, squamous cell carcinoma and sebaceous skin tumors. For Lynch syndrome patients the cumulative risk of squamous cell carcinoma and sebaceous carcinoma was twelvefold higher, at age 60, compared to the risk in the general Dutch population. For Li-Fraumeni syndrome patients the cumulative risk of melanoma was markedly increased, however the study population was quite small. Based on our results, for both Lynch syndrome and Li-Fraumeni syndrome patients, dermatological surveillance is recommended as soon as a malignant skin tumor is detected.

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An early, single consultation with a dermatologist may be advised, to raise awareness for skin cancer and inform about risk factors.

ANESTHESIOLOGY, INTENSIVE CARE MEDICINE AND PAIN MEDICINE

Sandra Huissoon, Karin Ariese-Beldman, Marloes Bolman, Sannine Buma, Katina Efthymiou, Tjomme de Graas, Christoph Hahn, Herlina Hakim, Aletta Houwink, Lenie Hulshoff, Anne Lukas, Anita Rothengatter-Ophof, Bart Schieveld, Michael Šrámek, Julia ten Cate, Liang Tjoa, Ingeborg Vergouwe, Jumoke Vreden, Esther Wolthuis

The principal aim of our department is to deliver the highest standard of anesthesiological and intensive care, pain therapy and supportive care and to continually work on the development of best practices in everyday patient care.

In 2017 there has been ongoing work on a comprehensive review on the effects of anesthetics on cancer recurrence and patient outcome.
In the pain medicine department current research focuses on persisting post-mastectomy pain.
Since 2011 a RCT is ongoing about the efficacy of pulsed radiofrequency treatment on the intensity of post mastectomy pain (PMPS)
In an additional study, sensory disturbances in patients with PMPS are analyzed.
In 2016 a study aiming to develop a prediction rule for the development of PMPS, based on somato-psycho-sensory profiling has been initiated.

In the supportive care department, a prospective study investigating an intervention to decrease hospital admissions at the end of life is currently running. Retrospective data will be presented at a research conference on palliative care.

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T3
A1

Research facilities (per ultimo 2017)

ANIMAL FACILITY	MARCO BREUER, HEAD IVO HUIJBERS, HEAD MARIEKE VAN DE VEN, HEAD ANNE MARIE RHEBERGEN ROEL SNEEPERS BEA ZOER AND OUR ANIMAL CARE-TAKERS
ANIMAL PATHOLOGY AND HISTOLOGY FACILITY	SJOERD KLARENBEEK, HEAD LEX DE VRIJE ELLEN RIEM JI-YING SONG JELRIK VAN DER MEER JOOST VAN OOIJ
BIOSTATISTICS	MICHAEL HAUPTMANN, HEAD KATARZYNA JOZWIAK WILMA HEEMSBERGEN PATRYCJA GRADOWSKA JOHN ZAVRAKIDIS
CORE FACILITY MOLECULAR PATHOLOGY AND BIOBANKING	ANNEGIEN BROEKS, HEAD LINDE BRAAF SANNE BROERSEN STEN CORNELISSEN INGRID HOFLAND ESTHER HOLMAN WOUTER KIEVIT RIANNE VAN DE LINDEN DONNE MAJOOR JOSE OVERWATER DENIS PETERS CHARLOTTE VAN ROOIJEN JOYCE SANDERS DAGMAR VERWEIJ ASTRID VONK RIANNE VAN DE WIEL
CRYOGENIC STORAGE	MINZE DIJKSTRA ERWIN KAMBEY JUFRY MAMUAJA
BIOIMAGING FACILITY	LENNY BROCKS MARJOLIJN MERTZ BRAM VAN DEN BROEK
ELECTRON MICROSCOPY FACILITY	HANS JANSSEN
FLOWCYTOMETRY FACILITY	ANITA PFAUTH MARTIJN VAN BAALEN FRANK VAN DIEPEN
GENOMICS CORE FACILITY	RON KERKHOVEN, HEAD SHAN BABAN WIM BRUGMAN IRIS DE RINK ROEL KLUIN MARIELLE KRETE JANNEKE KRUIZINGA MARJA NIEUWLAND CHARLAINE VAN STEENIS ARNO VELDS SAMANTHA ZWEERS

GLASSWARE	FRANCIS MAKATIPU-KAMBEY
MOUSE IMAGING FACILITY	JEFFREY STEINBERG NIELS DE WIT
MOUSE INTERVENTION FACILITY	MARIEKE VAN DE VEN, HEAD CHARLOTTE BAAK LEVI BUIL BJØRN SITEUR RENSKE DE KORTE-GRIMMERINK NATALIE PROOST BAS VAN GERWEN
LIBRARY	PATRICK BHAIROSING IRENE BENNE WINNIE SCHATS
PROTEIN FACILITY	PATRICK CELIE, HEAD JOHN DE WIDT ALEX FISH MAGDA STADNIK
PROTEOMICS FACILITY	MAARTEN ALTELAAR, HEAD ONNO BLEIJERVELD LIESBETH HOEKMAN
RADIONUCLIDE CENTER	DESIREE LUIJTEN-VERWOERD, HEAD THEO LAMERS
RESEARCH IT	JELLE TEN HOEVE, HEAD JAN HUDECEK BISHENG LIU RUBEN MORITZ RUBAYTE RAHMAN HENK VAN DER POL
ROBOTICS AND SCREENING FACILITY	RODERICK BEIJERSBERGEN, HEAD COR LIEFTINK BEN MORRIS
SEQUENCE FACILITY	ABDERRAHIM AJOUAOU ANKE BROUWERS ROELOF PRUNTEL
TECHNOLOGY TRANSFER OFFICE	KOEN VERHOEF, HEAD STEPHANIE DE MEZA HYLKE GALAMA FRANK HOORN MARIN HUBERTUS MARIJE MARSMAN ANJE RAVEN
TRANSGENIC CORE FACILITY	IVO HUIJBERS, HEAD RAHMEN BIN ALI LINDA HENNEMAN PAUL KRIMPENFORT LONA KROESE BISHENG LIU COLIN PRITCHARD FINA VAN DE AHÉ TANYA VERMEEREN-BRAUMULLER

Technology Transfer Office

Koen Verhoef

Manager Technology Transfer Office

Koen Verhoef Manager
Marije Marsman Senior business developer
Anje Raven Business developer
Hylke Galama Senior legal counsel
Marin Hubertus Legal counsel
Stephanie de Meza Legal counsel

INTRODUCTION

The Technology Transfer Office (TTO) helps NKI researchers and clinicians in concluding contractual agreements around research collaborations and -materials, both with other academic research institutions as well as with industry. In addition, TTO is the central support organization for the application of NKI research results in healthcare (valorization). TTO aims to maximize the chances of successful valorization by, amongst others, finding committed (commercial) partners and protecting the NKI's intellectual property.
TTO also handles all consultancy agreements for the institute and has a sizeable portfolio of research materials which it licenses to industry.

SELECTED ACHIEVEMENTS

License Agreement with Neon Therapeutics

Neon Therapeutics, an immuno-oncology company developing neo-antigen-based therapeutic vaccines and T cell therapies to treat cancer, has entered into an exclusive license agreement with the NKI for technology to be utilized in Neon Therapeutics' personalized neo-antigen T cell therapy program, NEO-PTC-01.
Under a collaborative research agreement established in 2016, Neon Therapeutics and the NKI have developed an *ex vivo* induction protocol which produces autologous T cells targeting each patient's own neo-antigens. This collaborative research has been led at the NKI by John Haanen, head of the Medical Oncology Division and Joost van den Berg, head of the Cell Therapy facility, with support from Neon co-founder Ton Schumacher, senior member of the Division of Molecular Oncology & Immunology. Neon Therapeutics has now licensed intellectual property and know-how from NKI to support further development of NEO-PTC-01 into clinical development.
NEO-PTC-01 is an autologous T cell therapy, where a proprietary induction protocol is used to induce multiple T cell populations specific for multiple neo-antigen targets. Neon Therapeutics will continue to work with the NKI to prepare for the initiation of a phase 1 clinical study by the end of 2018, which will amongst others will require a scale-up of the GMP manufacturing process that was jointly developed.

Oncode Institute

Oncode Institute is an independent research institute with a focus on beating cancer. It has three cornerstones: excellent research, intensive cooperation and bringing new treatments faster into the clinic. To this end, Oncode Institute has appointed a team of valorization experts to eventually increase the quality of life of patients.
Oncode brings together research groups from a number of different research institutions in the Netherlands in a virtual organization, meaning that all research groups remain embedded in their current home institution. Oncode Institute has started on 1 November 2017 and has taken on its valorisation obligations on Jan 1st 2018.
NKI signed an affiliation agreement with Oncode Institute in October 2017, the first research organization to do so. The affiliation agreement specifies the rights and obligations of both Oncode Institute and NKI around funding research within NKI research groups and makes arrangements for valorisation-related activities that – for the affiliated NKI research groups – will transfer from the NKI TTO to Oncode Institute.

SPIN-OFF COMPANIES FOUNDED IN 2017

Scenic Biotech

Scenic Biotech BV, a spin-off from the NKI and Oxford University, was set up in early 2017 by its founders Thijn Brummelkamp (NKI) and Sebastian Nijman (Oxford) to tackle diseases on the genetic level. Several licenses for the commercial use of NKI-owned technology were concluded between Scenic Biotech and NKI-AVL.
Scenic managed to secure a substantial amount in early stage funding to advance its immunotherapy technologies. The therapeutics spinout company raised €6.5m in Series A financing, which will be used to develop its 'genetic off-switch' for cancer and rare genetic diseases. The round was co-led by Netherlands-based life sciences investor BioGeneration Ventures (BGV) and peer INKEF Capital, with the participation of Oxford Sciences Innovation (OSI), the university venturing investor for Oxford University.
The underlying technology behind Scenic focuses on disease-suppressing genes, which until recently have proved problematic to uncover. As highlighted in a recent article in Nature, *Genetic wiring maps of single-cell protein states reveal an off-switch for GPCR signalling,* Scenic's propriety technology platform, Cell-Seq, changes the game.
Cell-Seq enables experimental assessment of nearly all genes that impinge on any cellular process with high precision and sensitivity. For the first time, genes that suppress processes that go awry in disease can be systematically identified. These genes can then serve as starting points for drug development and discovery to rebalance a variety of diseases. The first in-house lead program that resulted from the Cell-Seq technology is in the immuno-oncology space and additional programs in other indications, in particular in rare genetic diseases, will be added in the next two years.

Gen-X

Gen-X was founded by Joris van Arensbergen, a senior post-doc at NKI, who – while working in the Bas van Steensel group – developed a technology called SuRE, which was published in Nature Biotechnology in February 2017 and that can be used for genome-wide mapping of promotor activity in cells. By performing an exhaustive promoter screen for any genome of interest, Gen-X can provide its customers with the optimal gene promoter for their specific gene expression purposes.
Recombinant proteins are used to treat many diseases, such as cancer and diabetes and their current annual revenue amounts to >100 billion US$. These recombinant proteins are produced by overexpressing them in mammalian cell lines grown in large bioreactors, which is a cumbersome and costly process. A major determinant of protein expression – and therefore of revenue per production round – is the gene promoter used to drive the expression of the recombinant protein. The current industry workhorse is the strong viral-derived CMV promoter. However, a major drawback of the CMV promoter is that it suffers from progressive inactivation because of its viral origin, complicating the establishment of producer clones and negatively impacting protein yields. Currently, alternative non-viral promoters are hardly used because of their comparatively low expression levels.
The screening platform that Gen-X is exploiting has a throughput that is 100-1000 times larger than rival platforms. In a proof-of-concept study, promoters in the human genome were identified that showed more stable and 3-fold higher protein production levels than the benchmark CMV promoter. Gen-X is currently applying the SuRE method to identify promoters in Chinese Hamster Ovary (CHO) cells, the most commonly used protein production platform. The available proof-of-concept data from human cells have already convinced companies of the potential of the SuRE platform that Gen-X utilizes and, based on this, the company is currently building alliances to test newly-identified promoters in real-life industrial settings as well as alliances aimed at taking it closer to its potential customers.
Gen-X has a long-term vision to evolve into the highest quality provider of gene expression solutions, not only for the recombinant protein market, but also for human gene-therapy strategies.

TTO in numbers

- License income: € 3.637.000
- Freely disposable income from commercial research and consulting: € 1.148.000
- In total, 1061 contracts were negotiated and executed in 2017, of which 23 were license agreements.
- TTO received 22 invention disclosures and filed 10 priority patent applications in 2017.

Education in oncology

The Netherlands Cancer Institute offers a variety of opportunities for practical and theoretical training to (trainee) technicians, University Master students, PhD students and post-doctoral fellows. Research and clinical staff and their group members are involved in theoretical and practical training. Many staff members have joint appointments as professors at Dutch universities and even more contribute to the regular curriculum at various universities. The research divisions attract students from universities throughout the The Netherlands. The NKI has a formal affiliation with the Science faculty of the University of Amsterdam (UvA) and is committed to make a contribution to Master student teaching. The institute participates in the Oncology Graduate School Amsterdam, together with the medical faculties of the UvA and the VU University (VU), referred to as Academic Medical Center (AMC) and VU medical center (VUmc), respectively. All educational activities are supervised by the Teaching Committee, which consists of Jannie Borst (chair and dean Master students), Hein te Riele (general affairs and dean PhD students), Fred van Leeuwen (dean post-docs), Roderick Beijersbergen (Master course), Wilbert Zwart (HLO students and publicity), and Fons Balm (clinical teaching).

MASTER STUDENTS

The program in Experimental Oncology attracts Master students of all national universities (see www.nki.nl/topmenu/master-students/). Students generally have a background in (Medical) Biology, Health Sciences, Chemistry, Pharmacology, Medicine, or Psychology. The program offers combined practical and theoretical training in various aspects of experimental oncology. Practical training includes participation in ongoing research projects for a minimum of 4 months.
In 2017, 44 Dutch university Master students completed a placement of 6-10 months at the biomedical research divisions. The students came primarily from the University of Amsterdam (UvA) (12) and the VU University Amsterdam (VU) (18), but also from the universities of Utrecht (3), Leiden (8), Nijmegen (1) and Wageningen (1). Also 8 Master students from abroad completed a placement of 6-10 months at the biomedical research divisions. The institute also provides practical training opportunities for Bachelor students of the HLO (Universities of Applied Science), who stay for similar periods of time as the university students and like these, often make significant contributions to research progress of the PhD students and post-docs who supervise them.
The core element of theoretical training is the course in Experimental Oncology (Table 1). This course is from 2016 onwards offered as an elective to Master students who do an internship of more than 4 months at the NK in a biomedical discipline. This course is available for Master students doing an internship in the Institute for more than 4 months in the area of Biology, Medicine or Chemistry. From 2016 onwards, the master course has a more interactive program and participation in tutorials and assignments is limited to 32 participants who all take the associated exams in order to get study points. Other interested parties such as PhD students are welcome to come listen to the lectures upon enrolment as attendee (18 places). In the new set up, which was first tried out in the fall of 2016, the course evolved around four main themes for which assignments and exams were organized, in addition to lectures covering the field. The organizers will further develop this course in accordance with university guidelines and in consultation with NKI staff.

TABLE 1
COURSE IN EXPERIMENTAL ONCOLOGY

MEET THE PHD STUDENT	K BRESSER, M WELLENSTEIN
LECTURES:	
EPIDEMIOLOGY	F VAN LEEUWEN
NEXT GENERATION SEQUENCING	R KERKHOVEN
ADVANCED EARLY CANCER DIAGNOSTICS	B CARVALHO, R FIJNEMAN
RADIOTHERAPY + TOUR	M VERHEIJ
CONVENTIONAL CHEMOTHERAPY	F OPDAM
MEDICAL IMAGING	E VEGT
PROTEIN STRUCTURE AND DRUG DESING	T SIXMA
TUMOR MICROENVIRONMENT	K DE VISSER
(IMMUNOGENIC) CELL DEATH	J BORST
RADIOIMMUNOTHERAPY	I VERBRUGGE
EPIGENETICS IN CANCER	E DE WIT, F VAN LEEUWEN
MOUSE MODELS OF CANCER	I HUIJBERS
TELOMERASE AND CANCER	J JACOBS
DRUG DELIVERY	A SCHINKEL
PHARMACOLOGICAL ASPECTS OF (PRE)CLINICAL STUDIES	O VAN TELLINGEN
CANCER GENOMICS	L WESSELS
FUNCTIONAL GENOMIC SCREENING	T BRUMMELKAMP
TARGETED THERAPY IN THE CLINIC	J SCHELLENS
THEMATIC BLOCKS: EXAM ON BACKGROUND, STATE-OF-THE ART LECTURES, STUDENT PRESENTATIONS + QUESTIONS, RESEARCH PROPOSALS	
- HORMONE REGULATED CANCERS	W ZWART, H HORLINGS, M KOK
- IMMUNOLOGY AND IMMUNOTHERAPY	J BORST, P KVISTBORG, T SCHUMACHER
- DNA DAMAGE AND GENOMIC INSTABILITY	H TE RIELE, C VENS, M TIJSTERMAN (GUEST)
- TARGETED THERAPY AND RESISTANCE	R BEIJERSBERGEN, R BERNARDS

PHD STUDENTS

PhD students at the NKI-AVL participate in the Oncology Graduate School Amsterdam (OOA), an alliance of the oncology research divisions of the NKI-AVL and the two Amsterdam universities. The number of PhD students has been rising rapidly in the past years. In 2017, the institute had 328 PhD students registered at the OOA. 33 students defended a PhD thesis at a Dutch university.

Besides joining interdepartmental work discussions, the students follow the OOA training program that offers courses, meet-the-expert sessions and an annual retreat (Table 2). The OOA course program includes in-depth courses on different topics in cancer research, but also technical courses in English writing, biostatistics and -informatics, microscopy and animal handling. Students with an insufficient background in cancer research can attend the Experimental Oncology course for Master students. PhD students also have the opportunity to meet with experts in the field of oncology: the Friday morning seminar speakers are invited to a lunch meeting with a delegation of PhD students. Each graduate student can participate several times a year.

The annual PhD student retreat is entirely focused on the research of the graduate students themselves. First year students present their work in the form of a poster; advanced students give an oral presentation. Importantly, students are in charge of chairing sessions, monitoring discussions and selecting prizewinners for the best poster and best presentation. In this way, the retreat not only provides an overview

TABLE 2

OOA PHD STUDENT COURSES AND EVENTS 2017

JANUARY 23 - FEBRUARY 3	BIOBUSINESS
	A Griffioen, E Huijber, J van Beijnum (VUmc)
	8 participants
FEBRUARY 8 AND 20	HOW TO WRITE HIGH-IMPACT PAPERS AND WHAT TO DO WHEN YOUR MANUSCRIPT IS REJECTED
	Y Duijker, E Ruhé (VUmc)
	50 participants
MARCH 13-17	RADIATION ONCOLOGY
	P Sminia, JJ Sonke, L Stalpers (VUmc, AMC, NKI-AVL)
	29 participants
MARCH 24	HEAD AND NECK ONCOLOGY SYMPOSIUM
	CTO Utrecht
	5 participants
APRIL 3-13	MOUSE MORPHOLOGY, GENETICS AND FUNCTION
	J Seppen, E Reits (AMC)
	13 participants
MAY 15-19	IN THE FOOTSTEPS OF ANTONI VAN LEEUWENHOEK - BASIC MICROSCOPY
	E Reits, H van Veen, R Hoebe, J Stap, D Picavet, N van der Wel, M van den Bergh Weerman, L Brocks, M Mertz, H Janssen, J Beliën, T O'Toole, J Garcia-Vallejo (VUmc, AMC, NKI-AVL)
	16 participants
JUNE 12-16	GENETIC ENGINEERING IN MODEL ORGANISMS: TECHNOLOGY AND APPLICATION IN BASIC AND MEDICAL RESEARCH
	J Verbeek, E Robanus Maandag, H te Riele (MGC-LUMC, NKI-AVL)
	15 participants
JULY 4-6	MODERN CANCER PATHOLOGY
	CTO Utrecht
	13 participants
SEPTEMBER 15	PRESENTATION SKILLS FOR A BROAD AUDIENCE
	A Griffioen, H te Riele (VUmc, NKI-AVL)
	50 participants
OCTOBER 11-13	ANNUAL GRADUATE STUDENT RETREAT 2017
	P Lagerweij, H te Riele (NKI-AVL)
	188 participants
OCTOBER 23-27	IN THE FOOTSTEPS OF ANTONI VAN LEEUWENHOEK - BASIC MICROSCOPY
	E Reits, H van Veen, R Hoebe, J Stap, D Picavet, N van der Wel, M van den Bergh Weerman, L Brocks, M Mertz, H Janssen, J Beliën, T O'Toole, J Garcia-Vallejo (VUmc, AMC, NKI-AVL)
	16 participants
OCTOBER 30- NOVEMBER 1	MATLAB
	L Hoyng (VUmc)
	12 participants
NOVEMBER 13-17	BASIC MEDICAL STATISTICS
	M Hauptmann, P Gradowska, K Jozwiak, W Heemsbergen (NKI)
	66 participants
NOVEMBER 14-16	ADVANCED O2FLOW CYTOMETRY
	J Garcia Vallejo (VUmc)
	18 participants
NOVEMBER 19	MEET-THE-EXPERT VISHVA DIXIT
	CGC meeting Utrecht (NKI-AVL)
	12 participants
NOVEMBER 29 - DECEMBER 1	CLINICAL TRIAL DEVELOPMENT
	CTO Utrecht
THROUGHOUT THE YEAR	LUNCH MEETINGS WITH NKI-AVL SEMINAR SPEAKERS
	NKI seminar committee
	± 150 participants

Annual OOA retreat for PhD students took place in Renesse 10 - 12 October 2017
with a record number of 160 participants.

of the research in the OOA at an early stage of the student's career, but also training in presentation and interaction skills. We hope to stimulate translational interactions and bottom-up research, in which graduate students actively establish collaborations with other research groups, strengthening scientific exchange between the three Amsterdam oncology centers.

Senior graduate students can participate in a joint retreat with other cancer institutes in Europe. In 2017, this event was held in Berlin, Germany, organized by the students from the Max Delbruck Center for Molecular Medicine (MDC), with participants from:

- The CRUK Institutes (Cambridge, Glasgow, London, Manchester and Oxford)
- The Institute of Cancer Research (ICR)
- German Cancer Research Center (DKFZ)
- The Max Delbruck Center for Molecular Medicine (MDC)
- The Netherlands Cancer Institute (NKI)
- The European School of Molecular Medicine (SEMM: IFOM-IEO)

who attended and contributed to a program of scientific lectures and posters as well as an enthusiastic social session. This retreat gives students the opportunity to become acquainted with oncology centers of excellence throughout Europe.

Once a year, the PhD student meets with a supervisory committee to evaluate the progress of research. Each committee has independent members from within and outside the division. The committee discusses progress with the supervisor and the student jointly and separately. Two years after the appointment of the PhD student, a midterm review takes place. At this more elaborate meeting the likelihood of achieving a PhD within a reasonable time frame is discussed. This meeting can be used to redefine goals if necessary.

Each research division of the NKI-AVL has a delegate in the PhD student council that meets with the Dean of graduate students on a regular basis, as well as upon request. They also mediate communication between the graduate students and the board of directors. In 2016, an OOA PhD council has been installed consisting of representatives of the three Amsterdam oncology centers, which organizes events specifically focused on career development of graduate students.

POSTDOCS

In 2017 the NKI-AVL hosted approximately 140 postdoctoral fellows, almost half of which are from abroad and with equal gender representation. The postdocs at the NKI are represented by a very active postdoc committee (postdocs@nki). They organize workshops and special events such as grant writing courses, (alumni) career development seminars, and workshops about intellectual property, valorization of academic research and entrepreneurship. In addition, they regularly bring issues that matter to postdocs and others to the attention of NKI management.

The postdoc committee is also actively involved in the career development program that is offered by the NKI to all its postdocs. This program has been developed together with human resources and the postdoc dean. After an initial transition year, the first regular program was offered in 2015/2016. During their first year at the NKI postdocs participate in a basic program, which consists of three one-day workshops. The basic program is mandatory for new NKI postdocs. In 2017, ~36 postdocs started in the basic program.

Basic Postdoc Career Development Program

Day 1. Personal effectiveness: time and project management
Day 2. Communication & cooperation
Day 3. Creating your future, take ownership

All postdocs that have completed the basic program are invited in subsequent years to follow one of the one-day workshops as part of the Advanced Postdoc Career Development Program. In 2017, ~48 postdocs registered for a workshop of the advanced program.

Advanced Postdoc Career Development Program

1. Influence and impact (2017/2017 and 2017/2018)
2. Leading others (2016/2017 and 2017/2018
3. Managing your time and goals (2016/2017)
4. Marketing yourself and your research (2016/2017)
5. Shaping your career (2017/2018)
6. Scientific project management (2017/2018)

The goals of the program are to provide postdocs with the tools to take charge of their professional and personal development at the NKI, to promote maximum achievement of postdocs at the NKI, and to prepare postdocs for the next steps in their careers. The program, which is tailored to NKI postdocs, consists of special workshops of ~12 participants given by professional trainers but with input and active participation of NKI group leaders. The trainers all have a background in science and are fluent in English. The program is flexible and still being further developed. In 2017 a few adjustments were made to the advanced program. Two advanced workshop topics were replaced by new ones based on input from workshop participants, the trainers, and the postdoc committee.

Clinical trials

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
ALL SITES				
C14EMB	Prospective study on the treatment of unsuspected pulmonary embolism in cancer patients	Joke Baars	other	07/01/14
M09NIB	The NIB-Cohort study, therapeutic drug monitoring of tyrosine kinase inhibitors	Neeltje Steeghs	other	09/06/09
M10AZD	A phase I open-label, multicenter study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of ascending doses of AZD5363 under adaptable dosing schedules in patients with advanced solid malignancies	Jan Schellens	I	2/12/2010 (28/3/2017)
M11PCT	Development of a platform for next-generation DNA sequencing based personalized treatment for cancer patients: protocol to obtain biopsies from patients with metastatic cancer (CPCT-02)	Neeltje Steeghs	other	24/01/12
M12SEN	Observational study to evaluate pharmacokinetics and pharmacodynamics of docetaxel, paclitaxel, doxorubicine, gemcitabine, vinorelbine and capecitabine in elderly patients	Jan Schellens	other	13/09/12
M13ROS	Rapid on-site evaluation (ROSE) vs. randomly collected samples from mediastinal and abdominal lymph nodes obtained by endoscopic ultrasound-guided fine-needle-aspiration	Monique van Leerdam	other	7/8/2014 (1/11/2017)
M14BEE	A phase Ib dose-finding study of BYL719 plus everolimus and BYL719 plus everolimus plus exemestane in patients with advanced solid tumors, with dose-expansion cohorts in renal cell cancer, pancreatic neuroendocrine tumors, and advanced breast cancer patients	Jan Schellens	I	30/10/2014 (18/01/2017)
M14CDP	An open-label, multicenter, dose-escalation phase Ib study to investigate the safety, pharmacokinetics, pharmacodynamics, and therapeutic activity of RO7009789 (CD40 agonist) in combination with MPDL3280a (anti-PD-L1) in patients with locally advanced and/or metastatic solid tumors	Jan Schellens	I	23/01/15
M14CIP	Cancer in Pregnancy (CIP-study)	Christianne Lok	other	17/02/15
M14DPD	Safety, feasibility and cost-effectiveness of genotype- and phenotype-directed individualized dosing of fluoropyrimidines	Jan Schellens	other	31/03/15
M14DTR	A phase II, open-label, study in patients with BRAF V600E-mutated rare cancers with several histologies to investigate the clinical efficacy and safety of the combination therapy of Dabrafinib and Trametinib	Jan Schellens	II	13/11/14
M14HDM	A phase I, open label, multicenter, dose-escalation study of oral HDM201 in adult patients with advanced solid and hematological tumors characterized by wild-type TP53	Jan Schellens	I	18/12/14
M14HEP	An Open-label, Non-randomised, Multicentre, Comparative, Phase I Study to Determine the pharmacokinetics, Safety and Tolerability of Olaparib following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumours and Normal Hepatic Function or Mild or Moderate Hepatic Impairment	Jan Schellens	I	13/2/2014 (22/12/2016)
M14HUM	Hubrecht Organoid Technology-Metastasis, a resource for functional studies on drug development for cancer treatment	Emile Voest	other	11/08/14
M14HUP	Biobank Hubrecht Institute, a resource for functional studies on drug development for cancer treatment	Emile Voest	other	11/08/14
M14MCL	A Phase I Study of MCLA-128, a Human IgG1 Bispecific Antibody Targeting HER2 and HER3, in Patients with Solid Tumours	Jan Schellens	I/II	11/03/15
M14MPD	A phase Ib study of the safety and pharmacology of MPDL3280A administered with ipilimumab or interferon-alpha in patients with locally advanced or metastatic solid tumors (RAPID)	Christian Blank	I	28/1/2015 (14/11/2017)

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M14MSA	A Multicenter, Open-Label, Dose-Escalating Phase I Trial of the DNA-PK Inhibitor MSC2490484A in Subjects With Advanced Solid Tumors or Chronic Lymphocytic Leukemia	Jan Schellens	I	30/01/15
M14PIF	Phase I study evaluating indomethacin in combination with platinum-based chemotherapy	Emile Voest	I	16/12/2014 (09/10/2017)
M14ROM	A Phase 1B, open-label, multi-center, dose-escalation study of the safety, pharmacokinetics and therapeutic activity of RO6895882, an immunocytokine, which consists of a viariant of Interleukin-2 (IL-2v), that targets carcinoembryonic antigen (CEA), and MPDL3280A, an antibody that targets programmed death-ligand 1 (PD-L1), administered in combination intravenously, in patients with locally advanced and/or metastatic solid tumors	Jan Schellens	I/II	21/04/15
M14TBA	An open-label, multicenter, dose-escalation phase I study to evaluate the safety, pharmacokinetics, and therapeutic activity of RO6958688, a novel T-cell bispecific antibody that targets the human carcinoembryonic antigen (CEA) on tumor cells and CD3 on T-cells, administered intravenously in patients with locally advanced and/or metastatic CEA(+) solid tumors	Jan Schellens	I	14/01/15
M14VID	Ventilator-Induced Diaphragm Dysfunction in ICU patients	Koen Hartemink	other	19/5/2014 (2/11/2017)
M15CEG	A phase I/II, multicenter, open-label study of EGFRmut–TKI EGF816, administered orally in adult patients with EGFRmut solid malignancies	Egbert Smit	I/II	28/06/16
M15DRU	A National Study to Facilitate Patient Access to Commercially Available, Targeted Anti-cancer Drugs to determine the Potential Efficacy in Treatment of Advanced Cancers with a Known Molecular Profile; The Drug Rediscovery Protocol (DRUP)	Emile Voest	other	25/07/16
M15FAP	An open-label, multicenter, dose-escalation, Phase I study to evaluate safety, pharmacokinetics, and therapeutic activity of RO6874281, an immunocytokine consisting of interleukin 2 variant (IL-2v) targeting fibroblast activation protein-α (FAP), in patients with advanced and/or metastatic solid tumors	Jan Schellens	I	18/12/15
M15KEY	A clinical trial of Pembrolizumab (MK-3475) evaluating predictive biomarkers in subjects with advanced solid tumors (KEYNOTE 158)	Jan Schellens	II	29/02/16
M15MBG	A phase I-Ib/II, open-label, multi-center study of the safety and efficacy of MBG453 as single agent and in combination with PDR001 in adult patients with advanced malignancies	Jan Schellens	I/II	28/07/17
M15MPA	An open-label, multicohort, phase II study of MPDL3280A in advanced solid tumors (Basket)	Cecile Grootscholten	II	03/07/15
M15MSB	A phase 1B/2 open-label study to evaluate safety, clinical activity, pharmacokinetics and pharmacodynamics of Avelumab (MSB0010718C) in combination with other cancer immunotherapies in patients with advanced malignancies	Jan Schellens	I/II	27/7/2016 (6/11/2017)
M15MSR	An Open Label, Phase Trial of the DNA-PK Inhibitor MSC2490484A in Combination with Radiotherapy in Patients with Advanced Solid Tumors	Jan Schellens	I	17/07/15
M15NUT	A Phase I/II Open-Label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GSK525762 in Subjects with NUT Midline Carcinoma (NMC) and Other Cancers	Jan Schellens	I	24/03/16
M15OTD	Validation study of an assessment tool for Breakthrough Cancer Pain	Anne Lukas	other	5/8/2015 (2/11/2017)
M15PDR	Open label multicenter Phase I/II study of the safety and efficacy of PDR001 administered to patients with advanced malignancies	Jan Schellens	I/II	29/09/15
M15PEM	A Phase I, open-label study of GSK3174998 administered alone and in combination with anticancer agents including Pembrolizumab in subjects with selected advanced solid tumors (ENGAGE-1)	Jan Schellens	I	04/05/16

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M15PRM	A phase I, open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK3326595 in subjects with solid tumors and non-Hodgkin's lymphoma (PRMT5i)	Jan Schellens	I	27/10/16
M15ROA	An open-label, multicenter, dose-escalation and expansion phase Ib study to evaluate the safety, pharmacokinetics, and therapeutic activity of RO6958688 in combination with Atezolizumab in patients with locally advanced and/or metastatic CEA-positive solid tumors (CEA-TCB)	Jan Schellens	I	26/02/16
M15RVA	An open-label, multicenter, dose escalation phase 1b study with expansion cohorts to evaluate the safety, pharmacokinetics, pharmacodynamics and therapeutic activity of RO7009789 (CD40 agonistic monoclonal antibody) in combination with Vanucizumab (anti-ANG2 and anti-VEGF bi-specific monoclonal antibody) in patients with metastatic solid tumors (BP29889)	Jan Schellens	I	26/02/16
M15SRB	Postoperative local stereotactic radiotherapy versus observation following complete resection of a single brain metastasis	Dieta Brandsma	III	09/09/15
M15SYD	A two part first-in-human phase I study (with expanded cohorts) with the antibody-drug conjugate SYD985 to evaluate the safety, pharmacokinetics and efficacy in patients with locally advanced or metastatic solid tumours	Jan Schellens	I	01/06/16
M15TRE	A Phase II, multi-center, open-Label study of Tremelimumab monotherapy in patients with advanced solid tumors (TremeBasket)	Neeltje Steeghs	II	18/12/15
M16AOX	A Phase 1/2a Study of BMS-986178 Administered Alone and in Combination with Nivolumab or Ipilimumab in Advanced Solid Tumors	Jan Schellens	I/II	20/10/16
M16APF	Analysis of pleural fluid and ascites to improve diagnostics for patients with cancer	Jan Schellens	other	24/03/16
M16BAN	A Phase 1/2a Study of BMS-986179 Administered in Combination with Nivolumab (BMS-936558, anti-PD- 1 Monoclonal Antibody) in Advanced Solid Tumors	Neeltje Steeghs	I/II	02/09/16
M16BMN	A Phase 1/2a Dose Escalation and Cohort Expansion Study for Safety, Tolerability, and Efficacy of anti-GITR Monoclonal Antibody (BMS-986156) Administered Alone and in Combination with Nivolumab (BMS-936558, anti PD-1 Monoclonal Antibody) in Advanced Solid Tumors	Neeltje Steeghs	I/II	24/06/16
M16BMS	A Phase I/IIa Study of BMS 986148, a mesothelin directed antibody drug conjugate, in subjects with select advanced solid tumors	Jan Schellens	I/II	27/7/2016 (28/6/2017)
M16GAC	A Phase I Open Label study of GSK3359609 administered alone and in combination with anticancer agents in subjects with selected advanced solid tumors	Jan Schellens	I	30/05/17
M16LAG	A phase 1/2a dose escalation and cohort expansion study of the safety, tolerability, and efficacy of anti-LAG-3 monoclonal antibody (BMS- 986016) administered alone and in combination with anti-PD-1 monoclonal antibody (Nivolumab, BMS-936558) in advanced solid tumors	Jan Schellens	I/II	06/12/16
M16MDT	A Phase 1 Multicenter, Open-label, Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, Immunogenicity, and Antitumor Activity of MEDI0562 in Combination with Immune Therapeutic Agents in Adult Subjects with Advanced Solid Tumors	Neeltje Steeghs	I	15/09/16
M16MET	A Phase 1 Study of MEDI4736 (Anti-PD-L1 Antibody) in Combination with Tremelimumab (Anti- CTLA-4 Antibody) in Subjects with Advanced Solid Tumors	Michiel van der Heijden	I	08/08/16
M16MOL	A phase I/II study of MEDI4736 (anti-PD-L1 Antibody) in combination with Olaparib (PARP inhibitor) in patients with advanced solid tumors	Neeltje Steeghs	I/II	1/9/2016 (15/6/2017)
M16NFC	Multicenter study evaluating the hybrid approach using a novel fluorescence camera – Identifying the value of intraoperative fluorescence imaging during sentinel node biopsy procedures	Simon Horenblas	other	09/11/17

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M16STT	An open-label, multicenter, global phase 2 basket study of Entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbour NTRK1/2/3, ROSI or ALK gene rearrangements. (STARTRK-2)	Egbert Smit	II	24/08/16
M16SUP	Decision support for couples with hereditary cancer and child wish: weighing pros and cons of reproductive options regarding transmission of gene mutations	Lizet van der Kolk	other	07/11/16
M16TEM	Phase II, exploratory, multicenter, non randomized, single agent study to determine best tumor response with Trastuzumab Emtansine in HER2 overexpressing solid tumors (Kameleon)	Michiel van der Heijden	II	26/01/17
M17AFE	A randomised, open-label, phase I study to determine the effect of food on the pharmacokinetics of AZD1775 after oral dosing of a capsule formulation in patients with advanced solid tumours	Jan Schellens	I	27/09/17
M17AZD	An open-label, non-randomised, multicentre study to allow continued access to and assess the safety and tolerability of AZD1775 for patients enrolled in AZD1775 clinical pharmacology studies	Jan Schellens	other	02/10/17
M17CAN	An open label, dose escalation followed by dose expansion, safety and toler-ability trial of CAN04, a fully humanized monoclonal antibody against IL1RAP, in subjects with solid malignant tumors. (CANFOUR)	Jan Schellens	I/II	14/11/17
M17ITR	An open-label, Phase I study to asses the effect of itraconazole (CYP3A4 and P-gp inhibitor) on the pharmacokinetics of anetumab ravtansine and to asses the ECG effects, safety and immunogenicity of anetumab ravtansine given as a single agent and together with itraconazole in subjects with mesothelin-expressing advandced solid cancers.	Jan Schellens	I	06/10/17
M17QLQ	Validation of the EORTC computerized adaptive testing (CAT) instrument – Feasibilty and field study	Neil Aaronson	other	28/11/17
M17RIT	A phase I/II study of safety and efficacy of ribociclib (LEE011) in combination with trametinib (TMT212) in patients with metastatic or advanced solid tumors	Jan Schellens	I/II	23/05/17
M17TDM	Therapeutic drug monitoring for oral anti-cancer drugs	Neeltje Steeghs	other	09/08/17
N07DOW	Weekly administration of oral Docetaxel in combinaton with Ritonavir	Serena Marchetti	I	14/11/2007 (19/7/2017)
N10BOM	Weekly administration of (bi-) daily Oral Docetaxel in combination with Ritonavir	Serena Marchetti	I	17/5/2010 (13/2/2017)
N10CRC	Proof of principle and pharmacological phase 0 crossover study with controlled release capecitabine (ModraCape001)	Serena Marchetti	I	17/11/11
N10MOP	Development and clinical activity of low dose metronomic chemotherapy with oral paclitaxel	Jan Schellens	I	09/09/10
N12MTG	Middle ear thiosulfate-gel protection against cisplatin-induced hearing loss in patients carrying a single nucleotide polymorphism in the TPMT, COMT or LRP2 gene	Jan Schellens	other	11/04/13
N14CCT	Phase I pharmacological study of continuous and intermittent chronomodulated capecitabine therapy	Serena Marchetti	I	18/06/14
N14CEC	Development of an assay for detection of Circulating Endothelial Cells (CEC) and Circulating Endothelial Progenitor cells (CEP) by fluorescence-activated cell sorting (FACS) in cancer patients and healthy individuals	Jan Schellens	other	22/7/2014 (2/11/2017)
N15FED	Food-effect study of weekly administration of (bi-) daily Oral Docetaxel (ModraDoc006) in combination with ritonavir	Serena Marchetti	I	03/05/17
N15LDC	The effect of prehydration on the pharmacokinetics of low-dose Cisplatin	Wouter Vogel	other	06/11/15

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N15SGI	A phase I trial to assess the mass balance and pharmacokinetics of 14cguadecitabine in subjects with AML, MDS, or solid tumors	Jan Schellens	I	29/08/16
N16CLT	The use of fecal calprotectin in detecting immunotherapy induced colitis and feasibility for the use of immunohistochemical markers in patients receiving checkpoint inhibitors'- a pilot study (COLIT-1)	Jolanda van Dieren	pilot	23/05/16
N16CRY	The effect of Cryotherapy in preventing oral mucositis associated with doxorubicin treatment	Carolina Smorenburg	other	09/05/16
N16GEM	Phase 0 proof of concept study: a clinical pharmacokinetic microdosing trial with gemcitabine	Jan Schellens	other	19/04/17
N16LNA	In vivo identification of liver tumors during liver surgery using electromagnetic navigation: a pilot study (Navigation liver 1 study)	Theo Ruers	pilot	06/07/16
N16LND	Targeted Abdominal Lymph nodE dissections randomized for surgical NavigaTion (TALENT)	Theo Ruers	other	25/01/17
N16LUR	Mass Balance Study of PM01183 (lurbinectedin) Administered as a 1- hour Intravenous Infusion to Patients with Advanced Cancer	Jan Schellens	I	19/04/17
N16NVG	The effectiveness of patient navigation in cancer care	Eveline Bleiker	other	27/12/16
N16PDA	Validation of Pharmacokinetic Assays for determination of Nivolumab and Pembrolizumab concentrations in serum	Jan Schellens	other	16/01/17
N16PZN	Proof of principle and pharmacological phase 0 study with improved solubility Pazopanib (PazSol001)	Neeltje Steeghs	other	15/09/16
N16UMB	MR-sequence optimization and Workflow development for treatment guidance, using the integrated MR scanner of the MR Linac system. Towards MR guided Adaptive Radiation Therapy (UMBRELLA)	Marlies Nowee	other	26/04/17
N17DEX	Safety of extended use of the weekly oral docetaxel formulation ModraDoc006/r in patients with advanced solid tumours	Serena Marchetti	other	04/05/17
N17MRB	Monitoring MRI changes before and during Radiotherapy Treatment of Brain Tumors	Gerben Borst	other	31/08/17

BIOBANK

B15CTD	Circulating tumor DNA in cancer patients: development of a clinical diagnostic tests and establishment of a biobank	Michiel van der Heijden	biobank	07/10/15
B15HHC	Analyse van weefsel van patienten met een tumor in het hoofd-halsgebied	Lotje Zuur	biobank	03/09/15
B15IMM	Longitudinal tumor and blood sampling in patients with advanced stage urothelial cancer of the bladder for the analysis of mechanisms of response to immunotherapy	Michiel van der Heijden	biobank	07/10/15
B15OES	Tissue sampling of oesophagogastric cancer to enable tailored therapies (TOGETHER)	Johanna van Sandick	biobank	17/06/15
B15PON	Paired healthy & tumor organoid Biobank (carcinomas)	Emile Voest	biobank	09/09/15
B16BBC	Melanoma transcriptome protocol; Blood collection NETest	Margot Tesselaar	biobank	14/04/16
B16BHW	Blood sampling of healthy women and early stage breast cancer patients	Jelle Wesseling	biobank	11/07/16

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
B16CIT	Antigenic specificity and functional properties of colorectal cancer infiltrating human T cells, biobank protocol	Ton Schumacher	biobank	23/01/17
B16CLM	Determining the sensitivity and specificity of circulating tumor cells and cytology in cerebrospinal fluid of patients with suspicion of leptomenigual matastases	Dieta Brandsma	biobank	19/09/17
B16IMM	Biobank Immunotherapy baseline samples	Huub van Rossum	biobank	03/10/16
B16MEL	Understanding tumor immune escape in patients with stage III melanoma	Alexander van Akkooi	biobank	28/08/17
B16NBC	Tissue and blood sampling to find predictive markers for neoadjuvant chemotherapy benefit in breast cancer – Neoadjuvant Therapy Breast Cancer Biobank	Gabe Sonke	biobank	27/06/16
B16PON	Paired healthy & tumor organoid Biobank (adenomas)	Emile Voest	biobank	14/07/16
B16TGT	Translational Gastrointestinal Oncology – tissue	Gerrit Meijer	biobank	14/07/16
B17GEN	Biomarker analyse van weefsel/bloed van patiënten met een HPV-negatieve tumor in het hoofdhalsgebied	Michiel van den Brekel	biobank	27/09/17
B17PRE	Prevent Ductal Carcinoma In Situ Invasive Overtreatment Now (PRECISION)	Jelle Wesseling	biobank	28/11/17
BRAIN / CNS				
M15NFM	A randomized placebo-controlled study in patients with a Gallium-68 DOTATATE PET/CT positive, clinically non-functioning pituitary macroadenoma (NFMA) of the effect of Lanreotide autosolution on Tumor (adenoma) size (GALANT)	Marcel Stokkel	III	27/10/15
M15NTG	A Randomized Phase 3 Open Label Study of Nivolumab vs Temozolomide Each in Combination with Radiation Therapy in Newly Diagnosed Adult Subjects with Unmethylated MGMT (tumor O-6- methylguanine DNA methyltransferase) Glioblastoma (CheckMate 498)	Dieta Brandsma	III	06/06/16
M16NMG	A Randomized Phase 2 Single Blind Study of Temozolomide plus Radiation Therapy combined with Nivolumab or Placebo in Newly Diagnosed Adult Subjects with MGMT-Methylated (tumor O6- methylguanine DNA methyltransferase) Glioblastoma	Dieta Brandsma	II	17/06/16
N17MRB	"Monitoring MRI changes before and during	Gerben Borst	other	31/08/17
BREAST				
E1401	Management of low grade ductal carcinoma in situ (low-grade DCIS): a randomized, multicenter, noninferiority trial, between standard therapy approach versus active surveillance (LORD)	Jelle Wesseling	III	02/02/17
M05BRI	Long term risk of breast cancer following treatment of Hodgkin's disease (BRIGHT)	Nicola Russell	other	05/01/06
M08BCP	Prospective and Retrospective register study of the German Adjuvant Cancer Study Group (GABG) for diagnosis and treatment of breast cancer in pregnancy (BOOG 2003-04)	Sabine Linn	other	27/3/2008 (28/7/2017)
M11FAM	Breast density as indicator for the use of mammography or MRI to screen women with familiar risk for breast cancer (FaMRIsc)	Emiel Rutgers	other	30/11/11
M12DEN	Early detection of breast cancer in women with dense breasts (DENSE)	Claudette Loo	other	19/09/12

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M12SSU	Detectie van onstekingsgeassocieerde eiwitprofielen in het serum, speeksel en urine van patienten met mammatumoren	Emiel Rutgers	other	17/04/12
M13DDR	Breast cancer with low risk of local recurrence: partial and accelerated radiation with three-dimensional conformal radiotherapy (3DCRT) vs standard radiotherapy after conserving surgery (IRMA)	Nicola Russell	III	14/03/14
M13MBC	Male Breast Cancer: prospective into perspective	Nicola Russell	other	10/04/14
M13TNB	Biomarker discovery randomized phase IIb trial with Carboplatin-Cyclophosphamide versus Paclitaxel with or without Bevacizumab as first-line treatment in advanced triple negative breast cancer (TRIPLE-B)	Sabine Linn	II	09/07/13
M13WEL	Downsides of being well-informed: tracking and preventing chemotherapy-related cognitive problems in breast cancer patients (CONTEXT)	Sanne Schagen	other	14/10/13
M14CAT	The value of completion axillary treatment in sentinel node positive breast cancer patients undergoing a mastectomy. A Dutch randomized controlled multicentre trial (BOOG 2013-07)	Frederieke van Duijnhoven	III	24/07/14
M14CNB	Clinically node negative breast cancer patients undergoing breast conserving therapy: Sentinel lymph node procedure versus follow-up. A Dutch randomized controlled multicentre trial (BOOG 2013-08)	Frederieke van Duijnhoven	III	14/09/16
M14ECE	PI3K pathway analysis in tumor tumor tissue and circulating DNA to obtain further insight in the efficay of everolimus when combined with exemestane. A side-study attached to standard treatment with everolimus and exemestane for postmenopausal patients with hormone receptor-positive advanced metastatic breast cancer, who have progressed on anastrozole or letrozol (BOOG 2013-06)	Sabine Linn	other	24/3/2015 (15/2/2017)
M14HAR	Identifying subgroups with high cardiovascular risk in breast cancer survivors (HARBOR)	Floor van Leeuwen	other	13/04/15
M14POS	Phase I/prospective randomized phase II trial Of the Safety and Efficacy of tamoxifen in combination with the Isoform selective Pi3K inhibitor GDC-0032 compared with tamoxifen alONe in hormone receptor positive, HER2 negative, metastatic breast cancer patients with prior exposure to endocrine treatment (POSEIDON trial)	Sabine Linn	I/II	31/10/14
M14REV	A phase I followed by a randomized phase II trial of two cycles carboplatin-olaparib followed by olaparib monotherapy versus capecitabine in BRCA-1 or -2 mutated Her2 negative advanced breast cancer as first line treatment (REVIVAL study)	Jan Schellens	I/II	21/04/15
M15EVA	A randomized controlled trial of internet-based cognitive behavioral therapy for breast cancer patients with climacteric symptoms	Neil Aaronson	other	27/8/2015 (2/11/2017)
M15INF	Inflame; Towards optimal treatment of inflammatory breast cancer patients (INFLAME)	Gabe Sonke	other	10/05/16
M15OLY	A randomised double-blind parallel group placebo controlled multicenter phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline BRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy (OLYMPIA) (BOOG 2014-03)	Gabe Sonke	III	03/06/15
M15PAP	Pre- versus Postoperative Accelerated Partial Breast Irradiation in early stage breast cancer patients, A randomized phase III trial (PAPBI-2)	Astrid Scholten	III	17/08/16
M15PTN	A randomized open-Label phase III study of single agent Pembrolizumab versus single agent chemotherapy per physician's choice for metastatic triple negative breast cancer (mTNBC). (KEYNOTE 119)	Marleen Kok	III	2/3/2016 (21/2/2017)
M16BRC	Substantially improving the cure rate of high-risk BRCA1-like breast cancer patients with personalized therapy (SUBITO), an international randomized phase III trial	Sabine Linn	III	13/10/16

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M16MTR	How may exercise reduce fatigue in patients with cancer? A pilot study examining the role of muscular, immune and endocrine systems (Metric)	Cecile Grootscholten	pilot	22/6/2016 (11/5/2017)
M16PLE	Phase Ib, open-label, multi-center study to characterize the safety, tolerability and pharmacodynamics (PD) of PDR001 in combination with LCL161, Everolimus (RAD001) or Panobinostat (LBH589)	Jan Schellens	I	01/11/16
M16SDM	The development of a personalized decision aid: perspectives of patients and health care professionals on shared decision making and informational needs on radiotherapy for breast cancer	Nicola Russell		2/12/2016 (7/2/2017)
M17GEL	AssessinG Efficacy of carboplatin and ATezOlizumab in metastatic Lobular breast cancer: (GELATO)	Marleen Kok	I/II	06/10/17
M17PAB	Effect of a physical activity promotion program offered online or via blended care on physical activity level in breast and prostate cancer survivors: the PABLO trial	Wim Groen	other	19/10/17
M17PRP	Discovery of prognostic molecular markers within an early stage breast cancer patient population A study of the Dutch Breast Cancer Research Group BOOG 2016-03	Gabe Sonke	other	22/08/17
M17SDM	Implementing a decision aid for breast cancer and DCIS patients deciding on their radiation treatment: A pre- and post-intervention study	Nicola Russell	other	26/10/17
M17SJA	Endocrine therapy plus CDK 4/6 inhibition in first or second line for hormone receptor positive advanced breast cancer. (SONIA studie)	Gabe Sonke	other	09/11/17
M17TAN	Impact of a web-based decision aid for women considering breast reconstruction:a randomized controlled trial (TANGO)	Eveline Bleiker	other	02/08/17
N07BOS	Genetic determinants of survival and second breast cancer development in premenopausal breast cancer patients (BOSOM)	Marjanka Schmidt	other	12/12/07
N08AFT	A randomized prospective trial of 2-6 weeks pre-operative hormonal treatment for hormone receptor positive breast cancer: Anastrozole +/- fulvestrant or tamoxifen exposure - response in molecular profile (AFTER-study)	Sabine Linn	II	04/08/08
N08RMB	Tumorresponse monitoring in patients with breast cancer treated with primary systemic therapy: towards predicting response in both the primary tumor and in axillary lymph nodes	Marie Jeanne Vrancken Peeters	other	23/9/2008 (9/11/2017)
N09PRF	Analgesia and nerve function following pulsed radiofrequency for postmastectomy pain (PRF4PMPS)	Anne Lukas	II	2/6/2010 (25/9/2017)
N12CLM	Determining the sensitivity and specificity of circulating tumor cells and cytology in cerebrospinal fluid of patients clinically suspected for leptomeningeal metastases	Dieta Brandsma	I	19/6/2012 (19/9/2017)
N12OLG	High-dose alkylating chemotherapy in oligo-metastatic breast cancer harboring homologous recombination deficiency (OLIGO)	Gabe Sonke	III	03/07/12
N13MDS	Contrast-enhanced MR imaging of DCIS in supine position: a pilot study	Claudette Loo	pilot	27/1/2014 (29/11/2017)
N13ORB	Olaparib dose escalation combined with radiotherapy in patients with inoperable breast cancer	Gabe Sonke	I	23/08/13
N14FHS	Feasibility study to assess the incremental value of DeclipseSPECT during radioactive seed localisation in breast cancer surgery	Marie Jeanne Vrancken Peeters	other	15/12/2014 (9/11/2017)
N14MLS	Pilot for high-resolution SPECT imaging of breast cancer lumpectomy specimens for 3D identification and quantification of resection margins	Wouter Vogel	pilot	24/07/14

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N15CGC	A comparison of a hybrid compact gamma camera with planar lymphoscintigraphy to simplify the SN procedure (Xstrahl)	Marcel Stokkel	other	14/04/15
N15MML	MaMaLoc: Magnetic Marker Localisation for non- palpable breast lesions: a feasability study (MaMaLoc)	Theo Ruers	I	8/12/2015 (28/4/2017)
N15PPP	Prediction of persisting postmastectomy pain by psycho-somato-sensory profiling	Anne Lukas	other	25/01/16
N15TON	Adaptive phase II randomized non-comparative trial of nivolumab after induction treatment in triple-negative breast cancer (TNBC) patients: TONIC-trialM14PRT	Marleen Kok	II	10/09/15
N16LOG	A phase 1b, dose finding, open-label, monocenter study to assess the safety and tolerability of carboplatin-cyclophosphamide combined with atezolizumab, an antibody that targets programmed death ligand 1 (PD-L1), in patients with advanced breast cancer and gynaecologic cancer – the PROLOG study	Sabine Linn	I	9/1/2017 (1/11/2017)
N16MIC	MICRA study: Minimally Invasive Complete Response Assessment of the breast after neoadjuvant chemotherapy	Marie Jeanne Vrancken Peeters	other	06/04/16
N16NTL	Supine MRI-guided navigated radioactive seed localization in breast cancer patients: a feasibility study	Claudette Loo		02/02/17
N16PRB	Pre-operative Breast Irradiation (PROBI)	Astrid Scholten	I/II	18/04/17
N16SEN	Simplifying the sentinel node procedure in breast cancer using a portable gamma camera in order to replace conventional preoperative lymphatic mapping (SENTIMAP study)	Marcel Stokkel	other	06/07/17

GASTRO INTESTINAL

C14GIST	Prospectieve registratie GIST patienten	Neeltje Steeghs	other	13/01/14
C16TAS	Treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatinand irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents	Frans Opdam	other	07/01/16
E1409	A Prospective Colorectal Liver Metastasis Database with an Integrated Quality Assurance Program	Theo Ruers	other	13/01/16
M09OCB	A pilot evaluating response to induction chemotherapy with oxaliplatin, capecitabine and bevacizumab in patients with extensive peritoneal carcinomatosis of colorectar origin	Arend Aalbers	pilot	25/03/10
M12DEC	ART DECO: a randomized trial of dose escalation in definitive chemoradiotherapy for patients with oesophageal cancer	Berthe Aleman	III	12/02/13
M13DAP	Combination of dacomitinib and PD-0325901 in advanced KRAS mutation positive colorectal, non-small cell lung and pancreatic cancer	Jan Schellens	I	15/01/14
M13ORC	A randomized multicenter clinical trial for patients with multi-organ, colorectal cancer metastases comparing the combination of chemotherapy and maximal tumor debulking versus chemotherapy alone (ORCHESTRA)	Cecile Grootscholten	III	09/06/15
M13SCO	Peritoneal dissemination in stomach cancer patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (PERISCOPE)	Johanna van Sandick	I/II	15/1/2014 (10/11/2017)
M14AFS	Phase I/II study with the combination of afatinib and selumetinib in advanced KRAS mutant positive and PIK3CA wildtype colorectal, non-small cell lung and pancreatic cancer	Jan Schellens	I/II	19/05/15

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M14CR5	Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases - CAIRO5 - a randomised phase 3 study of the Dutch Colorectal Cancer Group (	Cecile Grootscholten	III	09/06/15
M14FMR	Pilot study evaluating the feasibility of endoscopy guided fiducial marker placement for rectal cancer	Monique van Leerdam	pilot	8/5/2014 (1/11/2017)
M14LTK	Phase I/II study with lapatinib plus trametinib in patients with metastatic KRAS mutant colorectal, non-small cell lung and pancreatic cancer	Jan Schellens	I/II	04/08/14
M14NEC	Phase II Study of cisplatin and everolimus in patients with metastatic or unresectable neuroendocrine carcinomas (NEC) of extrapulmonary origin	Margot Tesselaar	II	10/02/15
M14TUM	Tumor organoids: feasibility to predict sensitivity to treatment in cancer patients (TUMOROID trial)	Emile Voest	pilot	22/07/14
M15COL	Adjuvant hyperthermic intraperitoneal chemotherapy in patients with colon cancer at high risk of peritoneal carcinomatosis; the COLOPEC randomized multicentre trial	Arend Aalbers	III	30/04/15
M15CRI	A multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery vs. neoadjuvant chemotherapy and chemoradiotherapy followed by surgery vs. neo-adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer (CRITICS-II)	Marcel Verheij	II	23/06/17
M15DIS	Implementation of Resect and Discard strategy for diminutive polyps amongst accredited endoscopists for the Dutch bowel cancer screening program: training and long-term quality assurance (NTR 4635) - DISCOUNT II	Monique van Leerdam	other	18/8/2015 (1/11/2017)
M15HPV	Non-Comparative, Two-Cohort, Single-Arm, Open- Label, Phase 1/2 Study of Nivolumab (BMS-936558) in Subjects with Virus-Positive and Virus-Negative Solid Tumors	Jan Paul de Boer	I/II	27/10/15
M15MOC	Molecular stool test for colorectal cancer surveillance (MOCCAS)	Monique van Leerdam	other	20/01/16
M15MOD	A multi-centre randomised clinical trial of biomarker- driven maintenance treatment for first-line metastatic colorectal cancer (MODUL)	Cecile Grootscholten	II	14/01/16
M15PEC	Treatment of peritoneal dissemination in stomach cancer patients with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. PERISCOPE II - A multicentre randomised phase III trial	Johanna van Sandick	III	23/08/17
M15SCA	The sensitivity of scar-biopsies for residual colorectal adenocarcinoma after endoscopic resection with uncertain radicality (SCAPURA)	Monique van Leerdam	other	27/08/15
M15SOX	Feasibility study of adjuvant treatment with S-1 and oxaliplatin in patients with resectable esophageal cancer (SOX)	Cecile Grootscholten		26/06/15
M16BCR	A multicenter, randomized, open-label, 3-arm phase 3 study of Encorafenib +Cetuximab plus or minus Binimetinib vs. Irinotecan/Cetuximab or Infusional 5-Fluorouracil (5-FU)/Folinic Acid (FA) /Irinotecan (FOLFIRI)/Cetuximab with a safety lead-in of Encorafenib + Binimetinib + Cetuximab in patients with BRAF V600E-mutant metastatic colorectal cancer. The BEACON CRC Study (Binimetinib, Encorafenib, And Cetuximab COmbined to Treat BRAF-mutant ColoRectal Cancer)	Jan Schellens	III	23/09/16
M16EEW	Expectations and experiences of clinical complete responders after chemoradiation for rectal cancer, regarding the Wait-and-See policy: a qualitative multicenter study	Geerard Beets	other	03/05/16
M16EGJ	A Randomized, Multicenter, Double Blind, Phase III Study of Nivolumab or Placebo in Subjects with Resected Lower Esophageal, or Gastroesophageal Junction Cancer (CheckMate 577: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 577)	Cecile Grootscholten	III	27/10/16

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M16EPS	The European Polyp Surveillance study (EPoS): Two randomized controlled trials and an observational cohort study	Monique van Leerdam	other	29/03/17
M16INC	Intensive therapy for esophageal anastomotic strictures (INCA)	Jolanda van Dieren	II	12/04/17
M16MTR	How may exercise reduce fatigue in patients with cancer? A pilot study examining the role of muscular, immune and endocrine systems (Metric)	Cecile Grootscholten	pilot	22/6/2016 (11/5/2017)
M16PLE	Phase Ib, open-label, multi-center study to characterize the safety, tolerability and pharmacodynamics (PD) of PDR001 in combination with LCL161, Everolimus (RAD001) or Panobinostat (LBH589)	Jan Schellens	I	01/11/16
M16PTO	Preferences , barriers and facilitators for pre-operative exercise participation for elderly treated for colorectal cancer and their social network (PEPTONE)	Carla Agasi-Idenburg	other	20/04/17
M16SCR	Screening protocol to molecularly identify MSI-like, BRAF-like and TGFβ-like classifiers in patients with metastatic colorectal cancer (mCRC), to potentially participate in any of the H2020 MoTriColor Clinical Trials	Jan Schellens	other	25/01/17
M16STA	Can we Save the rectum by watchful waiting or TransAnal microsurgery following (chemo)Radiotherapy versus Total mesorectal excision for early REctal Cancer? (STAR-TREC)	Geerard Beets	II	26/07/17
M16TSR	Rectal preserving treatment for early rectal cancer. A multi-centred randomised trial of radical surgery versus adjuvant chemoradiotherapy after local excision for early rectal cancer (TESAR)	Monique van Leerdam	III	17/08/16
M16WAS	Multicentre evaluation of the "wait-and-see" policy for complete responders after chemoradiotherapy for rectal cancer	Geerard Beets	other	24/02/17
M17CR6	Investigating the benefit of perioperative systemic therapy in patients undergoing cytoreductive surgery with HIPEC for peritoneal metastases of colorectal cancer: the multicentre, phase II-III, prospective, randomised CAIRO6 study.	Arend Aalbers	other	07/09/17
M17CRC	Prospective data collection initiative on colorectal cancer - PLCRC, a prospective obeservational cohort study	Geerard Beets	IV	22/08/17
M17PLA	Evaluation of PET and Laparoscopy in STaging advanced gastric Cancer: a multicenter prospective study (PLASTIC)	Erik Vegt	other	16/10/17
N05STP	Serum and tissue protein profiling and tumour genetic analysis in patients with potential premalignant conditions or colorectal cancer	Annemieke Cats	other	19/1/2006 (29/11/2017)
N12CLM	Determining the sensitivity and specificity of circulating tumor cells and cytology in cerebrospinal fluid of patients clinically suspected for leptomeningeal metastases	Dieta Brandsma	I	19/6/2012 (19/9/2017)
N12INT	Pilot study to evaluate the tumor-reactiviity of infiltrating T cells in human malignancies	Wouter Scheper	pilot	05/09/12
N12RES	In vivo Response evaluation of colorectal livermetastases during systemic therapy using optical SPECTroscopic techniques (RESPECT)	Theo Ruers	pilot	24/9/2013 (2/11/2017)
N13NAV	Image-guided navigation during abdominal surgery	Theo Ruers	pilot	17/10/13
N13OME	Organ motion and early tumor response measurement during chemoradiotherapy for esophageal cancer	Francine Voncken	other	17/01/14
N14FDG	4D FDG PET-CT imaging in esophageal cancer- a pilot study	Francine Voncken	pilot	3/10/2014 (11/9/2017)
N14ITO	Immunogenicity of Tumor Organoids, a feasibility study	Emile Voest	other	22/07/14

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N14RCS	In vivo identification of rectum and coloncarcinoma during surgery using optical spectroscopy techniques (ColoSpect)	Theo Ruers	other	31/07/14
N14SNS	SENSOR study: Selecting cancer patients for treatment using Tumor Organoids	Emile Voest	other	16/08/16
N15MSC	The Mesenchymal Stem Cell biomarker study	Emile Voest	other	19/05/15
N15POS	Validity of Pre-operative screening in elderly patients who undergo Surgery for colorectal oncology, to predict postoperative complications and hospital stay. POSE	Carla Agasi-Idenburg	other	23/05/16
N16BTC	Blood Transcript Analysis in colorectal cancer patients	Margot Tesselaar	other	23/08/16
N16DWI	DWI MR imaging for dedicated staging of patients with peritoneal seeding (DISPERSE)	Max Lahaye	other	26/05/16
N16GMR	A Feasibility Study of MR- based target delineation for Radiotherapy Treatment Planning For Gastric Cancer	Marcel Verheij	pilot	02/09/16
N16NCI	Nivolumab, Ipilimumab and COX2-inhibition in early stage colon cancer: an unbiased approach for signals of sensitivity. The NICHE TRIAL	Myriam Chalabi	other	20/01/17
N16OCR	A prospective observational cohort for the clinical evaluation of innovative image guided surgical interventions in rectal cancer	Theo Ruers	other	13/10/16
N16TRS	Real-time in vivo sensor tracking of rectal tumours during colorectal cancer surgery	Theo Ruers	other	16/09/16

GYNAECOLOGICAL

E55102	A phase III Trial of postoperative chemotherapy or no further treatment for patients with node-negative stage I-II intermediate or high risk endometrial cancer	Hans Trum	III	24/08/16
M05PPO	Proteomic patterns in blood and tissue of ovarian cancer patients	Willemien van Driel	other	12/01/06
M07RCV	Phase II study of definitive radiochemotherapy for locally advanced squamous cell cancer of the vulva: an efficacy study	Baukelien van Triest	II	26/06/07
M10MKO	Phase II and pharmacological study with WEE-1 inhibitor MK-1775 combined with carboplatin in patients with p53 mutated epithelial ovarian cancer	Jan Schellens	II	08/07/10
M11CIR	Charting of immune reactivity against HPV in patients with HPV-induced (pre-) malignant lesions (Circle2)	Gemma Kenter	other	05/04/12
M13IMA	Repetitive Functional Imaging in Locally Advanced Cervical Cancer (IMAP)	Monique Bloemers	other	11/7/2014 (18/10/2017)
M14BBB	The Blood-Belly Barrier (tripleB)	Christianne Lok	nvt	03/05/16
M14ISA	A multicenter, open label Phase I/II study to determine the safety and immune modulating effects of the therapeutic Human Papilloma Virus Type 16 (HPV16) E6/E7 Synthetic Long Peptides Vaccine (ISA101) at different doses with or without interferon alpha as combination therapy with carboplatin and paclitaxel in women with HPV16 positive advanced or recurrent cervical cancer who have no curative treatment options (CervISA)	Gemma Kenter	I/II	29/4/2014 (2/11/2017)
M14SCM	Subcellular components and multi-drug resistance in epithelial ovarian carcinoma	Juliette van Baal	other	28/04/16
M15ATW	Cancer@ Work: a nurse-led web-based intervention to enhance return-to-work of cancer survivors - a multi-center randomised controlled trial	Gemma Kenter	other	20/11/2015 (16/8/2017)

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M15ENS	ENdometrial cancer SURvivors' follow-up carE (ENSURE): Less is more? Randomized controlled trial to evaluate patient satisfaction and cost-effectiveness of a reduced follow-up schedule	Hans Trum	other	20/10/15
M15HPV	Non-Comparative, Two-Cohort, Single-Arm, Open-Label, Phase 1/2 Study of Nivolumab (BMS-936558) in Subjects with Virus-Positive and Virus-Negative Solid Tumors	Jan Paul de Boer	I/II	27/10/15
M15MAM	Short drainage of the groins after inguinofemoral lymphadenectomy in patients with vulvar cancer (MAMBO IB)	Henry Zijlmans	other	29/6/2015 (18/1/2017)
M15PAG	Topical 5% imiquimod cream for vulvar Paget's Disease: clinical efficacy, safety and immunological response (PAGET)	Marc van Beurden	other	20/11/15
M15RHY	A randomized phase III trial comparing radical hysterectomy and pelvic node dissection vs simple hysterectomy and pelvic node dissection in patients with low-risk early-stage cervical cancer (SHAPE)	Willemien van Driel	III	29/12/15
M16HE4	Prospective evaluation of Human Epididymal protein 4 (HE4) as predictor of malignancy in patients with a ovarian mass	Christianne Lok	other	18/04/17
M16PEO	A phase II, open-label, single-arm, multicenter study to evaluate efficacy and safety of Pembrolizumab monotherapy in subjects with advanced recurrent ovarian cancer (KEYNOTE 100)	Gabe Sonke	II	30/06/16
M16RTE	Randomised Phase III Trial of molecular profile- based versus standard recommendations for adjuvant radiotherapy for women with early stage endometrial cancer. (PORTEC 4a)	Monique Bloemers	III	08/02/17
M16SOL	Biomarker detection in cytology samples of women with gynaecologic cancer: a multicentric study (SOLUTION)	Gemma Kenter	other	30/01/17
M16SON	Sentinel node in ovarian cancer (SONAR-2)	Willemien van Driel	I	15/09/16
M16TUB	Early salpingectomy (Tubectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers (TUBA)	Marc van Beurden	other	01/06/16
N12INT	Pilot study to evaluate the tumor-reactiviity of infiltrating T cells in human malignancies	Wouter Scheper	pilot	05/09/12
N15TCH	Isolation of T cell receptors from human papilloma virus (HPV)-reactive or other tumor-reactive T cells from patients with oropharyngeal, cervical or vulvar cancer	Lotje Zuur	other	13/07/16
N16DWI	DWI MR imaging for dedicated staging of patients with peritoneal seeding (DISPERSE)	Max Lahaye	other	26/05/16
N16LOG	A phase 1b, dose finding, open-label, monocenter study to assess the safety and tolerability of carboplatin-cyclophosphamide combined with atezolizumab, an antibody that targets programmed death ligand 1 (PD-L1), in patients with advanced breast cancer and gynaecologic cancer (PROLOG)	Sabine Linn	I	9/1/2017 (1/11/2017)
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/16
N16OPE	Feasibility study of neo-adjuvant treatment with carboplatin, paclitaxel and pembrolizumab in primary stage IV serous ovarian cancer	Gabe Sonke	I	19/07/17
N16SIG	Safety, immunogenicity and clinical response of sig- HELP-E6SH/E7SH-kdel, injected in the epidermis by DNA tattoo vaccination, in HPV16-positive vulvar intraepithelial neoplasia: a phase I/II study.	Gemma Kenter	I/II	09/11/16

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
HEAD AND NECK HEAD AND NECK				
M11ART	Adaptive and innovative radiation treatment for improving cancer treatment outcome (ARTFORCE)	Olga Hamming-Vrieze	II	20/12/11
M11FOR	FORECAST: Functional Outcome of Radiotherapy and Laser in Early Glottic Carcinoma	Martin Klop	III	25/10/2011 (2/3/2017)
M14PAR	TachoSil patch application as replacement of closed suction wound drainage by parotid gland surgery: a prospective study	Fons Balm	other	22/01/15
M14SEA	Phase-2 clinical trial on the treatment of chronic dysphagia in head and neck cancer patients with dedicated strengthening exercises using the Swallow Exercise Aid	Michiel van den Brekel	II	1/9/2015 (2/11/2017)
M14VOX	Clinical assessment of a new speaking valve for hands-free speech in laryngectomized subjects: Provox® FreeHands FlexiVoice	Michiel van den Brekel	other	2/5/2014 (2/11/2017)
M15CRH	Dutch randomized multicenter trial COmparing twO PalliativE RAdiaTION schemes for incurable head and neck cancer (COOPERATION)	Abrahim Al-Mamgani	III	12/11/15
M15EVR	Externe validatie van het risicopredictie model van patienten met T3T4 larynxcarcinoom	Michiel van den Brekel	other	13/11/2015 (2/11/2017)
M15HPV	Non-Comparative, Two-Cohort, Single-Arm, Open-Label, Phase 1/2 Study of Nivolumab (BMS-936558) in Subjects with Virus-Positive and Virus-Negative Solid Tumors	Jan Paul de Boer	I/II	27/10/15
M15PFO	A phase I, open-label, dose escalation study of PF-04518600 in patients with locally advanced or metastatic hepatocellular carcinoma (HCC), melanoma, clear cell renal cell carcinoma (RCC) or squamous cell head en neck cancer (SCCHN)	Jan Schellens	I	09/09/15
M16HME	A multicenter randomized crossover study of a new peristomal adhesive and Heat and Moisture Exchanger (HME) for nighttime pulmonary rehabilitation in laryngectomized patients.	Michiel van den Brekel	other	29/09/17
M16NIH	A Double-Blind, Randomized, Two Arm Phase 2 Study of Nivolumab in Combination with Ipilimumab versus Nivolumab in Combination with Ipilimumab Placebo In Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)	Margot Tesselaar	II	19/04/17
M16OPS	Optical properties of the sinonasal cavity after surgical tumor resection	Baris Karakullukcu	other	01/03/17
M16SPS	Combination of salvage surgery and adjuvant photodynamic therapy in management of recurrent or residual sinonasal tumors.	Baris Karakullukcu	other	26/01/17
M17CPI	Validation and psychometric properties of the Dutch version of the Communicative Participation Item Bank (CPIB) short form.	Michiel van den Brekel	other	16/10/17
N05HME	De korte termijn invloed van een Heat and Moisture Exchanger op de endotracheale temperatuur en luchtvochtigheid bij gelaryngectomeerden	Michiel van den Brekel	other	01/09/05
N10VMO	Evaluation of tumor variability with MRI during radiotherapy treatment in patients with an oropharyngeal or oral cavity carcinoma	Olga Hamming-Vrieze	other	8/11/2010 (28/11/2017)
N12MAC	Exploring the contribution of Macrophages in the microenvironment of HPV-induced squamous cell carcinoma of the head and neck (M&M)	Jan Paul de Boer	other	31/08/12
N13ORH	Olaparib dose escalation trial in patients treated with radiotherapy for stage II-III laryngeal and stage II-III HPV-negative oropharyngeal squamous cell carcinoma	Marcel Verheij	I	20/02/14

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N14BNI	An early clinical feasibility study of a new prosthesis: the NewBreez® Intralaryngeal device; a possible solution for severe aspiration in head and neck cancer patients	Michiel van den Brekel	pilot	12/2/2016 (2/11/2017)
N14IMR	The immunological aspects of conventional therapies for the treatment of head and neck squamous cell carcinoma (HNSCC). An exploratory study to study the mmunological effects of (chemo)radiotherapy in HNSCC patients	Lotje Zuur	other	23/03/15
N14LMN	Lymphatic mapping of the neck in patients with oral cavity malignancies using ICG-nanocolloid	Martin Klop	other	10/06/15
N14SUS	Sentinel node mapping Using SPECT to tailor highly-selective elective nodal irradiation in node-negative neck of patients with head and neck cancer (SUSPECT)	Abrahim Al-Mamgani	II	19/6/2015 (9/11/2017)
N15HTC	Longitudinal analysis of head and neck cancer- specific immunity in patients treated with (salvage) surgery	Lotje Zuur	other	16/12/15
N15PAH	Feasibility of position averaged planning-CT for head- neck tumours	Wouter Vogel	other	16/12/15
N15SHA	Effect of a silicone foam dressing (XtraSorb Foam) and hydrocolloid dressing (XtraSorb HCS) compared to silicone foam dressing (Mepilex) or an alginate (Kaltostat) combined with a semipermeable film (Tegaderm) on the donor site after split-thickness skin graft: a randomized controlled trial (SHAFEstudy)	Peter Lohuis	other	31/05/16
N15TCH	Isolation of T cell receptors from human papilloma virus (HPV)-reactive or other tumor-reactive T cells from patients with oropharyngeal, cervical or vulvar cancer	Lotje Zuur	other	13/07/16
N16BIR	Bioimmunoradiotherapy (BIR) with concurrent Avelumab, Cetuximab and Radiotherapy as first line treatment in patients with locally advanced squamous cell carcinoma of the head and neck. A feasibility study in patients unfit for cisplatin	Jan Paul de Boer	I	02/12/16
N16EMS	The effectiveness of device-driven Expiratory Muscle Strength Training (EMST) in total laryngectomy patients; a pilot study.	Michiel van den Brekel	pilot	19/04/17
N16IGM	Intraoperative verification of maxillary malignancy resection with cone-beam computed tomography	Baris Karakullukcu	pilot	21/02/17
N16IMC	ImmunoModulation by the Combination of Ipilimumab and nivolumab neoadjuvant to Surgery In advanced Or recurrent head and Neck carcinoma (IMCISION)	Lotje Zuur	I	08/12/16
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/16
N16PVX	Exploration of advantages and limitations of a new voice prosthesis (Provox Vega XtraSeal) with CEmark for laryngectomized patients	Michiel van den Brekel	other	04/10/17
N16QPS	Quality check of PSMA PET for imaging salivary gland toxicity	Wouter Vogel	pilot	02/09/16
N17ADM	Adaptive Dose-Escalated Multi-modality Image-guided RadiothErapy (ADMIRE) for head and neck cancer by twice reimaging, re-delineation and re-planning during the course of radiotherapy	Abrahim Al-Mamgani	other	31/08/17
N17BTM	Personalization of a biomechanical tongue model for the prediction of treatment outcome: a feasibility study	Ludi Smeele	other	22/06/17
N17DSI	Determining the dose-effect relation of salivary gland irradiation and cell loss with PSMA PET	Wouter Vogel	other	23/05/17
N17SDC	Salivary duct carcinoma: treatment outcomes of 14 patients in the Netherlands Cancer Institute	Martin Klop	other	10/11/17
N17SWU	Shear wave ultrasound elastography of the tongue – a feasibility study.	Ludi Smeele	other	14/06/17
N17TOT	Tracking of oral cavity carcinomas in head and neck surgery	Baris Karakullukcu	other	18/04/17

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
LEUKAEMIA / MDS				
M11APO	Protocol apoptose regulatie van CLL	Joke Baars	other	29/9/2011 (31/10/2017)
LUNG				
C15MER	Merelitinib (AZD9291) compassionate use program for metastasized EGFR T790M mutation positive NSCLC	Egbert Smit	other	25/8/2015 (2/11/2017)
C15MET	Compassionate use programma crizotinib voor patienten met een MET mutatie	Michel van den Heuvel	other	28/01/15
C15NIV	Nivolumab EA program for metastasized NSCLC (NIVOLUMA)	Michel van den Heuvel	other	13/8/2015 (2/11/2017)
C15RET	Compassionate use programma sunitinib voor patienten met een RET mutatie	Michel van den Heuvel	other	27/01/15
C15ROC	Compassionate use Rociletinib	Egbert Smit	other	09/12/15
C17LOR	Compassionate use programma lorlatinib	Michel van den Heuvel	other	08/03/17
M09PBO	Dose escalation by boosting radiation dose within the primary tumor on the basis of a pre-treatment FDG-PET-CT scan in stage Ib, II and III NSCLC: a randomised phase II trial (PET-BOOST trial)	José Belderbos	II	26/11/2009 (9/11/2017)
M11LUN	Lungscape: a project of European Thoracic Oncology Platform	Paul Baas	other	29/12/11
M11VOL	Treatment of larger tumor volumes or > 2 lung tumors simultaneously in lung cancer patients using SBRT in a mean-lung dose escalation study (VOLUMES)	Heike Peulen	I/II	29/9/2011 (27/11/2017)
M12PHA	Prophylactic Cranial Irradiation with or without hippocampal avoidance in SCLC (HAPCI)	José Belderbos	III	27/03/13
M13DAP	Combination of dacomitinib and PD-0325901 in advanced KRAS mutation positive colorectal, non-small cell lung and pancreatic cancer	Jan Schellens	I	15/01/14
M13N19	Switch maintenance treatment with gemcitabine for patients with malignant mesothelioma who do not progress after 1st line therapy with a pemetrexed-platinum combination. (NVALT19)	Sjaak Burgers	II	04/03/14
M14AFS	Phase I/II study with the combination of afatinib and selumetinib in advanced KRAS mutant positive and PIK3CA wildtype colorectal, non-small cell lung and pancreatic cancer	Jan Schellens	I/II	19/05/15
M14ALK	Non Small Cell Lung Cancer (NSCLC) ALK IHC positive study	Daphne de Jong		28/4/2014 (1/1/2017)
M14CPR	Open-Label phase Ib/II,multicenter study of the combination of RO5479599 with Carboplatin and Paclitaxel in patients with advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) of squamous histology who have not received prior chemotherapy or targeted Therapy for NSCLC.	Jan Schellens	I/II	19/1/2015 (25/10/2017)
M14ENI	A phase II, multicenter, open-label study of EGF816 in combination with Nivolumab in adult patients with EGFR mutated non-small cell lung cancer and of INC280 in combination with Nivolumab in adult patients with cMet positive non-small cell lung cancer	Willemijn Engels-man-Theelen	II	09/06/15

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M14HAM	Determination of peripheral immune cell activity during treatment with either surgery or radiotherapy in patients with early stage non-small cell lung cancer (HAMLET)	Koen Hartemink	other	17/3/2015 (2/11/2017)
M14LTK	Phase I/II study with lapatinib plus trametinib in patients with metastatic KRAS mutant colorectal, non-small cell lung and pancreatic cancer	Jan Schellens	I/II	04/08/14
M14N15	Phase II study with oral fibroblast growth factor-1 inhibitor BIBF1120 as second line treatment in lung carcinoma patients harboring fibroblast growth factor receptor-1 gene amplification (NVALT-15)	Sjaak Burgers	II	12/09/14
M14PRT	Randomized Phase II, 2-arm study of Pembrolizumab after high dose radiation (SBRT) versus Pembrolizumab alone in patients with advanced non-small cell lung cancer	Paul Baas	II	03/07/15
M14STA	Complete endosonographic intrathoracic nodal staging of lung cancer patients in whom SABR is considered (STAGE)	Wieneke Buikhuisen	other	15/12/2014 (2/11/2017)
M14TUM	Tumor organoids: feasibility to predict sensitivity to treatment in cancer patients (TUMOROID trial).	Emile Voest	pilot	22/07/14
M15ATZ	A phase III, open-label, randomized study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with best supportive care following adjuvant cisplatin-based chemotherapy in PD-L1-selected patients with completely resected stage IB-IIIA Non Small Cell Lung Cancer	Michel van den Heuvel	III	3/10/2016 (28/3/2017)
M15CER	A phase II, multi-center, open-label, five-arm study to evaluate the efficacy and safety of oral ceritinib treatment for patients with ALK-positive non-smal cell lung cancer metastatic to the brain and/or to leptomeninges	Egbert Smit	II	16/12/15
M15CIN	A phase II, multicenter, three-cohort study of oral cMET inhibitor INC280 in adult patients with EGFR wild-type (wt), advanced non-small cell lung cancer (NSCLC) who have received one or two prior lines of systemic therapy for advanced/matastatic disease	Egbert Smit	II	15/09/15
M15ETO	ETOP Lungscape 005 - PD-L1 Testing		other	12/5/2016 (2/11/2017)
M15IEP	A phase Ib/II, open-label, multicenter trial with oral cMET inhibitor INC280 alone and in combination with erlotinib versus platinum/pemetrexed in adult patients with EGFR mutated, cMET-amplified, locally advanced/metastatic nonsmall cell lung cancer (NSCLC) with acquired resistance to prior EGFR tyrosine kinase inhibitor (EGFR TKI)	Egbert Smit	I/II	16/12/2015 (10/10/2017)
M15LEM	Lung cancer Early Molecular Assessment trial	Michiel van den Heuvel	other	29/06/16
M15LYS	A phase 2 study of LY2606368 in patients with extensive stage disease small cell lung cancer	Egbert Smit	II	2/11/2016 (18/1/2017)
M15N22	First line chemotherapy in KRAS mutated non-small cell lung cancer patients: a phase III comparing cisplatin-pemetrexed with carboplatin-paclitaxelbevacizumab: NVALT22	Egbert Smit	III	05/07/16
M15NIC	Afatinib in pretreated patients with advanced NSCLC harbouring HER2 exon 20 mutations	Egbert Smit	II	5/11/2015 (20/12/2016)
M15NPI	An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab plus Ipilimumab, or Nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in Subjects with Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) (CHECKMATE 227)	Jaak Burgers	III	12/11/15

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M15PDL	A phase III, open-label, multicenter, randomized study evaluating the efficacy and safety of MPDL3280A (anti-PDL-1 antibody) in combination with Carboplatin + Paclitaxel or MPDL3280A in combination with Carboplatin + NAB Paclitaxel versus carboplatin + NAB Paclitaxel in chemotherapy naïve patients with stage IV squamous non-small cell lung cancer	Wieneke Buikhuisen	III	07/03/16
M16ATS	Phase III randomized clinical trial of Lurbinectedin (PM01183)/Doxorubicin (DOX) versus Cyclophosphamide(CTX), Doxorubicine(DOX) and Vincristine(VCR) (CAV) or Topotecan as treatment in patients with small cell lung cancer (SCLC) who failed one prior Platinum-containing line (ATLANTIS - Trial)	Egbert Smit	III	22/05/17
M16BRI	A phase 3 multicenter open-label study of Brigatinib (AP26113) versus Crizotinib in patients with ALKpositive advanced lung cancer	Sjaak Burgers	III	3/11/2016 (28/7/2017)
M16N24	A phase III prospective double blind placebo controlled randomized study of adjuvant MEDI4736 in completely resected non-small cell lung cancer. (NVALT 24)	Sjaak Burgers	III	28/03/17
M16NAP	Phase III study of carboplatin and paclitaxel or nano particle albumin-bound paclitaxel (nab-paclitaxel) with or without pembrolizumab in first line metastatic squamous NSCLC	Michel van den Heuvel	III	6/9/2016 (27/1/2017)
M16NPM	A phase III, randomized, open label trial of Nivolumab in combination with Ipilimumab versus Pemetrexed with Cisplatin or Carboplatin as first line therapy in unresectable pleural mesothelioma.	Paul Baas	III	07/07/17
M16PLE	Phase Ib, open-label, multi-center study to characterize the safety, tolerability and pharmacodynamics (PD) of PDR001 in combination with LCL161, Everolimus (RAD001) or Panobinostat (LBH589)	Jan Schellens	I	01/11/16
M16STT	An open-label, multicenter, global phase 2 basket study of Entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbour NTRK1/2/3, ROS1 or ALK gene rearrangements. (STARTRK-2)	Egbert Smit	II	24/08/16
M17ARC	Phase Ib multi-indication study of Anetumab ravtensine (BAY 94-9343) in patients with mesothelin expressing advanced or recurrent malignancies (ARCS-Multi)	Egbert Smit	I	07/09/17
M17DUT	A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment in Patients with Extensive Disease (Stage IV) Small-Cell Lung Cancer (SCLC)	Egbert Smit	III	10/05/17
M17PPD	PDR001 in combination with platinum-doublet chemotherapy in PD-L1 unselected metastatic NSCLC patients	Sjaak Burgers	I	02/11/17
M17ZRP	[89]Zirconium-labeled pembrolizumab as predictive imaging biomarker of response and toxicity in pembrolizumab treated patients with non-small-cell lung cancer – a feasibility study.	Joop de Langen	pilot	14/08/17
N11ORL	Olaparib dose escalating trial in patients treated with radiotherapy with or without daily dose cisplatin for locally advanced non-small lung cancer	Michel van den Heuvel	I	21/02/12
N12CLM	Determining the sensitivity and specificity of circulating tumor cells and cytology in cerebrospinal fluid of patients clinically suspected for leptomeningeal metastases	Dieta Brandsma	I	19/6/2012 (19/9/2017)
N12HYB	Phase I Hybrid study: combined stereotactic radiotherapy and conventional fractionation in stage II and III non small cell lung cancer with peripheral tumors smaller than 5 cm	Heike Peulen	I	12/7/2012 (6/2/2017)
N12LON	Longitudinal analysis of lung cancer-specific immunity in stage III and IV lung cancer patients	Michel van den Heuvel	other	18/01/13
N12LPR	Early FDG-PET/CT response evaluation of lung cancer during chemoradiation	Wouter Vogel	other	10/12/2012 (23/10/2017)

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N12PRO	Pharmacogenomic profiling of short-term cultures of malignant pleural mesothelioma	Josine Quispel	other	21/09/12
N13FPB	Fluid phase biopsy (circulating tumour DNA and serum tumour markers) in patients with non-small cell lung cancer	Michel van den Heuvel	other	17/12/13
N14ITO	Immunogenicity of Tumor Organoids, a feasibility study	Emile Voest	other	22/07/14
N14PLU	Personalized treatment with combination therapy for patients with pleural effusion due to malignant pleural mesothelioma or lung cancer in second or third line. An open label phase II study (PROOF)	Paul Baas	II	03/10/14
N16HYP	Feasibility trial on combination of platinum doublets and hypofractionated radiotherapy for locally advanced stage non-small cell lung carcinoma (HYPOLAN)	Judi van Diessen	II	6/10/2017 (22/11/2017)
N16INM	Ipilimumab and Nivolumab in the Treatment of malignant Pleural Mesothelioma. (INITIATE)	Paul Baas	II	28/09/16
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/16

LYMPHOMA - HODGKIN'S DISEASE

M13SOP	Study of Menopause in ex-patients with Hodgkin Lymphoma: influence on long-term adverse events (SOPHIA)	Floor van Leeuwen	other	17/01/14
M14CHL	Diagnostic yield of screening colonoscopy in Hodgkin lymphoma survivors (DICHOS)	Monique van Leerdam	other	21/10/14
M17SPA	The effect of light therapy on fatigue and psychosocial functioning in long-term survivors of (non-)Hodgkin lymphoma: a randomized controlled trial (SPARKLE)	Eveline Bleiker	other	13/07/17

LYMPHOMA - NON-HODGKIN'S

M12H110	ReBel study: a randomized Phase I/II trial of lenalidomide and rituximab with or without bendamustine in patients >= 18 years with a relapsed follicular lymphoma. ((ReBeL/HOVON110)	Joke Baars	II	12/6/2012 (2/11/2017)
M15PRM	A phase I, open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK3326595 in subjects with solid tumors and non-Hodgkin's lymphoma (PRMT5i)	Jan Schellens	I	27/10/16
M17SPA	The effect of light therapy on fatigue and psychosocial functioning in long-term survivors of (non-)Hodgkin lymphoma: a randomized controlled trial (SPARKLE)	Eveline Bleiker	other	13/07/17

MELANOMA / SKIN

C14PDI	Expanded access program MK3475	Christian Blank	other	12/05/14
E1208MG	Minitub: Prospective registry of Sentinel Node (SN) positive melanoma patients with minimal SN tumor burden who undergo Completion Lymph Node Dissection (CLND) or Nodal Observation	Alexander van Akkooi	other	23/04/15
E18081	Adjuvant peginterferon alfa-2b for 2 years vs observation in patients with an ulcerated primary cutaneous melanoma with T(2-4)bN0M0: a randomized phase III trial of the EORTC Melanoma Group	Alexander van Akkooi	III	27/5/2015 (22/12/2016)

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M11TCR	Feasibility study using T-cel receptor gene therapy in metastatic melanoma	John Haanen	II	17/04/12
M14REP	A Phase II, Open-Label, Multicenter Study of Vemurafenib plus Cobimetinib (GDC-0973) in Unresectable Stage IIIc or Metastatic Melanoma -Response Monitoring and Resistance Prediction with Positron Emission Tomography and Tumor Characteristics- (REPOSIT)	Bernies van der Hiel	II	24/11/14
M14TIL	Randomized phase III study comparing a non-myeloablative lymphocyte depleting regimen of chemotherapy followed by infusion of tumor infiltrating lymphocytes and interleukin-2 to standard ipilimumab treatment in metastatic melanoma	John Haanen	III	06/08/14
M15HPV	Non-Comparative, Two-Cohort, Single-Arm, Open-Label, Phase 1/2 Study of Nivolumab (BMS-936558) in Subjects with Virus-Positive and Virus-Negative Solid Tumors	Jan Paul de Boer	I/II	27/10/15
M15HSI	To obtain proof of principle for the use of a portable hyperspectral imaging device for discrimination between various pigmented naevi and cutaneous malignant melanoma: an evolving concept in the early detection of malignant melanoma	Germaine Relyveld	pilot	28/4/2016 (2/11/2017)
M15PFO	A phase I, open-label, dose escalation study of PF-04518600 in patients with locally advanced or metastatic hepatocellular carcinoma (HCC), melanoma, clear cell renal cell carcinoma (RCC) or squamous cell head en neck cancer (SCCHN)	Jan Schellens	I	09/09/15
M16CNI	Phase IIIb/IV, Randomized, Double Blinded, Study of Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg vs Nivolumab 1 mg/kg in Combination with Ipilimumab 3 mg/kg in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma (CHECKMATE 511)	Christian Blank	III	19/8/2016 (1/6/2017)
M16COW	Phase 2 Study testing the COmbination of Vemurafenib With Cobimetinib in BRAF V600 mutated Melanoma Patients to Normalize LDH and Optimize immunotherapY with Nivolumab and Ipilimumab (COWBOY)	Christian Blank	II	06/07/17
M16GUL	Gamma Probe and Ultrasound Guided Fine Needle Aspiration Cytology of the Sentinel Node Trial (GULF)	Alexander van Akkooi	other	19/2/2016 (7/8/2017)
M16OPN	Multicenter Phase 2 Study to Identify of the Optimal neo-Adjuvant Combination Scheme of Ipilimumab and Nivolumab (OpACIN-neo)	Christian Blank	II	01/11/16
M16PEP	A Phase 3 randomized, double-blind, placebo- controlled study of Pembrolizumab (MK-3475) in combination with Epacadostat or Placebo in subjects with unresectable or metastatic melanoma (Keynote-252 / ECHO-301)	John Haanen	III	5/9/2016 (21/2/2017)
M17IVR	In vivo reflectance confocal microscopy, a novel non- invasive tool for diagnosing skin cancer - a randomized controlled trial	Marianne Crijns	other	12/06/17
M17TVC	A Phase 1b/3, Multicenter, Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresectable Stage IIIB to IVM1c Melanoma (MASTERKEY-265)	Hans van Thienen	III	21/08/17
N03LAM	Longitudinal analysis of melanoma-specific immunity in stage III and IV melanoma patients	John Haanen	other	22/08/03
N06TIS	Integrated analyses of melanoma-T cell interactions; relevance for immunotherapy	John Haanen	other	29/08/06
N10MSN	Pilot study on the use of fluorescence imaging of lymph nodes during melanoma sentinel node procedure, using indocyanine green	Michel Wouters	pilot	20/12/10
N12CLM	Determining the sensitivity and specificity of circulating tumor cells and cytology in cerebrospinal fluid of patients clinically suspected for leptomeningeal metastases	Dieta Brandsma	I	19/6/2012 (19/9/2017)
N12VDT	Therapeutic drug monitoring of BRAF- and MEK-inhibitors in a "Real Life" Cohort of Melanoma Patients	Jan Schellens	other	18/6/2013 (2/11/2017)

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N13GEN	Regulation of skin tumorgenesis by integrin alpha3beta1	Arnoud Sonnenberg	other	27/11/13
N13ICG	99mTc-Senti-Scint vs ICG-99mTc-nanocolloid for sentinel node biopsy of malignant melanoma of the trunk, of an extremity or in the head and neck region	Jos van der Hage	other	17/6/2014 (30/11/2017)
N13NDT	Cytoreductive treatment of dabrafenib combined with trametinib to allow complete surgical resection in patients with BRAF mutated, prior unresectable stage III or IV melanoma (REDuCTOR)	John Haanen	II	06/12/13
N15IMP	Phase 2 Study Comparing Pembrolizumab with Intermittent/Short-term Dual MAPK Pathway Inhibition Plus Pembrolizumab in patients harboring the BRAFV600 mutation (IMPemBra)	Christian Blank	I	31/03/16
N16IGM	Intraoperative verification of maxillary malignancy resection with cone-beam computed tomography	Baris Karakullukcu	pilot	21/02/17
N16MME	MeMaLoc: Magnetic Marker Localization for Melanoma Surgery. A feasibility study.	Theo Ruers	other	25/01/17
N16VOM	HDAC inhibitor vorinostat in resistant BRAF V600 mutated advanced melanoma	Jan Schellens	other	24/06/16
N17BCC	Noninvasive diagnostics and subtyping of basal cell carcinoma in the head and neck by dermoscopy and handheld reflectance confocal microscopy	Fons Balm	other	19/04/17
N17LMC	Lentigo maligna: Diagnostic accuracy of in vivo handheld reflectance confocal microscopy for pigmented macules in the head and neck (LM-COMI Study)	Marianne Crijns	other	19/04/17

MISCELLANEOUS

M14AFS	Phase I/II study with the combination of afatinib and selumetinib in advanced KRAS mutant positive and PIK3CA wildtype colorectal, non-small cell lung and pancreatic cancer	Jan Schellens	I/II	19/05/15
M14FAS	FASTHYNA Trial: 'Fast-track' thyroidectomy and radioiodine ablation therapy in patients with differentiated thyroid cancer, a multicenter randomized controlled trial	Jos van der Hage	other	28/1/2015 (31/1/2017)
M15CLA	Efficacy and safety of Lanreotide Autogel 120 mg administered every 14 days in well differentiated, metastatic or locally advanced, unresectable pancreatic or midgut neuroendocrine tumours having progressed radiologically while previously treated with Lanreotide Autogel 120 mg administered every 28 days (CLARINET FORTE)	Margot Tesselaar	III	27/06/16
M15GRA	GRAFITI Registration study. Prospective registration study on growth behavior of aggressive fibromatosis without therapeutic intervention	Frits van Coevorden	other	15/09/15
M15PFO	A phase I, open-label, dose escalation study of PF-04518600 in patients with locally advanced or metastatic hepatocellular carcinoma (HCC), melanoma, clear cell renal cell carcinoma (RCC) or squamous cell head en neck cancer (SCCHN)	Jan Schellens	I	09/09/15
M15TLP	A multicenter, long-term extension study to further evaluate the safety and tolerability of Telotristat Etiprate (LX1606). TELEPATH (Telotristat Etiprate-expanded treatment for patients with carcinoid syndrome)	Margot Tesselaar	III	16/10/15
M16NET	An open label phase II study to evaluate the efficacy and safety of PDR001 in patients with advanced or metastatic non-functional neuroendocrine tumors of pancreatic, gastrointestinal (GI), or thoracic origin who have progressed on prior treatment	Wieneke Buikhuisen	II	21/04/17
M16STT	An open-label, multicenter, global phase 2 basket study of Entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbour NTRK1/2/3, ROS1 or ALK gene rearrangements. (STARTRK-2)	Egbert Smit	II	24/08/16

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M17ARC	Phase Ib multi-indication study of Anetumab ravtensine (BAY 94-9343) in patients with mesothelin expressing advanced or recurrent malignancies	Egbert Smit	I	07/09/17
M17CLE	CLE in diagnosing Pleural Malignancies, a comparison with pathology	Paul Baas	other	16/08/17
M17LAN	A phase 3, prospective, randomized, double-blind, multi-center study of the efficacy of lanreotide Autogel/Depot 120 mg plus BSC vs placebo plus BSC for tumour control in subjects with the well differentiated, metastatic and/or unresectable, typical or atypical, lung neuroendocrine tumors	Wieneke Buikhuisen	III	05/07/17
N12OST	Discrimination of benign and malignant human tissue during percutaneous interventions using optical spectroscopy techniques (PercuSpect)	Theo Ruers	other	13/9/2012 (2/11/2017)
N14ONP	A prototype opto-nuclear probe for combined radio- and fluorescence tracing of the sentinel node	Henk van der Poel	other	3/10/2014 (2/11/2017)
N14SRO	Somatostatin receptor expression and occupancy during lanreotide therapy	Marcel Stokkel	other	12/09/14
N15HNT	Hepatic NET metastasis embolization biomarker evaluation	Margot Tesselaar	other	13/01/16
N16URA	Food-effect study on uracil and dihydrouracil levels as a diagnostic marker of DPD activity	Jan Schellens	other	14/4/2016 (22/6/2017)
N17MRD	Healthy volunteer imaging techniques development for motion management in MR-guided adaptive radiotherapy	Gabe Sonke	other	09/11/17

SOFT TISSUE / OSTEOSARCOMA

E1321	A randomised phase II trial of imatinib alternating with regorafenib compared to imatinib alone for the first line treatment of advanced gastrointestinal stromal tumour (ALT-GIST)	Neeltje Steeghs	II	20/07/16
E1506	A Phase II multicenter study comparing the efficacy of the oral angionenesis inhibitor Nintedanib with the intravenous cytotoxic compound Ifosfamide for treatment of patients with advanced metastatic soft tissue sarcoma after failure of systemic nonoxazaphosporine- based first line chemotherapy for inoperable disease (ANITA)	Neeltje Steeghs	II	03/11/17
E62092	A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patiens with retroperitoneal sarcoma (RPS)	Rick Haas	III	11/1/2012 (22/8/2017)
M13MIG	A prospective, multicenter, randomized, open-label, active-controlled, 2-parallel group, Phase III study to compare efficacy and safety of AB1010 at 7,5 mg/kg/day to imatinib at 400 or 600 mg in treatment of patients with gastro-intestinal stromal tumor in first line medical treatment	Neeltje Steeghs	III	26/08/13
M13MSG	A prospective, multicenter, randomized, open label, active controlled phase 3 study to compare the efficacy and safety of Masitinib to Sunitinib in patients with gastrointestinal stromal tumor after progression with Imatinib at 400 mg as first line treatment	Neeltje Steeghs	III	05/09/13
M15DIC	Individualizing Pazopanib therapy by exploring the role of early metabolic response and drug exposure as a predictor for treatment outcome in patients with STS (PREDICT)	Neeltje Steeghs	other	14/4/2016 (6/7/2017)
M15GCD	Gastrointestinal stromal tumors (GIST): assessment of mutation in tumors and in circulating tumor DNA and measurement of TKI plasma exposure to optimize treatment (GALLOP)	Neeltje Steeghs	other	12/03/15

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M15PAS	Phase II clinical study of concurrent PAzopanib for non-metastatic SArcoma patients to be treated with RadioTherapy, localized in the extremities, trunk and chest wall or the head and neck region (PASART-2)	Rick Haas	II	30/12/15
M16GTDM	Persoonlijk aangepast doseren van anti-tumor medicatie in GIST patiënten op basis van geneesmiddel-spiegels: de GIST-TDM cohort studie	Neeltje Steeghs	other	08/08/16
M16ITF	Three versus five years of adjuvant imatinib as treatment of patients with operable GIST with a high risk for recurrence: A randomised phase III study	Neeltje Steeghs	III	04/07/17
N10DMY	Dose reduction of preoperative radiotherapy in Myxoid liposarcomas (DOREMY)	Rick Haas	II	15/12/10
N15MSC	The Mesenchymal Stem Cell biomarker study	Emile Voest	other	19/05/15
N16STS	Development of a platform of Patient Derived Xenografts (PDX) of Soft Tissue Sarcomas (STS): Protocol to obtain biopsies from patients with nonmetastatic STS	Rick Haas	other	30/01/17
N17PSI	Increasing pazopanib exposure by splitting intake moments	Neeltje Steeghs	IV	22/05/17

URO-GENITAL

E1407	A randomised phase III trial comparing conventional- Dose chemotherapy using paclitaxel, ifosfamide, and cisplatin (TIP) with high dose chemotherapy using mobilizing paclitaxel followed by High-dose carboplatin and etoposide (TI-CE) as first salvage treatment in relapsed or refractory germ cell tumours (TIGER)	Martijn Kerst	III	20/10/16
M10PCM	Prostate cancer molecular medicine (PCMM)	Henk van der Poel	other	17/02/11
M11PRC	Impact of new approaches to pharmacological management of patients with renal cell carcinoma: a population-based study of process outcomes in The Netherlands (PERCEPTION)	Simon Horenblas	other	18/08/11
M13PMR	Validation of multiparametric MRI with histopathology for prostate cancer	Floris Pos	other	10/2/2014 (18/10/2017)
M13PSN	Prospective randomized multicenter comparison of indocyanine green (ICG)-99mTc-nanocolloid vs. 99mTcnanocolloid plus an intraoperative injection of ICG for the detection and surgical resection of the sentinel nodes in patients with prostate cancer	Henk van der Poel	II	17/04/14
M14HSN	Sentinel node biopsy for bladder cancer using the hybrid tracer	Bas van Rhijn	other	26/02/15
M14LET	A case-cohort study to identify risk factors for cardiovascular disease in testicular cancer survivors (TACkLE)	Martijn Kerst	other	15/12/2014 (2/11/2017)
M14ROT	Registry of Treatment Outcomes in a non-study population of Symptomatic Metastasized Castration Resistant Prostate Cancer (mCRPC) Patients Treated with Radium-223 (ROTOR)	André Bergman	other	17/9/2015 (21/9/2017)
M15CRB	Prospective trial evaluating the outcome of induction chemotherapy followed by extended lymph node dissection and chemoradiation for high risk invasive bladder cancer (CHEMORAD)	Simon Horenblas	II	30/10/2015 (04/12/2017)
M15MED	A phase III, randomized, open-label, controlled, multi- center, global study of first-Line MEDI4736 monotherapy and MEDI4736 in combination with Tremelimumab versus standard of care chemotherapy in patients with unresectable stage IV urothelial bladder cancer. (DANUBE)	Michiel van der Heijden	III	22/12/2015 (5/1/2017)
M15MPB	A phase II study investigating preoperative MPDL3280A prior to surgery in operable transitional cell carcinoma of the bladder (ABACUS)	Michiel van der Heijden	II	18/11/16

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M15MPO	A phase III, open-label, multicenter, randomized study of MPDL3280A (anti-PDL-1 antibody) versus observation as adjuvant therapy in patients with PD-L1-selected, high-risk muscle-invasive bladder cancer after cystectomy	Michiel van der Heijden	III	16/11/15
M15PFO	A phase I, open-label, dose escalation study of PF-04518600 in patients with locally advanced or metastatic hepatocellular carcinoma (HCC), melanoma, clear cell renal cell carcinoma (RCC) or squamous cell head en neck cancer (SCCHN)	Jan Schellens	I	09/09/15
M15RAM	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Ramucirumab plus Docetaxel Versus Placebo plus Docetaxel in Patients with Locally Advanced or Unresectable or Metastatic Urothelial Carcinoma Who Progressed on or After Platinum-Based Therapy	Michiel van der Heijden	III	24/9/2015 (2/5/2017)
M15RTO	Registry of Treatment Outcomes in a non-study population of Symptomatic Metastasized Castration Resistant Prostate Cancer (mCRPC) Patients Treated with Radium-223 (ROTOR-registry)	André Bergman	other	30/10/15
M16AAS	A phase 3, multinational, randomized, open-label, parallel-arm study of Avelumab (MSB0010718C) in combination with Axitinib (INLYTA®) versus Sunitinib (SUTENT®) monotherapy in the first-line treatment of patients with advanced renal cell carcinoma	John Haanen	III	15/9/2016 (21/11/2017)
M16ARA	A randomized, double-blind, placebo-controlled Phase III study of ODM-201 versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormonesensitive prostate cancer (ARASENS)	André Bergman	III	10/05/17
M16ATL	A randomized, double-blind, placebo-controlled phase 3 study of JNJ-56021927 in subjects with highrisk, localized or locally advanced prostate cancer receiving treatment with primary radiation therapy. (ATLAS)	Baukelien van Triest	III	29/12/2016 (8/9/2017)
M16EAD	A multinational, phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of Enzalutamide plus androgen deprivation therapy (ADT) versus placebo plus ADT in patients with metastatic hormone sensitive prostate cancer (mHSPC)	Henk van der Poel	III	23/12/16
M16FPV	Vascular fingerprint to identify patients at risk for arterial cardiovascular events within the first year after start of cisplatin-based chemotherapy for testicular cancer: a validation study	Martijn Kerst	other	07/10/16
M16HFL	Hypofractionated Focal Lesion Ablative Microboost in prostatE cancer (Hypo-FLAME)	Floris Pos	other	13/07/16
M16OEA	A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib (Lynparza TM) Versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have Homologous Recombination repair Gene Mutations (PROfound)	André Bergman	III	14/03/17
M16OST	A randomized, open label, Phase IIB trial of Optimal Sequencing of Treatment Options for Poor Risk Metastasized Castration Resistant Prostate Cancer Previously Treated with Docetaxel (OSTRICh)	André Bergman	II	01/06/17
M16PMP	Phase II Trial of Pembrolizumab (MK-3475) in Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Previously Treated with Chemotherapy (KEYNOTE-199)	André Bergman	II	13/10/16
M16SAU	An open label, single arm, multicenter, safety study of Atezolizumab in locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract	Michiel van der Heijden	III	19/04/17
M17AAT	A phase III, multicenter, randomized, placebo- controlled double-blind study of Atezolizuamb (anti- PD-L1 antibody) as adjuvant therapy in patients with renal cell carcinoma at high risk of developing metastasis following nephrectomy	Axel Bex	III	09/06/17

Type of cancer study	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M17AIR	A Phase 3 Randomized Study Comparing Nivolumab and Ipilimumab Combination vs Placebo in Participants with Localized Renal Cell Carcinoma Who Underwent Radical or Partial Nephrectomy and Who Are at High Risk of Relapse	Hans van Thienen	III	21/08/17
M17CAP	Towards early identification of response to CABAZItaxel in patients with metastatic castrationresistant prostate cancer: potential of 18F-Choline PET-CT (CABAZIPET)	Marcel Stokkel	II	30/08/17
M17DOC	Multicenter safety, feasibility and pharmacokinetic phase I-II trial of ModraDoc006/r in patients with metastatic castration-resistant prostate cancer	André Bergman	I	26/04/17
M17NIU	A Phase 3, Open-label, Randomized Study of Nivolumab Combined with Ipilimumab versus Standard of Care Chemotherapy in Participants with Previously Untreated Unresectable or Metastatic Urothelial Cancer	Michiel van der Heijden	III	29/05/17
M17PAB	Effect of a physical activity promotion program offered online of via blended care on physical activity level in breast and prostate cancer survivors: the PABLO trial	Wim Groen	other	19/10/17
M17REB	REduce BIAdder CAncer REcurrence in patients treated for upper urinary tract urothelial carcinoma (REBACARE)	Kees Hendricksen	other	24/11/17
N08SNR	Site and distribution of sentinel lymph nodes in renal cell carcinoma, a phase II study	Axel Bex	II	19/03/09
N12IGP	The use of indocyanine green for accurate sentinel node detection and removal in a group of high-risk nodal metastasis prostate cancer patients	Henk van der Poel	II	08/05/13
N12LAR	Longitudinal analysis of RCC-specific immunity in renal cell carcinoma patients	Christian Blank	other	14/12/12
N13CCI	Confirming the pharmalogical interaction between colchicine and 18F-choline PET	Wouter Vogel	other	18/12/13
N13END	Laat de met de Endopat gemeten endotheel functie na een chemische castratie voor prostaat carcinoom veranderingen zien en zo ja op welke termijn (Endopat 2)	Henk van der Poel	other	17/3/2014 (2/11/2017)
N13KCM	Longitudinal kinetics of cancer mutations in the plasma, urine and tumor of patients with urothelial cancer treated with chemotherapy	Michiel van der Heijden	other	24/01/14
N14DAR	Dynamics of Androgen Receptor genomics and transcriptomics after neoadjuvant androgen ablation (DARANA)	Henk van der Poel	other	27/08/14
N14ITO	Immunogenicity of Tumor Organoids, a feasibility study	Emile Voest	other	22/07/14
N15CMR	Investigation of the signature of recurrence and radiation effects after External-Beam radiotherapy on multi-parametric MRI	Floris Pos	other	20/04/15
N15DOP	Weekly ModraDoc/r in combination with hormonal treatment and high-dose intensity-modulated radiation therapy in patients with high-risk early stage prostate cancer	Baukelien van Triest	I	12/05/16
N15MSC	The Mesenchymal Stem Cell biomarker study	Emile Voest	other	19/05/15
N15PEN	Chemoradiation in the treatment of loco-regionally advanced Penile Cancer	Floris Pos	other	31/08/15
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/16
N17PSI	Increasing pazopanib exposure by splitting intake moments	Neeltje Steeghs	IV	22/05/17

Invited speakers

Angelika Amon, Cambridge, United States
Aneuploidy and cancer - a complicated relationship

Meredith Ashby, Menlo Park, United States
Revealing the hidden landscape of cancer variants with PacBio long read sequencing

Andrew Belmont, Urbana-Champaign, United States
TSA-Seq: Genome-wide mapping of cytological distances to specific nuclear compartments

Christian Blank, Amsterdam, The Netherlands
Combining targeted and immunotherapy in melanoma

Louise Brinton, Rockville, United States
Population-based multidisciplinary study of breast cancer in Ghana: Challenges and opportunities

Peter de Keizer, Rotterdam, The Netherlands
Targeting senescence against therapy resistance in cancer

Emmanouil Dermitzakis, Geneva, Switzerland
Contribution of non-coding DNA to complex traits and cancer

Caroline Dive, Manchester, United Kingdom
Lung Cancer CTCs: What are they good for?

Nir Friedman, Jerusalem, Israel
Dynamics of transcription and chromatin

Eileen Furlong, Heidelberg, Germany
Genome regulation during developmental transitions: Generating robustness and precision

Gary Gilliland, Springhouse, United States
Integrating structural biology into antibody engineering

Luca Giorgetti, Basel, Switzerland
A quantitative analysis of chromosome structure in mammals

David Huntsman, Vancouver, Canada
Cell context, mutation and the origins of ovarian cancer

Ivo Huijbers, Amsterdam, The Netherlands
Highly efficient generation of genetically modified mice allows for direct phenotyping in founder mice

Heinz Jacobs, Amsterdam, The Netherlands
Profiting from mutations

Raymond Kaempfer, Jerusalem, Israel
Targeting human costimulatory receptor engagement to protect from severe inflammation and cytokine storm

Karen Knudsen, Philadelphia, United States
Targeting hormone-DNA repair crosstalk in advanced prostate cancer

Erez Lieberman-Aiden, Houston, USA
A 3D code in the human genome

David Livingston, Boston, United States
Control of mammary epithelial differentiation by BRCA1

Chris Lord, London, United Kingdom
Synthetic lethality - BRCA and beyond

Fan Lui, Utrecht, The Netherlands
Developing structural interactomics and its application in cell biology

Ilaria Malanchi, The Francis Crick Institute, London
Cancer: The evil companion corrupting good behaviour

Jane Mellor, University of Oxford, United Kingdom
Transcription and RNA fate

Gordon Mills, MD Anderson Cancer Center, Houston, United States
Systems approach to rational combination therapy

Klaas Mulder, Nijmegen, The Netherlands
Towards single cell proteomics using immuno-sequencing technologies

Christine Mummery, Leiden, The Netherlands
Human pluripotent stem cells: models for cardiac disease, safety pharmacology and drug discovery

Dale Preston, Hiroshima, Japan
Estimates of radiation effects on cancer risks in the Mayak worker, Techa river and atomic bomb survivor studies

Hans-Ulrich Proskosch, Erlangen-Nuremberg, Germany
MIRACUM: Data integration across eight German university hospitals

Nikolaus Rajewsky, Berlin, Germany
Knocking out circRNAs and reconstructing tissues from single-cell sequencing

Julian Sale, Cambridge, United Kingdom
How replication impediments impair epigenetic memory

Shyam Sharan, Rockville, United States
Synthetic viability: how cells overcome BRCA2-loss induced cell-lethality

Titia Sixma, Amsterdam, The Netherlands
Mechanisms of ubiquitin signaling at the nucleosome to organize DNA repair

Evi Soutoglou, Illkirch, France
Nuclear organization in DNA repair

Sarah Teichmann, Hinxton, United Kingdom
Understanding cellular heterogeneity

Marcel Verheij, Amsterdam, The Netherlands
Targeted radiosensitization

Jan-Jaap Visser, London, United Kingdom
The future of radiology in the era of value-based health care

Bing Xia, New Brunswick, United States
Mechanisms of tumor suppression by the BRCA1-PALB2-BRCA2 complex

Kenneth Zaret, Philadelphia, United States
Overcoming chromatin barriers to control cell fate

Lars Zender, Tübingen-Stuttgart, Germany
Targeting therapeutic windows in essential cellular processes for tumor therapy

Research projects supported by the Dutch Cancer Society

Principal investigator	Number of projects	Title	Started	Ended / Ends
Aaronson, Neil	NKI 2014-6788	A randomized controlled trial of internet-based cognitive behavioral therapy for breast cancer patients with climacteric symptoms	01/02/15	01/02/19
Agami, Reuven	10315	Diricore, a platform for the discovery of novel amino acid vulnerabilities in aggressive cancer	01/01/17	01/01/21
Agami, Reuven	11037	Exploiting proline vulnerability for cancer therapy	01/11/17	01/11/21
Agami, Reuven	2013-5814	Identification and characterization of protein translation events of drug sensitivity in cancer cells	01/07/13	01/07/17
Akkari, Leila	10658	Improving the effects of standard of care therapy in glioma by modulating tumor-associated macrophages and microglia functions	01/06/17	01/06/22
Al-Mamgani, Abrahim	NKI 2015-8054	Dutch randomized multicenter trial COmparing twO PalliativE RAdiaTION schemes for incurable head and neck cancer	18/12/15	18/12/19
Amant, Frederic	10094	Cancer tReAtment During pregnancy: from fetaL safety to maternal Efficacy	01/05/17	01/05/21
Amant, Frederic	11132	Postpartum breast cancer diagnosed during involution	01/01/18	01/01/22
Baas, Paul	NKI 2015-7823	Defining new and personalized treatment options for patients with malignant mesothelioma	01/01/16	01/01/20
Beets-Tan, Regina	10138	Development and validation of a multiparametric imaging model for pre-treatment response prediction in rectal cancer: the road towards organ-preservation	01/10/17	01/10/21
Beets-Tan, Regina	10611	Radiomics for the prediction of response to neoadjuvant treatment in rectal carcinoma	01/10/17	01/10/19
Beets, Geerard	UM 2015-7738	Multicentre evaluation of the "wait-and-see" policy for complete responders after chemoradiotherapy for rectal cancer	01/10/15	01/10/21
Belderbos, Jose	2013-6096	Prophylactic Cranial Irradiation with or without hippocampal avoidance in SCLC: a randomized phase III study	01/03/14	01/03/18
Bernards, Rene	2013-5859	Engineering a liver cancer model on a chip	01/09/17	01/09/19
Bernards, Rene	2015-7803	Evolution of resistant clones to novel target-directed drugs in colorectal tumors - A genetic and epigenetic study of intratumoral heterogeneity dynamics	01/11/16	01/11/19
Bernards, Rene	NKI 2012-5401	Finding genetic dependencies in cancer: the missing link in personalized medicine	01/01/13	01/01/19
Bleiker, Eveline	NKI 2014-7031	Choices in breast surgery and reconstruction: implementation and testing of a web-based psycho-educational intervention to facilitate decision making	01/10/15	01/10/20
Bleiker, Eveline	2014-6944	Het informeren van familieleden met een hoog risico op kanker: ondersteuning van erfelijkheidsadviesvragers bij familiecommunicatie door middel van een digitaal stamboom portaal	01/01/15	01/02/18
Bleiker, Eveline	NKI 2015-7909	The effect of light-therapy on fatigue and psychosocial functioning in long-term survivors of (non-) Hodgkin lymphoma: a randomized controlled trial	01/08/16	01/08/20
Boekhout, Annelies	NKI 2012-5356	Developing (shared-care) breast cancer survivorship programs in the Netherlands	01/09/12	01/01/17
Borst, Gerben	10902	New era of radiosensitization by modulating radiosensitizing agents during RT	01/01/18	01/01/23
Borst, Jannie	10894	Achieving synergy between radiotherapy and immunotherapy to increase control of metastatic cancer	01/02/18	01/02/23

Principal investigator	Number of projects	Title	Started	Ended / Ends
Borst, Jannie	11079	CytotoxicTcell programming at the dendritic cell interface	01/09/17	01/09/21
Borst, Jannie	NKI 2012-5397	Defining the nature of CD4 T-cell help for the CTL response to optimize immunotherapy of cancer	01/04/12	01/04/17
Borst, Jannie	NKI 2013-5951	Enhancing the anti-tumour efficacy of immunotherapy by localized radiotherapy	01/05/14	01/05/20
Borst, Jannie	10764	Inducing and sustaining anti-tumor immunity by chemo-radiotherapy	01/01/18	01/01/20
Brummelkamp, Thijn	NKI 2015-7609	A mutation-based approach to examine the principles of synthetic lethality in human cells	01/04/16	01/04/20
De Visser, Karin	10623	Dissecting how tumor-associated myeloid cells counteract chemotherapy response of breast cancer	01/05/18	01/05/22
De Visser, Karin	10083	Enhancing the success of immunotherapy for metastatic breast cancer by overcoming tumor associated immunosuppressive mechanisms	01/05/17	01/05/21
Faller, William	10535	The role of translation elongation in models of intestinal cancer	01/07/17	01/07/22
Haanen, John	2013-5924	Feasibility study using T-cell receptor gene therapy in metastatic melanoma	05/02/13	05/02/19
Haanen, John	10034	POINTING: Towards patient-tailored cancer immunotherapy supported by a multifaceted predictive signature composed of integrative omics and molecular imaging	01/09/17	01/09/21
Haas, Rick	NKI 2015-8069	Dose Reduction of preoperative radiotherapy in Myxoid liposarcomas	01/01/16	01/01/20
Hauptmann, Michael	10603	Novel statistical methods for efficient identification of biomarkers for personalized cancer treatment	01/09/17	01/09/21
Hauptmann, Michael	10004	Statistical assessment of cancer risks from therapeutic radiation exposure incorporating the spatial distribution of radiation dose in the target organ	01/12/17	01/12/21
Huijbers, Ivo	2017-8231	CustoMICE: a facility for production and distribution of engineered mouse models for cancer research	01/09/17	01/09/20
Jacobs, Heinz	NKI 2012-5713	Exploring DNA-Damage Tolerance as a Drug-Target for Chemosensitization and a Mechanism of Chemoresistance	01/06/13	01/06/18
Jacobs, Heinz	10032	Precision CancerTherapy: Profiting from Tumor Specific Defects and Synthetic Lethality in the DNA Damage Tolerance System	01/03/17	01/03/21
Jacobs, Heinz	10796	Role of DNA Damage Tolerance Pathways in Genome Maintenance, Tissue Homeostasis, and Cancer Suppression	01/10/17	01/10/21
Jacobs, Jacqueline	NKI 2012-5305	How ubiquitination controls telomere-induced genomic instability	01/10/12	01/10/17
Jacobs, Jacqueline	10999	Mechanisms of DNA repair pathway control at DNA double-strand breaks and telomeres	01/10/17	01/10/21
Jonkers, Jos	NKI 2015-7589	Cancer-associated fibroblasts as therapeutic targets in invasive lobular breast carcinoma	01/01/16	01/07/20
Jonkers, Jos	2015-7835	Combatting therapy resistance by integrating genomic, transcriptomic and proteomic data from mouse models of invasive lobular breast carcinoma	01/01/17	01/01/21
Jonkers, Jos	2014-7048	Ex vivo assays for selection of breast and ovarian cancer patients for PARP inhibitor treatment	01/09/15	01/09/20
Jonkers, Jos	NKI 2015-7877	Functional analysis of BRCA1 variants and domains to improve genetic counselling and treatment strategies	01/01/16	01/01/20

Principal investigator	Number of projects	Title	Started	Ended / Ends
Jonkers, Jos	NKI 2011-5220	Resistance to Parp inhibitors:assocciation with DNA damage response alterations	01/08/12	01/08/17
Jonkers, Jos	NKI 2014-6532	Tumor escape from radiotherapy: identification and targeting of the underlying mechanisms	01/08/14	01/08/18
Kok, Marleen	NKI 2015-7710	Adaptive phase II randomized non-comparative trial of nivolumab after induction treatment in triple-negative breast cancer (TNBC) patients	01/07/15	01/07/17
Kok, Marleen	NKI 2015-7542	KWF fellowship	01/06/15	01/06/19
Kok, Marleen	10653	Mapping immunosuppressive cascades in breast cancer patients treated with immunotherapy	01/09/17	01/09/19
Kvistborg, Pia	NKI 2015-7978	How checkpoint blockade alters the quality of tumor specific T cells	01/09/16	01/09/21
Lenstra, Tineke	BUIT 2012-5349	Single cell analysis of the sense-antisense transcriptional balance	01/12/16	01/12/18
Linn, Sabine	2015-7808	Clinical Impact of Intratumor heterogeneity in metastatic breast cancer	01/07/16	01/07/19
Linn, Sabine	NKI 2014-7052	The substantially improving the cure rate of high-risk BRCAi-like breast cancer patients with personalized therapy (SUBITO) trial; an international randomized phase III trial	01/02/16	01/02/20
Medema, Rene	NKI 2014-6787	Determinants of cell fate after DNA damage	01/04/15	01/04/19
Medema, Rene	NKI 2015-7742	Enhancing chromosome segregation errors in cancer therapy	01/07/15	01/07/19
Medema, Rene	NKI 2015-7832	Exploring the vulnerabilities of chromosome unstable tumor cells	01/05/16	01/05/20
Medema, Rene	NKI 2014-7474	Regulation of ATR activation in the DNA damage	01/02/15	01/04/17
Meijer, Gerrit	2013-5885	DCR1 and its role in response of colorectal cancer patients to irinotecan treatment	01/04/15	01/07/19
Meijer, Gerrit	NKI 2014-6635	Deciphering diagnostic and companion therapies for mesenchymal colorectal cancer	01/04/15	01/04/19
Meijer, Gerrit	KWF 2014-6813	Identifying signaling pathways	01/09/15	01/09/19
Meijer, Gerrit	10438	Liquid biopsy analyses of cell-free circulating tumor DNA as predictive and prognostic biomarker for colorectal cancer patients with metastatic disease	01/10/17	01/10/21
Meijer, Gerrit	KWF 2013-6338	Molecular Stool test for postpolypectomie surveillance	01/07/15	01/07/19
Meijer, Gerrit	8166	Sustaining FAIR data stewardship support for translational cancer research	01/02/17	01/02/20
Meijer, Gerrit	KWF 2013-6025	Tumor-specific protein biomarkers for early detection of colorectal cancer	01/04/15	01/09/18
Peeper, Daniel	NKI 2015-7595	Function-based unbiased discovery of clinically exploitable metabolic vulnerabilities of cancer cells	26/09/16	25/09/20
Peeper, Daniel	NKI 2013-5799	Improving personalized melanoma treatment: functional screening for companion drug targets in transplanted human melanomas	15/07/13	15/07/17
Peeper, Daniel	2014-7241	In vivo cancer drug target discovery screens exploiting T cell immunity	01/09/15	01/09/19
Peeper, Daniel	10304	Increasing drug holiday impact on therapy-refractory cancers for more durable responses	01/01/17	01/01/21

Principal investigator	Number of projects	Title	Started	Ended / Ends
Peeper, Daniel	10425	Targeting phenotype switching as a therapy for melanoma	21/08/17	21/08/21
Perrakis, Anastassis	10215	Membrane glycerophosphodiesterases: novel players in cell differentiation and cancer biology	01/01/17	01/01/21
Rookus, Matti	NKI 2014-6987	A nationwide prospective cohort study among 59,947 female nurses to elucidate the potential association between shift work and risk of breast cancer	01/02/16	01/02/20
Rookus, Matti	CANCER12-054-TransIBCCS	Development of a Comprehensive Risk Prediction Model for BRCA1 and BRCA2 mutation carriers	01/04/14	01/04/18
Rowland, Benjamin	UU 2011-5103	Cohesin loading and stripping: two fundamental principles for the maintenance of genomic stability	01/10/11	01/10/17
Rowland, Benjamin	NKI 2015-7657	Locking Together the Sister Chromatids	01/11/15	01/11/19
Ruers, Theo	NKI 2014-6596	Clinical implementation of image-guided surgery in rectal cancer	01/05/15	01/05/19
Ruers, Theo	10747	Improving the outcome of breast cancer surgery by real time assessment of resection margins using Hyperspectral Imaging	01/01/18	01/01/22
Ruers, Theo	NKI 2016-8162	TomTom voor de OK	01/01/17	01/01/20
Schagen, Sanne	UU 2015-7954	Effect of physical exercise on cognitive function after chemotherapy in patients with breast cancer	01/09/16	01/09/20
Schagen, Sanne	NKI 2015-7937	Monitoring, understanding and managing cognitive problems in cancer patients without central nervous system disease: putting knowledge into practice	01/01/17	01/01/23
Schagen, Sanne	NKI 2012-5495	Prospective predictors of late cognitive decline after anthracycline-based adjuvant chemotherapy for breast cancer: the role of brain white matter	01/01/13	01/01/17
Schagen, Sanne	NKI 2015-7737	Trajectories of cognitive decline in survivors of non-CNS cancers: from precancer diagnosis to late life after cancer	01/09/16	01/09/20
Schellens, Jan	NKI 2013-6249	Safety, feasibility and cost-effectiveness of genotype- and phenotype-directed individualized dosing of fluoropyrimidines	01/09/14	01/09/20
Schmidt, Marjanka	2015-7632	Breast cancer prognosis: identification of hereditary genetic variants	01/03/16	01/03/20
Schmidt, Marjanka	2013-6253	Risk management of contralateral breast cancer: development and validation of an online decision aid for physicians and patients	01/10/14	01/10/19
Schumacher, Ton	NKI 2013-6122	Linking cancer exomes to cancer immunotherapy	01/08/14	01/08/20
Schumacher, Ton	NKI 2017-8244	Netherlands Facility for Cancer immune Analysis (N-CIA)	01/05/18	01/05/23
Sixma, Titia	NKI 2015-8082	Elucidating regulation of tumor suppressor BAP1 in genome stability maintenance	01/12/16	01/12/20
Sixma, Titia	NKI 2012-5398	Regulation of the USP7/HAUSP switch	01/07/12	01/07/17
Sixma, Titia	NKI 2014-6858	Structure and function of the activated USP1 complex and its paralogs Providing a structural and biochemical basis for targeting USP1 in cancer	01/11/14	01/11/18
Smit, Egbert	VU 2013-6097	Iressa RE-challenge in advanced NSCLC EGFR M+ pts who responded to an EGFR-TKI used as 1st line or previous treatment ?	01/10/15	01/10/17
Sonke, Jan-Jakob	NKI 2012-5716	Optimized targeting for surgery and radiotherapy of breast cancer with a DCIS component	01/10/13	01/01/18

Principal investigator	Number of projects	Title	Started	Ended / Ends
Sonke, Gabe	NKI 2012-5685	High-dose alkylating chemotherapy in oligo-metastatic breast cancer harboring homologous recombination deficiency	01/07/12	01/10/19
Sonke, Gabe	2014-6838	Improving the outcome of ovarian cancer patients: when and why to use neoadjuvant chemotherapy or primary surgery in advanced ovarian cancer	01/10/17	01/10/18
Sonnenberg, Arnoud	NKI 2013-5971	Regulation of tumorigenesis by integrin alpha3beta1	01/11/13	01/11/18
Steeghs, Neeltje	NKI 2015-8074	Nederlands GIST consortium	01/02/16	01/02/17
Tan, Bing	NKI 2012-5423	Optimizing Nasopharyngeal Carcinoma management through increasing awareness in Yogyakarta	01/10/12	01/10/17
Te Riele, Hein	NKI 2014-7176	Development of prevention strategies for intestinal cancer in lynch syndrome using novel mouse models	01/08/15	01/08/19
Te Riele, Hein	10645	INVUSE: Investigation of variants of uncertain clinical significance for use in clinical practice	01/05/17	01/05/21
Te Riele, Hein	NKI 2014-6702	Replication stress in cancer: mechanisms and consequences for therapy	01/10/14	01/10/18
Te Riele, Hein	11074	Targeting replication rescue pathways	01/09/17	01/09/22
Van Boven, Hester	2013-5869	Fellowship van Hugo Horlings	01/08/14	01/08/18
Van Boven, Hester	10510	Genetic properties of breast carcinomas associated with cancer-immune interactions	01/11/17	01/11/21
Van de Poll, Lonneke	NKI 2015-7932	A randomized study, PROstate cancer follow-up care in secondary and Primary health care	01/09/17	01/09/22
Van der Heide, Uulke	2013-6311	Brachytherapy for rectal cancer: a better balance between tumor control and side effects	01/11/14	01/11/20
Van der Heide, Uulke	10088	Focal escalation of the radiation dose to the tumor in prostate cancer	01/04/17	01/04/21
Van der Heide, Uulke	NKI 2013-5937	Quantitative multi-parametric MR imaging for tumor delineation in focal radiotherapy of prostate cancer	01/05/14	01/05/18
Van der Heijden, Michiel	NKI 2014-7080	Genetic causes of resistance to new androgen receptor signaling inhibitors in circulating tumor DNA of metastasized castration resistant prostate cancer patients	01/06/15	01/06/20
Van Driel, Willemien	2011-5149	Nederlandse Studiegroep Gynaecologische Oncologie Dutch Gynaecological Oncology Group (DGOG) Start-studie	01/02/12	01/01/18
Van Driel, Willemien	2006-4176	Phase III randomised clinical trial for stage III ovarian carcinoma randomising between secondary debulking surgery with or without hyperthermic intraperiotoneal chemotherapy	14/03/07	01/01/17
Van Harten, Wim	NKI 2015-7904	A randomized controlled trial of an internet-based tailored physical activity support program in breast and prostate cancer survivors	01/09/16	01/09/20
Van Harten, Wim	NKI 2014-6078	Advanced Logistics Optimization of the Radiotherapy Treatment	01/02/15	01/02/20
Van Harten, Wim	10325	Does physical exercise during adjuvant cardiotoxic chemotherapy protect against cardiac injury among women with breast cancer?	01/09/17	01/09/20
Van la Parra, Raquel	NKI 2015-7533	The role of the breast surgeon in primary systemic treatment for breast cancer; towards optimizing locoregional treatment	01/09/15	01/09/17
Van Leerdam, Monique	10274	Evaluation of optimal intervals for colonoscopy surveillance: a randomized trial	01/02/17	01/02/29

Principal investigator	Number of projects	Title	Started	Ended / Ends
Van Leeuwen, Floor	NKI 2011-5270	A nationwide survivorship care program for adult (non-)Hodgkin lymphoma survivors	01/06/12	01/08/18
Van Leeuwen, Floor	10933	A risk prediction tool for cardiovascular disease in breast cancer patients	01/12/17	01/09/21
Van Leeuwen, Floor	NKI 2010-4720	Assessment of late effects of treatment for Hodgkin's lymphoma	01/05/11	01/12/17
Van Leeuwen, Floor	10424	Cardiotoxicity and second cancer risk after treatment of aggressive B-cell Non-Hodgkin lymphoma	01/12/17	01/12/21
Van Leeuwen, Floor	10164	Favorable and unfavorable effects of risk-reducing salpingo-oophorectomy (RRSO) in women at high genetic risk of ovarian cancer	01/07/17	01/07/21
Van Leeuwen, Floor	NKI 2011-5209	Long-term risk of cardiovascular disease and second malignancies after platinum-based chemotherapy for malignant testicular germ cell tumors	01/03/12	01/03/17
Van Leeuwen, Floor	VU 2017-8288	Psychosocial factors and cancer incidence: a pre-planned meta-analysis of the pSychosocial	01/12/17	01/12/21
Van Leeuwen, Floor	NKI 2017-8237	The BETER-REFLECT biobank: A REsource For studies on Late Effects of CancerTreatment	01/02/18	01/02/22
Van Leeuwen, Fred	NKI 2014-7232	Epigenetic Pathways in Cancer Development and Treatment: Crosstalk between Conserved Histone Modifiers in T-cell Lymphoma	01/11/15	01/11/19
Van Lohuizen, Maarten	NKI 2013-6030	Functional identification of novel genes implicated in Glioblastoma Multiforme	01/09/13	01/09/17
Van Lohuizen, Maarten	2012-5665	Silencing of DNA damage signaling by USP3 deubiquitinating enzyme: molecular mechanism and role in tumor suppression	01/01/14	01/01/18
Van Lohuizen, Maarten	NKI 2014-7208	Testing therapeutic responses to Polycomb inhibition in preclinical mouse models of Kras mutant lung cancer	01/07/15	01/07/19
Van Ramshorst, Gabrielle	2015-7506	Surgical, functional and reconstructive treatment of pelvic tumours - a multidisciplinary approach	01/06/16	01/12/18
Van Rheenen, Jacco	2013-5847	How to win or loose: The role of cell competition in tumor growth	01/10/17	31/12/18
Van Rheenen, Jacco	10123	The intermediate filament network in glioma invasion	01/05/17	01/05/21
Van Rheenen, Jacco	2015-7838	Understanding the role of SOX4 in educating the mammary tumor niche: the potential for personalized therapeutic targeting	01/10/17	01/01/20
Van Tellingen, Olaf	11165	Radiosensitization of glioma through induction of mitotic enrichment	01/01/18	01/07/20
Vens, Conchita	VU 2014-7072	A multiparameter radiogenomics-based decision support system for personalized treatment of advanced stage head and neck cancer patients	01/11/15	01/11/19
Verheij, Marcel	10327	Multicentre randomised phase II trial of neo-adjuvant chemotherapy vs chemotherapy/chemoradiotherapy vs chemoradiotherapy followed by surgery in resectable gastric cancer	01/12/17	01/12/21
Voest, Emile	HUBR 2014-7006	Exploring The Use Of Lung Cancer Organoids In Personalized Medicine	01/02/16	01/02/20
Voest, Emile	10014	The Drug Rediscovery Protocol (DRUP trial)	01/06/17	01/06/20
Voest, Emile	2015-7732	Tumor organoids : feasibility to predict sensitivity to treatment in cancer patients	01/07/15	01/07/18
Vogel, Wouter	10606	Comprehensive functional salivary gland management to avoid an iatrogenic dry mouth	01/11/17	01/11/21

Principal investigator	Number of projects	Title	Started	Ended / Ends
Wesseling, Jelle	11105	Improving breast cancer screening among young high risk women by blood-based methods	01/08/17	01/08/21
Wesseling, Jelle	NKI 2015-7711	Management of low grade ductal carcinoma in situ: active surveillance or not? A randomized, non-inferiority phase III trial	01/07/15	01/07/19
Wesseling, Jelle	NKI 2014-6250	Management of low risk ductal carcinoma in situ: watchful waiting or not? A randomized, non-inferiority trial	01/02/15	01/02/21
Wesseling, Jelle	NKI 2014-7167	Secondary prevention of breast cancer: risk stratification for personalized management of screen-detected ductal carcinoma in situ (DCIS)	01/10/15	01/10/19
Wessels, Lodewyk	NKI 2014-7080	Genetic causes of resistance to new androgen receptor signaling inhibitors in circulating tumor DNA of metastasized castration resistant prostate cancer patients	01/06/15	01/06/20
Wessels, Lodewyk	NKI 2013-6007	Prediction of response to neoadjuvant chemotherapy in luminal (ER-positive/ HER2-negative) breast cancer	01/10/14	01/10/18
Zwart, Wilbert	10084	Biomarker discovery for prognostication and treatment selection in prostate cancer through Androgen Receptor profiling	01/06/17	01/06/21
Zwart, Wilbert	NKI 2015-7733	Companion diagnostics for endocrine treatment selection in breast cancer	01/07/15	01/07/19
Zwart, Wilbert	NKI 2014-6711	Drugging steroid hormone receptors in novel tumor types; new applications of existing drugs	01/09/14	01/09/18

Research projects supported by other organisations

Principal investigator	Granting agency	Title	Started	Ended / Ends
Aaronson, Neil	Pink Ribbon	A prospective, randomized study of the efficacy of an internet-based cognitive behavioral therapy program in alleviating sexuality and intimacy problems in women treated for breast cancer	01/01/13	01/01/17
Aaronson, Neil	Pink Ribbon	Zorg op maat om fysieke fitheid en welzijn van vrouwen met gemetastaseerde borstkanker te bevorderen	01/09/15	01/09/18
Agami, Reuven	EEG-CEC / EU	enhReg, Exploring enhancers Achilles Heel	01/10/13	01/10/18
Agami, Reuven	EEG-CEC / EU	The European non-coding RNA training network RNA TRAIN project	01/10/13	01/10/17
Agami, Reuven	Stichting Oncode Institute	Oncode Agami	01/11/17	01/11/22
Agami, Reuven	ZonMw	Genome-wide identification of cancer-induced alterations in protein translation	01/06/11	01/06/17
Agami, Reuven	ZonMw	Uncovering cancerous enhancers of prostate and breast cancers	01/03/17	01/03/21
Akkari, Leila	AVL Foundation	Immunologie & Kanker Akkari	01/01/18	01/01/20
Akkari, Leila	NWO	Zwaartekracht programma	01/01/17	01/01/22
Akkari, Leila	SFN	Startgeld Akkari	01/01/17	01/01/22
Altelaar, Maarten	NWO	Proteins@Work; A large-scale proteomics research facility for the life sciences	01/05/13	30/06/19
Amant, Frederic	EEG-CEC / EU	CRADLE: Cancer tReAtment During pregnancy: from fetaL safety to maternal Efficacy	01/10/15	01/10/20
Baas, Paul	>1 Funding partner	Mesoscape	01/09/17	01/01/20
Baas, Paul	EEG-CEC / EU	DC-based immunotherapy to treat Malignant Mesothelioma	01/01/16	01/01/20
Baas, Paul	Synthon Biop-harmaceuticals	Evaluate whether 5T4 expression is an independent prognostic marker for patients with malignant pleural mesothelioma and a suitable antigen for targeted therapy	01/03/16	01/07/18
Bartelink, Harry	EEG-CEC / EU	Adaptive and innovative Radiation Treatment FOR improving Cancer patients treatment outcomE	01/04/11	01/10/17
Beets-Tan, Regina	ZonMw	Clinical impact of dedicated MR staging of ovarian cancer patients	01/12/17	01/12/21
Beijersbergen, Roderick	AVL Foundation	Pixels tegen darmkanker	01/08/11	01/01/18
Beijersbergen, Roderick	Merck Sharp & Dohme Corp	Identification of chromatin modifiers genes that upon inactivation show a synthetic lethal phenotype with Switch/Sucrose NonFermentable (SWI/SNF) chromatin-remodeling complex mutations in tumor cell lines	08/09/15	08/09/19
Beijnen, Jos	ZonMw	Optimizing drug development for the neglected tropical disease visceral leishmaniasis through a systems pharmacology model	01/12/16	01/12/19
Belderbos, Jose	>1 Funding partner	Ontwikkeling en invoering van PRO-CTCAE criteria bij patienten met longkanker	01/01/17	31/12/18
Bernards, Rene	Astex UK	ERN1 inhibition in KRAS mutant solid tumors and in BRAF mutant melanoma	01/09/14	01/09/18
Bernards, Rene	Astex UK	SHP2 inhibition in KRAS mutant solid tumors	01/03/16	01/03/18
Bernards, Rene	AstraZeneca NL	Identification and validation of new targets for colorectal cancer through molecular redefinition of the disease	01/01/11	01/01/17

Principal investigator	Granting agency	Title	Started	Ended / Ends
Bernards, Rene	CGC	POC clinical trial voor melanoma patienten	01/12/15	01/12/17
Bernards, Rene	EEG-CEC / EU	A European Platform for Translational Cancer Research	01/01/11	01/01/17
Bernards, Rene	EEG-CEC / EU	A treatment for BRAF inhibitor resistant melanoma	01/05/16	01/11/17
Bernards, Rene	EEG-CEC / EU	Molecularly guided trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of colorectal cancer	01/10/15	01/10/19
Bernards, Rene	EEG-CEC / EU	RATHER Rational Therapy for Breast Cancer: Individualized Treatment for Difficult-to-Treat Breast Cancer Subtypes	01/01/11	01/07/18
Bernards, Rene	Eli Lilly and Company Limited	Abemaciclib (LSN2813542) CDK4/6 mesylate salt synthetic lethal interactions in KRAS mutant colorectal cancer	12/01/16	12/01/18
Bernards, Rene	KNAW	KNAW hoogleraarschap	01/10/13	01/10/18
Bernards, Rene	NWO	CRISPR library	01/04/15	01/01/22
Bernards, Rene	NWO	NWO Diamond Graduate Program J Kahn	01/09/15	01/09/19
Bernards, Rene	NWO	Zwaartekracht programma 2012 (Bernards)	01/01/13	01/01/22
Bernards, Rene	Overig	Therapie op maat door mutatieanalyse bij kanker	01/07/11	01/08/18
Bernards, Rene	Stichting Oncode Institute	Oncode Bernards	01/11/17	01/11/20
Bernards, Rene	University of California (UCLA)	Interrogation of Resistance Mechanisms to Checkpoint Inhibitors Using Functional Genomics	01/11/17	01/11/19
Berns, Ton	EEG-CEC / EU	Combination therapies for personalized cancer medicine	01/05/13	01/05/19
Berns, Ton	NWO	Mouse Clinic for Cancer and Aging research (MCCA)	01/10/12	01/01/19
Berns, Ton	Stichting Oncode Institute	Oncode Berns	01/11/17	01/11/22
Blank, Christian	Bristol Myers Squibb France	A prospective multicenter cohort study of late physical, psychological and social effects in patients treated with IO for advance melanoma	01/07/16	01/06/19
Blank, Christian	Bristol Myers Squibb USA	Feasibility Study to Identify of the Optimal Adjuvant Combination Scheme of Ipilimumab and Nivolumab	01/01/17	01/01/18
Blank, Christian	Bristol Myers Squibb USA	Impact of NSAIDs on the response to checkpoint therapy	02/08/17	02/08/19
Blank, Christian	Bristol Myers Squibb USA	Improve the understanding of systemic melanoma-mediated immune suppression by deep serum profiling	01/06/17	01/06/18
Blank, Christian	Bristol Myers Squibb USA	Systematic analysis of Cutaneous and Uveal Melanoma	01/06/17	01/06/18
Bleiker, Eveline	EORTC	EORTC kwaliteit van leven data	01/12/15	01/12/17
Bleiker, Eveline	Pink Ribbon	Optimale voorlichting en zorg voor mannen met borstkanker	01/09/15	01/10/17
Bleiker, Eveline	Zorginstituut Nederland	Mannen met Borstkanker	01/12/17	01/09/19
Borst, Jannie	Aduro Biotech, Europe BV	Identification and validation of novel T-cell modulators in Immune Oncology	01/07/17	01/07/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Borst, Jannie	Elekta Ltd	Radio-immunotherapy in cancer treatment	01/06/16	01/06/21
Borst, Jannie	Landsteiner Stichting	Tracing human dendritic cell development from a common precursor of dendritic cells and osteoclasts	01/08/14	01/08/17
Borst, Jannie	NWO	Exploiting T cell metabolism as a target for therapeutic intervention	01/01/15	01/01/19
Borst, Jannie	NWO	Mechanisms of action of the Ubiquitin-like modifier ISG15 in immune regulation	01/01/15	01/01/19
Borst, Jannie	ZonMw	Discriminating signaling nodes in conventional and regulatory T cells to guide clinical targeting of costimulatory receptors in cancer, autoimmunity and transplant rejection	01/04/14	01/08/19
Broeks, Annegien	BBMRI-NL	Art 20 , a national application and request tool for studies using biobank material	01/11/16	01/04/18
Brummelkamp, Thijn	EEG-CEC / EU	A global alliance for Zika virus control and prevention	01/10/16	01/10/19
Brummelkamp, Thijn	EEG-CEC / EU	Breaking down arenavirus cell entry	01/10/15	01/10/17
Brummelkamp, Thijn	EEG-CEC / EU	Viral Host Factors, Identification of Host Determinants for Virus Entry using a Haploid Genetic Approach	01/01/13	01/01/18
Brummelkamp, Thijn	NWO	Human Genes and Intracellular Phenotypes	01/03/17	01/03/22
Brummelkamp, Thijn	NWO	Zwaartekracht programma 2012	01/01/13	01/01/22
Brummelkamp, Thijn	Stichting Ammodo	Ammodo Award 2015 voor Biomedical Sciences	04/03/16	04/03/19
Brummelkamp, Thijn	Stichting Oncode Institute	Oncode Brummelkamp	01/11/17	01/11/22
Brummelkamp, Thijn	ZonMw	Tissue size control and the regulation of Hippo pathway activity in mammals	01/04/11	01/04/17
Burgers, Sjaak	>1 Funding partner	Switch maintenance treatment with gemcitabine for patients with malignant mesothelioma who do not progress after 1st line therapy with a pemetrexed-platinum combination A randomised open label phase II study	01/03/13	01/01/19
Chalabi, Myriam	Bristol-Myers Squibb International Belgie	Towards deciphering immune escape mechanisms of early colon cancers and developing rationales for future treatment strategies: translational research plan for the NICHE trial	01/10/17	01/10/20
De Visser, Karin	EEG-CEC / EU	Mechanistic insights into the impact of tumor-associated neutrophils on metastatic breast cancer	01/03/14	01/03/19
De Visser, Karin	NWO	OOA NWO Diamond KKos	01/10/16	01/10/20
De Visser, Karin	Roche	To study the anti-cancer efficacy of a triple combination treatment consisting of the Roche murinized antibody against CSF-1 receptor, cisplatin, and another modulator in a spontaneous mammary tumor mouse model	01/05/13	01/09/19
De Visser, Karin	Stichting Oncode Institute	Oncode de Visser	01/09/17	01/09/22
De Wit, Elzo	EEG-CEC / EU	From haplotype to phenotype: a systems integration of allelic variation, chromatin state and 3D genome data	01/09/15	01/09/20
De Wit, Elzo	NWO	Impact of sequential driver mutations on epigenetic regulation during intestinal carcinogenesis	01/09/17	31/08/20
De Wit, Elzo	NWO	The role of transcription factors in 3D genome organization	01/10/16	01/10/21

Principal investigator	Granting agency	Title	Started	Ended / Ends
De Wit, Elzo	SFN	Junior PI De Wit	01/09/15	01/09/20
De Wit, Elzo	Stichting Oncode Institute	Oncode de Wit	01/11/17	01/11/22
Faller, William	NWO	Zwaartekracht programma 2012 Faller	01/01/17	01/01/22
Faller, William	SFN	Start-up package PI Faller	01/11/16	01/11/21
Haanen, John	>1 Funding partner	Leven met niet meer te genezen kanker	01/08/17	01/08/18
Haanen, John	Bristol Myers Squibb USA	Analysis of PD-1 Blockade in Virus-Associated Cancers	01/12/14	01/06/18
Haanen, John	Bristol Myers Squibb USA	Fresh TIL in Heme Malignancies	01/02/16	01/02/18
Haanen, John	Merck	Dissection of the role of pembrolizumab (MK-3475) on the circulating tumor-specific T cell pool specific for shared tumor-associated antigens	01/11/14	01/01/18
Haanen, John	Neon Therapeutics	T Cell Program, Stimulation of neo-antigen specific T cell responses from patient PBMC	01/02/16	01/01/19
Haanen, John	ZonMw	Randomized controlled trial comparing TIL treatment to ipilimumab for the treatment of advanced stage melanoma	01/07/15	01/07/19
Haas, Rick	>1 Funding partner	Radiobiology of Sarcomas	01/06/16	01/12/19
Hauptmann, Michael	AVL Foundation	Startgeld Hauptmann	17/07/17	17/07/18
Hauptmann, Michael	EEG-CEC / EU	Epidemiological study to quantify risks for pediatric computerized tomography and to optimise doses	01/02/11	01/02/17
Hauptmann, Michael	EEG-CEC / EU	Implications of Medical Low Dose Radiation Exposure	01/06/17	01/06/21
Heijden, van der Michiel	AVL Foundation	ctDNA	01/01/15	01/10/17
Horenblas, Simon	AVL Foundation	Immunological aspects of the microenvironment of primary tumours, tumour-positive and tumour-negative lymph nodes in HPV+ and HPV- penile cancer patients	01/01/17	01/01/19
Huitema, Alwin	Merus BV	Support of (pre)-clinical development program of the Merus HER2/HER3 bispecific monoclonal antibody (MCLA-128)with PK/PD modeling and simulation	18/04/14	31/08/19
Huitema, Alwin	Merus BV	Support of clinical development program of the Merus bispecific monoclonal antibody MCLA-117 with PK/PD modeling and simulation	01/09/16	01/09/18
Jacobs, Heinz	ZonMw	The role of stable immunoglobulin transcripts in establishing allelic exclusion	01/04/14	31/03/18
Jacobs, Jacqueline	EEG-CEC / EU	Genome-wide identification of factors controlling the telomere damage response and telomere-driven genomic instability	01/10/12	01/10/17
Jacobs, Jacqueline	EMBO	EMBO Small Grant for funding of research materials	01/01/17	01/01/20
Jacobs, Jacqueline	NWO-ALW	A critical role for WHSC1 at telomeres	01/11/12	01/10/17
Jacobs, Jacqueline	NWO-ALW	EMBO Young Investigators	01/01/13	01/01/20
Jalink, Kees	AVL Foundation	Super Resolution Microscopy	01/08/16	01/08/17

Principal investigator	Granting agency	Title	Started	Ended / Ends
Jalink, Kees	STW	Labeling strategies for nanoscopy of complex biological specimens	01/09/11	01/01/17
Jalink, Kees	STW	New Film Camera for molecular microscopy	01/09/16	01/09/19
Jonkers, Jos	EEG-CEC / EU	Development of mouse mutant resources for functional analyses of human diseases - Enhancing the translation of research into innovation Intrafrontier-I3 project J Jonker	01/01/13	01/01/17
Jonkers, Jos	EEG-CEC / EU	Generation of the CanPath prototype - a platform for predictive cancer pathway modeling	01/03/16	01/03/21
Jonkers, Jos	EEG-CEC / EU	Targeting SYNthetic lethal interactions for new cancer treatments TRAINing network (MC)	01/09/16	01/09/20
Jonkers, Jos	EEG-CEC / EU	Towards enduring mouse resources and services advancing research into human health and disease	01/01/17	01/01/21
Jonkers, Jos	NWO	Finding novel Achilles' heels to prevent and target BRCA1-associated breast cancer	01/02/14	01/02/19
Jonkers, Jos	NWO	Zwaartekracht programma 2012 (Jonkers)	01/01/13	01/01/22
Jonkers, Jos	Stichting Oncode Institute	Oncode Jonkers	01/11/17	01/11/22
Jonkers, Jos	WCR	Epithelial -to-mesenchymal transition and therapy resistance in BRCA1-associated breast cancer	01/02/14	01/02/17
Jonkers, Jos	ZonMw	The role of mitotic spindle orientation in mammary gland and biology and breast cancer	01/01/15	01/01/18
Karakullukcu, Baris	AVL Foundation	3D Lab - Verwelius	01/04/17	01/01/20
Karakullukcu, Baris	Biolitec	Treatment of head and neck cancer	01/09/15	01/09/18
Karakullukcu, Baris	PCI Biotech AS	multi-site study	01/06/12	01/08/17
Kenter, Gemma	EEG-CEC / EU	Rational molecular Assessments and Innovative Drug Selection	01/10/12	01/04/17
Kenter, Gemma	NanoNextNL	Drug Delivery	18/07/11	01/01/17
Kerkhoven, Ron	AVL Foundation	Startup money to set-up single cell RNA sequencing using droplet based microfluidics (DropSeq) at the Genomics Core Facility	01/07/16	01/07/18
Kok, Marleen	Pink Ribbon	Discovery of biomarkers to select metastatic breast cancer patients for immunotherapy using anti-PD1	01/09/16	01/09/19
Kvistborg, Pia	Bristol Myers Squibb USA	Quantitative and qualitative changes in tumor-specific T cells upon anti-PD-1 therapy	01/02/16	18/11/18
Kvistborg, Pia	Merck Sharp & Dohme Corp	Feasibility study of neo-adjuvant treatment with carboplatin, paclitaxel and pembrolizumab in stage IV epithelial ovarian cancer	01/10/16	01/10/18
Kvistborg, Pia	SFN	Inhuizing Kvistborg (start-up package PI Kvistborg)	01/09/16	01/09/21
Lenstra, Tineke	EEG-CEC / EU	Single-molecule visualization of transcription dynamics to understand regulatory mechanisms of transcriptional bursting and its effects on cellular fitness	01/01/18	01/01/23
Lenstra, Tineke	NWO	Zwaartekracht programma 2012 Lenstra	01/01/17	01/01/22
Lenstra, Tineke	SFN	Start-up package PI Lenstra	01/12/16	01/12/21

Principal investigator	Granting agency	Title	Started	Ended / Ends
Linn, Sabine	A Sister's Hope	Estrogen Receptor interactome from biopsies to guide endocrine treatment	01/01/12	01/01/19
Linn, Sabine	A Sister's Hope	Mutational analysis and BRCA1-like classification in WSG-ADAPT TN-Trial	01/01/17	01/07/18
Linn, Sabine	A Sister's Hope	PI3K pathway activation in primary and metastatic estrogen receptor alpha (ERa) positive breast cancer and the association with drug response	01/12/12	01/09/20
Linn, Sabine	A Sister's Hope	Toward personalized medicine by using the nationwide population-based breast cancer registry (1989-2009) coupled with biobanking:NBCP	01/06/12	01/03/18
Linn, Sabine	AVL Foundation	Learning from unexpected cures	01/04/14	01/09/20
Linn, Sabine	AVL Foundation	Materiaal budget TONIC-Trial	01/09/15	01/01/20
Linn, Sabine	AVL Foundation	STARZ Foundation	01/01/14	01/01/19
Linn, Sabine	EEG-CEC / EU	Rational Therapy for Breast Cancer: Individualized Treatment for Difficult-to-Treat Breast Cancer Subtypes	01/11/14	01/07/18
Linn, Sabine	ZonMw	NBCP: Towards personalized medicine by using the nationwide population-based breast cancer registry	01/12/13	01/03/17
Linn, Sabine	ZonMw	Substantiele verbetering van de overleving van stadium III, BRCA1-like borstkanker patienten met doelgerichte behandeling	01/01/17	01/01/23
Lok, Christianne	>1 Funding partner	Onderzoek Eierstokkanker -E-learning over genetische screening bij ovariumcarcinoom	01/08/15	01/02/18
Lok, Christianne	AstraZeneca NL	GenOva 20	01/04/17	01/09/18
Loo, Claudette	CTMM	COmputer-aided predIction of breast Cancer therapy response by means of multimodality imaging	01/06/15	01/01/18
Medema, Rene	EEG-CEC / EU	The impact of chromosomal instability on health: Molecular causes and consequences of aneuploidy	01/10/13	01/10/17
Medema, Rene	NWO	Zwaartekracht programma (Medema)	01/01/13	01/01/22
Medema, Rene	NWO-ALW	Spatial and temporal control of the microtubule by kinase activity	16/01/15	16/01/18
Medema, Rene	Stichting Oncode Institute	Oncode Medema	01/11/17	01/11/22
Medema, Rene	ZonMw	Impact of chromatin context on DNA double-strand break repair kinetics, fidelity and signaling	01/07/16	01/07/20
Meijer, Gerrit	>1 Funding partner	A multivariable prediction model for prognosis of early stage colorectal cancer: comparing clinicopathological characteristics and molecular markers	01/04/15	01/04/19
Meijer, Gerrit	AACR	AACR GENIE Project	01/07/16	01/01/18
Meijer, Gerrit	AVL Foundation	Darmkanker en biomarkers	01/03/17	01/03/19
Meijer, Gerrit	BBMRI-NL	BBMRI 20	01/01/15	01/01/19
Meijer, Gerrit	BBMRI-NL	Dutch National Tissue Portal	01/04/15	01/01/18
Meijer, Gerrit	EEG-CEC / EU	Coordinated Research Infrastructures Building Enduring Life-science services	01/11/16	01/09/19
Meijer, Gerrit	Health-Holland	CRC Bioscreen 20	01/09/16	01/09/18
Meijer, Gerrit	Health-Holland	Liquid biopsy-based molecular diagnostics to monitor therapy response in metastatic colorectal cancer: PLCRC-ORCA EXTended beyond RAS	01/01/17	01/01/21

Principal investigator	Granting agency	Title	Started	Ended / Ends
Meijer, Gerrit	MAAG LEVER DARM Stichting	Detectie hoog-risisco adenomen	01/02/17	01/08/18
Meijer, Gerrit	MAAG LEVER DARM Stichting	Opslag Poep Samples, Logistiek en Analyse van Gegevens	15/10/15	01/10/18
Moolenaar, Wouter	NWO Chemische Wetenschappen	Autotaxin, a secreted phosphodiesterase with diverse roles in disease: structural and functional studies	01/02/11	01/02/17
Moolenaar, Wouter	Overig	Neuroblastomen en longkankeronderzoek	01/03/13	01/03/17
Nederlof, Petra	Roche	Roche CGH Array	01/10/12	01/12/19
Neefjes, Jacques	NWO	Visualizing macromolecular complexes in MHC antigen presentation	01/10/14	01/10/18
Nuijen, Bastiaan	Modra Pharmaceuticals BV	Chemistry, Manufacturing and Control of ModraDoc006 tablets	07/04/17	01/11/18
Peeper, Daniel	AVL Foundation	Empowering n=1: converting unexplained responses into clinical benefits- a proof-of- concept study	01/05/15	01/01/18
Peeper, Daniel	AVL Foundation	Screening novel therapeutic targets for immuno oncology	01/12/17	01/12/18
Peeper, Daniel	Bristol Myers Squibb USA	Defining and tackling immunotherapy resistance in melanoma and lung cancer	01/08/17	01/08/21
Peeper, Daniel	Genmab	Research into cell signal pathways and oncogenic divers	01/05/15	01/10/20
Peeper, Daniel	Merck Sharp & Dohme Corp	Identification of chromatin modifiers genes that upon inactivation show a synthetic lethal phenotype with Switch/Sucrose NonFermentable (SWI/SNF) chromatin-remodeling complex mutations in tumor cell lines	08/09/15	08/09/18
Peeper, Daniel	Stichting Oncode Institute	Oncode Peeper	01/11/17	01/11/22
Perrakis, Anastassis	EEG-CEC / EU	INEXT JRA	01/09/15	01/09/19
Perrakis, Anastassis	EEG-CEC / EU	Infrastructure for NMR, EM and X-ray crystallography for translational research	01/09/15	01/09/19
Perrakis, Anastassis	EEG-CEC / EU	World-wide E-infrastructure for structural biology	01/11/15	01/11/18
Perrakis, Anastassis	Janssen Research & Development	Enhancement of PDB_REDO algorithms and software	01/01/16	01/01/19
Perrakis, Anastassis	NWO	Optimised protein knowledge through transfer of evolutionary conserved features and chemical knowledge	15/11/14	14/11/19
Perrakis, Anastassis	NWO	The molecular interactions allowing Mps1 to safeguard cell division	01/10/15	30/09/18
Perrakis, Anastassis	NWO Chemische Wetenschappen	Structural and chemical basis for the biosynthesis and propagation of base J	01/09/14	01/09/19
Perrakis, Anastassis	Universiteit Utrecht	Releasing the full potential of Instruct to expand and consolidate infrastructure services for integrated structural life science research	01/01/17	01/01/21
Rookus, Matti	>1 Funding partner	HEBON Centers	15/11/13	15/11/18
Rookus, Matti	Pink Ribbon	Improved risk prediction to allow for a more personalized advice regarding the performance and timing of prophylactic surgeries for BRCA 1/2 mutation carriers	01/04/14	01/04/18

Principal investigator	Granting agency	Title	Started	Ended / Ends
Rookus, Matti	Universiteit Utrecht	Shift work and risk of breast cancer, a prospective cohort study among Dutch nurses	01/09/08	01/01/18
Rowland, Benjamin	NWO Chemische Wetenschappen	How does cohesin release DNA?	01/01/16	01/01/19
Rowland, Benjamin	SFN	Startgeld Rowland	01/04/17	01/04/22
Ruers, Theo	AVL Foundation	Optical guided surgery	01/11/14	01/06/20
Ruers, Theo	AVL Foundation	Pixel analyse voor (vroeg)detectie van dikke darmkanker	01/01/17	01/01/19
Ruers, Theo	EEG-CEC / EU	Advancing Smart Optical Imaging and Sensing for Health	01/06/16	01/06/19
Ruers, Theo	Health-Holland	TomTom project	01/12/16	01/12/19
Ruers, Theo	Holland High Tech	ECSEL project ASTONISH	01/06/16	01/06/19
Ruers, Theo	Innovation Exchange Amsterdam	MaMaLoc: Magnetische Marker voor Chirurgische Lokalisatie	01/06/16	01/06/18
Ruers, Theo	Philips	Research collaboration Philips	01/04/10	01/01/19
Ruers, Theo	STW	Combining Optics and Acoustics For Real-time Guidance during Cancer Surgery	01/09/17	01/09/20
Schagen, Sanne	Fonds NutsOhra	Analyse en reductie van neurocognitieve afwijkingen bij hersenbestraling bij kankerpatienten	01/10/11	01/04/17
Schellens, Jan	CBG	Convenant CBG Jorn Mulder	01/05/17	01/05/22
Schellens, Jan	EEG-CEC / EU	Molecularly guided trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of colorectal cancer	01/10/15	01/10/19
Schellens, Jan	GlaxoSmithKline	Oncology Clinical and Translational consortium	22/10/13	22/10/19
Schellens, Jan	NWO	Zwaartekracht programma 2012 (Schellens)	01/01/13	01/01/22
Schmidt, Marjanka	EEG-CEC / EU	Breast CAncer STratification: understanding the determinants of risk and prognosis of molecular subtypes	01/09/15	01/09/20
Schmidt, Marjanka	ZonMw	Fostering the responsible use of residual biospecimens and data in medical	01/05/17	01/05/19
Schmidt, Marjanka	ZonMw	Personalized medicine: servicedesk ethiek en recht	01/09/17	01/09/19
Schumacher, Ton	>1 Funding partner	Cell Therapy NKI	01/07/11	01/07/18
Schumacher, Ton	Cancer Research Institute	Unraveling the biology of CMTM6: A novel regulator of PD-Li identified through genome-wide genetic screening	01/01/17	01/01/20
Schumacher, Ton	EEG-CEC / EU	Advanced T-cell Cancer Gene-Therapy	01/12/13	01/12/18
Schumacher, Ton	EEG-CEC / EU	APERIM: Advanced bioinformatics platform for PERsonalised cancer IMmunotherapy	01/05/15	01/05/18
Schumacher, Ton	EEG-CEC / EU	Mapping the life histories of T cells	01/05/11	01/02/17
Schumacher, Ton	EEG-CEC / EU	Quantitative T cell Immunology	01/10/13	01/05/17

Principal investigator	Granting agency	Title	Started	Ended / Ends
Schumacher, Ton	EEG-CEC / EU	Sensitivity of human tumors to T cell attack	01/12/17	01/12/22
Schumacher, Ton	Kristian Gerhard Jebsen foundation	Jebsen grant	01/06/13	01/01/20
Schumacher, Ton	MD Anderson Cancer Center	Acceleration of the Clinical Testing of CTLA-4 and P1 Blockade for Melanoma	01/03/14	01/03/18
Schumacher, Ton	MD Anderson Cancer Center	Immunologic Checkpoint Blockade and Adoptive Cell Transfer in Cancer Therapy	01/03/13	01/03/17
Schumacher, Ton	Merck KGaA	Single cell analysis of the tumour-immune ecosystem in human cancer: Dissecting the dynamics of immune-tumour cross talk following checkpoint blockade	01/06/17	01/06/20
Schumacher, Ton	NWO	Zwaartekracht Schumacher ICI-00003	01/08/14	01/08/19
Schumacher, Ton	NWO	Zwaartekracht Schumacher ICI-00105	01/10/14	01/10/19
Schumacher, Ton	Roche	T cell responses and mapping of neo-antigen-specific T cell repertoires in follicular lymphoma patients after local anti-CD20 therapy	01/04/14	01/07/19
Schumacher, Ton	Stichting Oncode Institute	Oncode Schumacher	01/11/17	01/11/22
Schumacher, Ton	WCR	Antigen-specificity and kinship of intratumoral regulatory T cells	01/04/14	01/04/17
Sixma, Titia	EEG-CEC / EU	Regulated Assembly of Molecular Machines for DNA REPAIR: a Molecular Analysis training Network	01/01/17	01/01/21
Sixma, Titia	NWO	Investering Therpophoresis HPLC imager	01/04/13	01/01/22
Sixma, Titia	NWO	The molecular mechanism of USP48, a BRCA1 antagonist during DNA damage response	01/01/18	01/01/23
Sixma, Titia	NWO	Zwaartekracht programma 2012 (Sixma)	01/01/13	01/01/22
Sixma, Titia	NWO Chemische Wetenschappen	A movie of DNA mismatch repair: how information is transmitted by conformational change	01/01/17	01/01/23
Sixma, Titia	NWO Chemische Wetenschappen	Regulation of H2A ubiquitination	01/08/12	01/03/17
Sixma, Titia	NWO-ALW	Cellular activation of the allosterically inhibited UCHL5/INO80G complex	01/12/16	01/12/19
Sixma, Titia	Stichting Oncode Institute	Oncode Sixma	01/11/17	01/11/22
Sonke, Jan-Jakob	>1 Funding partner	Personalized Radiotherapy Collaboration Agreement	01/01/15	01/01/20
Sonke, Gabe	A Sister's Hope	Long-term Survival in Metastatic HER2+ Breast Cancer	01/04/17	01/04/18
Sonke, Gabe	AVL Foundation	Donatie Team Westland G Sonke	07/12/17	07/12/20
Sonke, Gabe	Pink Ribbon	Learning from long-term survivors in metastatic breast cancer	01/11/16	01/11/19
Sonnenberg, Arnoud	DEBRA AUSTRIA	High-content screening for new therapies for Epidermolysis Bullosa Simplex associated with Muscular Dystrophy	01/04/17	01/04/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Sonnenberg, Arnoud	NWO-ALW	Identification and characterization of proteins involved in coordinating the function of focal adhesions and hemidesmosomes in promoting stable keratinocyte adhesion	01/01/15	01/01/19
Steeghs, Neeltje	>1 Funding partner	REGISTER - REgistratie GIST nEdeRland	01/01/14	01/01/19
Stokkel, Marcel	AVL Foundation	Tumour specific imaging of prostate cancer using PSMA-PET	01/07/16	01/06/18
Stokkel, Marcel	Interne financiering	Reposit studie DOD	01/09/15	01/01/19
Stokkel, Marcel	ONCO Vision	Sentinella	01/11/16	01/11/17
Stokkel, Marcel	STW	A feasibility study on Cerenkov Luminescence Imaging during prostate cancer surgery using Gallium-68 PSMA	01/08/17	01/11/19
Stuiver, Martijn	Nutricia Nederland BV	Voedingsstatus en het beloop van de behandeling van stadium III longkanker	01/11/17	01/01/20
Tan, Bing	Ergomed Clinical Research ltd	Educational Project related to the treatment of head and neck cancer	01/01/14	01/01/17
Te Riele, Hein	NWO-ALW	Oligonucleotide directed gene targeting: evading mismatch repair	01/09/13	01/09/17
Te Riele, Hein	STW	Phenotypic assessment of intra- and extra-exonic variants of disease-related genes present in the human population	01/01/17	01/01/21
Ten Hoeve, Jelle	CTMM	Translational Research IT	01/01/14	01/01/17
Trum, Hans	ZonMw	GERiatric Screening in the treatment of elderly patients with Ovarian Carcinoma	15/08/17	15/08/21
Van Akkooi, Alexander	Amgen BV	the infra structure registry: prospective melanoma stadium III registry	01/07/17	01/07/18
Van de Poll, Lonneke	EORTC	Phase II and III development of an EORTC QOL cancer survivorship questionnaire	01/02/17	01/08/19
Van de Poll, Lonneke	SFN	Start-up package PI van de Poll	01/01/16	01/01/19
Van den Berg, Joost	Bristol Myers Squibb USA	Urelumab to improve tumor reactivity of Tumor Infiltrating Lymphocytes (TIL) derived from ovarian cancer and NSCLC using urelumab	31/07/17	31/01/19
Van den Berg, Joost	MedImmune	Immunomagnetic selection of PD1 + Peripheral Blood Mononuclear Cells (PBMC's)	10/07/17	10/10/18
Van den Brekel, Michiel	>1 Funding partner	Head and neck cancer research	01/10/10	01/01/20
Van den Brekel, Michiel	>1 Funding partner	Virtual Therapy Prediction of functional loss	01/10/16	01/10/19
Van den Brekel, Michiel	ATOS	research and new product development NKI-AvL	01/01/14	01/07/20
Van den Brekel, Michiel	AVL Foundation	Hoofd-Hals Targeted therapy	01/01/15	01/01/19
Van den Brekel, Michiel	EEG-CEC / EU	Training Network on Automatic Processing of PAthological Speech	01/11/17	01/11/21
Van den Broek, Daan	Stichting EC Noyons	Development and validation of a digital droplet PCR panel for the detection of clinical relevant mutations in circulating tumor DNA in Non-Small-Cell-Lung-Carcinoma (NSCLC)	01/06/15	01/01/17

Principal investigator	Granting agency	Title	Started	Ended / Ends
Van den Heuvel, Michel	Bristol Myers Squibb USA	Introducing an easily accessible biomarker based on an active immune expression array can optimize personalized immunotherapy	01/11/16	01/11/18
Van der Heide, Uulke	>1 Funding partner	System Technologies for Adaptive Real-time Image-guided Therapies	01/10/17	01/10/20
Van der Heide, Uulke	Philips	Feasibility of MR-only in Radiation Oncology	13/12/17	13/12/20
Van der Heide, Uulke	ZonMw	Quantivision project - perfect cut	15/05/15	15/05/19
Van der Poel, Henk	CTMM	Prostate Cancer Molecular Medicine	01/12/09	01/07/18
Van Driel, Willemien	AVL Foundation	Onderzoek voor ovarium carcinoom	01/10/17	01/10/18
Van Harten, Wim	Agendia BV	Kosten-effectiviteits-analyses op MINDACT data	01/07/17	01/01/19
Van Harten, Wim	AVL Foundation	Monopolie met maatschappelijk rendement - Verantwoord omgaan met patenten in de oncologie	01/01/17	01/03/21
Van Harten, Wim	ZonMw	Technology Assessrnent of Next Generation Sequencing in Personalized Oncology (TANGO)	31/12/16	01/01/20
Van Leerdam, Monique	MAAG LEVER DARM Stichting	Diagnostic yield of screening colonoscopy in Hodgkin lymphoma survivors at increased risk of treatment-induced colorectal cancer	01/05/15	01/05/18
Van Leeuwen, Floor	BBMRI-NL	Complementatieproject Enrichment of the Multicenter Dutch Hodgkin's Lymphoma Cohort to Study Susceptibility Genes for the Development of Adverse Late Effects of Treatment	01/07/13	01/07/17
Van Leeuwen, Floor	BBMRI-NL	Use of encrypted BSN in record linkage of epidemiological cohorts and biobanks with disease registries to ensure valid linkages with optimal privacy protection	01/09/16	01/09/17
Van Leeuwen, Floor	CTSU	valvular after breast cancer case-control study	01/04/15	01/08/17
Van Leeuwen, Floor	DES	Onderzoek CCAC van DES-dochters ouder dan 50 jaar	01/10/17	01/01/19
Van Leeuwen, Floor	EORTC	GetReal	01/01/16	01/07/17
Van Leeuwen, Floor	Erasmus Medisch Centrum	Long-term risk of endometrial cancer after ovarian stimulation for in-vitro fertilization A case-cohort analysis	01/01/11	01/12/18
Van Leeuwen, Floor	KIKA Stichting Kinderen Kankervrij	Risk of cancer in children and adolescents conceived by assisted reproductive technologies	01/09/14	01/04/17
Van Leeuwen, Floor	NIH	LIFT-OMEGA	01/09/17	01/06/22
Van Leeuwen, Floor	Pink Ribbon	Assessment of myocardial strain: a novel method for early detection of subclinical cardiotoxicity after anthracycline-based chemotherapy in young breast cancer patients	01/12/16	01/12/18
Van Leeuwen, Floor	Pink Ribbon	Cardiovascular morbidity and mortality in breast cancer survivors: identifying high risk subgroups	01/10/13	01/02/18
Van Leeuwen, Floor	Social & Scientific Systems inc	Preparing and providing tissue samples and clinical data from histologically confirmed second gastric tumor cases among survivors of Hodgkin lymphoma and testicular cancer for a study characterizing the molecular characteristics of second primary gastric cancers	02/09/16	02/09/18
Van Leeuwen, Floor	University of Oxford	CORAL Oxford	01/10/16	01/10/17

Principal investigator	Granting agency	Title	Started	Ended / Ends
Van Leeuwen, Fred	NWO	Principles of epigenetic inheritance	23/07/13	23/07/19
Van Leeuwen, Fred	NWO Chemische Wetenschappen	Development of antibodies targeted at site-specific protein ubiquitylation	01/09/16	01/09/19
Van Lohuizen, Maarten	NWO	Zwaartekracht programma 2012 (Lohuizen)	01/01/13	01/01/22
Van Lohuizen, Maarten	NWO-ALW	New technology to study genome-wide effects of local chromatin environment and epigenetic states on gene regulation	01/07/13	01/07/17
Van Lohuizen, Maarten	Stichting Oncode Institute	Oncode van Lohuizen	01/11/17	01/11/22
Van Luenen, Henri	EEG-CEC / EU	Libra	01/10/15	01/04/19
Van Luenen, Henri	NWO	Stimulering Europees Onderzoek	01/12/15	01/12/20
Van Luenen, Henri	ZonMw	Haem	01/09/16	01/01/17
Van Rheenen, Jacco	CGC	CGC IV van Rheenen	01/10/17	31/12/21
Van Rheenen, Jacco	Dr Josef Steiner Krebsstiftung	Dr Josef Steiner Cancer Research Award 2017	01/10/17	01/10/21
Van Rheenen, Jacco	EEG-CEC / EU	Integrated Component Cycling in Epithelial Cell Motility	01/10/17	01/01/19
Van Rheenen, Jacco	EEG-CEC / EU	Tumor cell death supports recurrence of cancer	01/10/17	01/10/20
Van Rheenen, Jacco	EMBO	EMBO Fellowship Jessica Morgner	01/10/17	31/12/18
Van Rheenen, Jacco	NWO	Intravital stem cell imaging to reveal the cellular processes that drive colorectal tissue homeostasis and tumour initiation	01/10/17	01/10/18
Van Rheenen, Jacco	NWO-ALW	Identifying the physiological relevance of RNA transfer by microvesicles	01/10/17	15/04/18
Van Rheenen, Jacco	SFN	inhuizing senior groepsleider van Rheenen voor aanstelling van personeel	01/10/17	01/10/27
Van Rheenen, Jacco	Stichting Oncode Institute	Oncode van Rheenen	01/11/17	01/11/22
Van Sandick, Johanna	Vrolijk	Slokdarmkankeronderzoek Stichting Vrolijk	01/01/08	01/07/20
Van Sandick, Johanna	ZonMw	Combinatie behandeling van cytoreductieve chirurgie en hypertherme intraperitoneale chemotherapie (HIPEC) bij patienten met een maagcarcinoom en synchrone buikvliesmefasfasen en/of tumorpositief buikvocht	01/10/17	01/10/22
Van Steensel, Bas	AVL Foundation	Ontwikkeling Chromatin Genomics	01/11/14	01/11/24
Van Steensel, Bas	EEG-CEC / EU	Genomics of Chromosome Architecture and Dynamics in Single Cells	01/03/17	01/03/22
Van Steensel, Bas	EEG-CEC / EU	Principles of Chromatin Organization	01/03/12	01/03/17
Van Steensel, Bas	Stichting Oncode Institute	Oncode van Steensel	01/11/17	01/11/22
Van Steensel, Bas	University of Illinois	Additional Tool Development or Data Generation module	01/09/17	01/09/20
Van Steensel, Bas	ZonMw	Control of chromosome architecture by nuclear lamins: role in laminopathies	01/09/12	01/09/17
Van Steensel, Bas	ZonMw	Impact of chromatin context on DNA double-strand break repair kinetics, fidelity and signaling	28/01/16	28/01/20

Principal investigator	Granting agency	Title	Started	Ended / Ends
Van Tellingen, Olaf	CellProtect Australia PTY Ltd	Efficacy study of S-CP201 and radiotherapy against orthotropic intracranial tumor models	01/01/17	01/01/19
Van Tellingen, Olaf	Reneuron Limited	Efficacy study of exosomes against orthotopic intracranial tumor models	01/06/16	01/06/18
Van Tellingen, Olaf	Stop Hersentumoren	Improving chemoradiation therapy of GBM by inhibition of glioma invasion: A Proof-of-Concept study	01/12/17	01/12/18
Van Tinteren, Harm	CPCT	CPCT-02	01/07/16	01/01/18
Van Tinteren, Harm	IKNL	Overeenkomst zelfregisterend melanoomcentrum DMTR	01/05/16	01/07/17
Van Triest, Baukelien	Astellas Pharma	The radiosensitizing potential of enzalutamide (MDV3100)	01/07/14	01/01/17
Van Trommel, Nienke	AVL Foundation	Onderzoek ADP Ovariumcarcinoom	01/07/17	01/07/21
Vens, Conchita	AstraZeneca NL	Olaparib- Radiation combination studies: evaluating the potential of Olaparib to mitigate RT-induced lung toxicity and comparing this combination to conventional chemo-radiation	01/01/14	01/01/18
Verheij, Marcel	AbbVie	Utility of the combination of APG880 with radiotherapy	12/07/16	12/07/18
Verheij, Marcel	AVL Foundation	Image Guided Therapy onderzoek met de Gamma Knife	01/01/17	01/01/19
Verheij, Marcel	EEG-CEC / EU	Clinical proof of concept through a randomised phase II study: a combination of immunotherapy and stereotactic ablative radiotherapy as a curative treatment for limited metastatic lung cancer	01/01/17	01/01/23
Verheij, Marcel	EOS / voorheen Philips	Framework Research Agreement between Elekta and NKI/AvL	10/08/10	10/08/20
Voest, Emile	EIT Health eV	EiT Health Cancer Core Europe	01/01/16	01/01/18
Voest, Emile	NWO	Zwaartekracht programma 2012 (Voest)	01/03/14	01/01/22
Voest, Emile	Pink Ribbon	Prediction of treatment outcome in patients with metastatic breast cancer by in vitro drug testing using individual patient derived tumor organoids	01/04/14	01/10/18
Vrancken Peeters, Marie Jeanne	Pink Ribbon	Towards patient tailored locoregional treatment of breast cancer in patients treated with neoadjuvant systemic therapy	01/09/16	01/09/19
Wesseling, Jelle	Cancer Research UK	Precision Cancer Research UK	01/05/17	01/05/22
Wesseling, Jelle	Pink Ribbon	Low Risk Ductal carcinoma In Situ - a Randomised, Non-inferiority trial	01/04/14	01/04/18
Wesseling, Jelle	Pink Ribbon	Preventing overtreatment of microcalcification-associated in situ breast lesions by implanting more accurate prognostic biomarkers	01/04/14	01/04/18
Wessels, Lodewyk	CGC	Bioinformatica CGC	01/11/13	01/01/22
Wessels, Lodewyk	CPCT	Prospective Use of DNA-Guided Personalized Cancer Treatment	01/01/13	01/05/17
Wessels, Lodewyk	CPCT	Tumor Organoids: A new preclinical model for drug sensitivity analysis	01/05/14	01/05/18
Wessels, Lodewyk	EEG-CEC / EU	Identification and functional validation of drugable targets/pathways for triple negative breast cancer	01/04/13	01/04/18
Wessels, Lodewyk	Genmab	Identification of Biomarkers for HexaBodyR-DR5/DR5 therapy	01/09/17	01/09/19
Wessels, Lodewyk	GlaxoSmithKline	Computational analyses to unravel the mechanism of action of BET and EZH2 inhibitors and define biomarkers	01/02/16	01/02/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Wessels, Lodewyk	NWO	Zwaartekracht programma 2012 (Wessels)	01/01/13	01/01/22
Wessels, Lodewyk	Stichting Oncode Institute	Oncode Wessels	01/11/17	01/11/22
Wessels, Lodewyk	STW	Computer-aided Risk Assessment of Breast Cancer using Gene-Correlated Dynamic Contrast-enhanced MRI	01/01/13	01/04/18
Wessels, Lodewyk	ZonMw	COLOSYS: A systems approach to preventing drug resistance in colon cancer	01/02/17	01/02/20
Zwart, Wilbert	A Sister's Hope	Estrogen Receptor interactome from biopsies to guide endocrine treatment	01/01/12	01/10/17
Zwart, Wilbert	A Sister's Hope	Ex-vivo intervention of metastatic breast cancers for novel drug testing and development in endocrine therapy-resistance	01/12/17	01/12/18
Zwart, Wilbert	AVL Foundation	Integrative Androgen Receptor genomics as a readout for recurrence risk and treatment resistance of prostate cancer	01/09/17	01/09/18
Zwart, Wilbert	Movember	Integrative Androgen Receptor genomics as a readout for recurrence risk and treatment resistance of prostate cancer	01/01/13	01/10/17
Zwart, Wilbert	SFN	Startgeld Zwart	01/10/11	01/10/19
Zwart, Wilbert	Stichting LSH-TKI	Deubiquitinating enzyme inhibitors as novel drugs in Estrogen Receptor-positive breast cancer	01/03/14	01/03/18
Zwart, Wilbert	Stichting Oncode Institute	Oncode Zwart	01/11/17	01/11/22
Zwart, Wilbert	ZonMw	Proteomic and genomic evaluation of metastatic breast cancer to facilitate personalized treatment selection	01/12/16	01/12/21

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FOTOGRAFIE Martin Hogeboom, Epe | www.martinhogeboom.nl |
DRUKKER NPN drukkers, Breda | www.npndrukkers.nl |