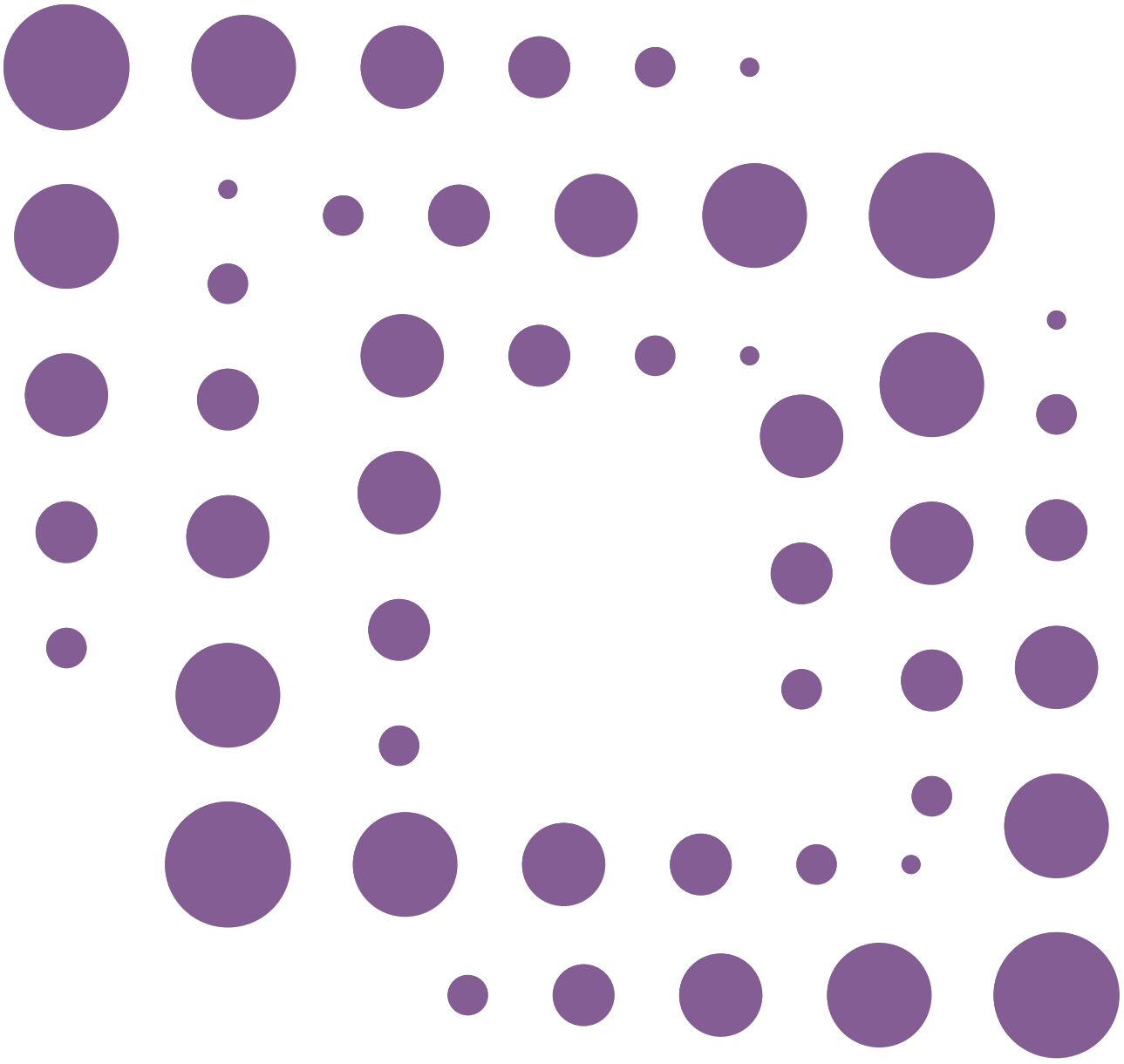


Scientific Annual Report 2018

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Contents

Netherlands Cancer Institute
Plesmanlaan 121
1066 CX Amsterdam
The Netherlands
www.nki.nl

Scientific Annual Report 2018

Director of Research
René Medema

Introduction

It is my pleasure to present the 2018 Scientific Annual Report of the Netherlands Cancer Institute, which contains an overview of our scientific discoveries and achievements. The Netherlands Cancer Institute is one of ten European Comprehensive Cancer Centers accredited by the Organisation of European Cancer Institutes (OECI), and the only Dutch center to officially carry this title.

The year 2018 started well for us, as the European Academy of Cancer Sciences had just designated our institute a Comprehensive Cancer Centre of Excellence for translational research. Cancer Research UK Cambridge and the Netherlands Cancer Institute are the first two centers in Europe to have received this designation.

The year also ended well. In November, an international committee of experts, led by Nobel Prize laureate Harold Varmus, visited the Netherlands Cancer Institute to assess the course and quality of our research institute. We are very pleased with the committee's extremely positive feedback on our research strategy, on the quality and impact of our research, and on the visionary outlook of our research leaders. The committee also applauded the increased number of active clinicians engaged in research since the 2015 review.

In 2018, we further developed our five strategic research themes, by appointing five pioneering theme leaders: Thijn Brummelkamp for Molecular Oncology, Rene Bernards for Personalized Medicine, John Haanen for Immunology and Immunotherapy, Jan-Jakob Sonke for Image-Guided Therapy and Lonneke van der Poll for the theme of Survivorship. Our scientific output has once again been both substantial and of excellent quality, thanks to all our highly talented, innovative and hard-working researchers. In 2018, our researchers published 669 scientific papers, some of which are highlighted below, and 23 of our PhD students defended their thesis at a one of the Dutch universities, in which 49 of our senior group leaders hold chairs.

In 2018, 23% of our patients were included in a clinical trial. Over the years, our hospital has built a large repository of patient data and a large collection of tumor and normal tissues. The Netherlands Cancer Institute specializes in innovative phase I/II trials that are run in close collaboration with our basic and translational research groups. This cross-fertilizing way of working has frequently led to new diagnostic tools or therapies. In 2018, the American medicines agency FDA has assigned the Breakthrough Therapy Designation to a combination therapy that has its roots in the Netherlands Cancer Institute.

To highlight the many practice-changing clinical innovations developed within the NKI that benefit cancer patients, the Board of Directors of the NKI has installed a new annual award: the Patient Impact Award. In December 2018, the MammaPrint team and the OVHIPEC team were its very first winners.

In February 2018, Oncode Institute was officially launched. This is an independent Dutch virtual institute, funded by the government and the Dutch Cancer Society, which is dedicated to understanding cancer and translating research into practice. At the start, 16 NKI group leaders were selected to establish an Oncode research group. Later in the year, two more NKI researchers joined Oncode.

As a comprehensive cancer center, we take our societal responsibility very seriously. In February, our institute was the first hospital in the Netherlands to lend its support to the criminal proceedings brought against the tobacco industry for deliberately damaging public health and for forgery. Unfortunately, the public prosecutor did not proceed with the case.

To conclude on a more positive note, 2600 enthusiastic visitors attended our Open Doors Day on the 6th of October, to take a look in our labs and our hospital and learn more about how we try to unravel and fight cancer.

Again, we are very grateful to the Dutch Ministry of Health, Welfare and Sport and to the Dutch Cancer Society (KWF) for their generous institutional funding (figure 1). Our funding is still in large part coming from external project grants, donations and short-term research agreements with third parties. Our principal investigators have continued to be very competitive in obtaining this type of funding. However, the relatively low ratio of core funding for our institute provides us with big challenges to maintain the underlying infrastructure.

HIGHLIGHTS

It is impossible to provide a complete overview of the total impact generated by our institute in 2018. 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 here present just a few 2018 highlights of our five research themes.

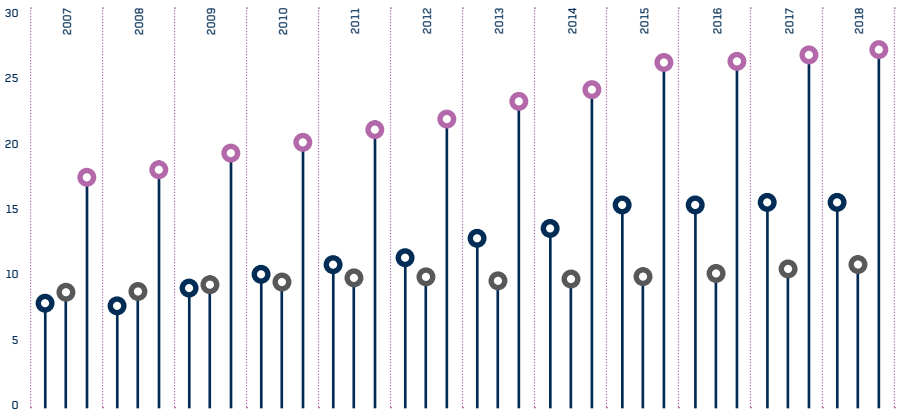
MOLECULAR ONCOLOGY

How cancer cells help each other migrate

Cancer cells influence each other's metastatic behavior by exchanging biomolecules through extracellular vesicles (EVs). The group of Jacco van Rheenen characterized the content of these vesicles shed *in vivo* by two clones of melanoma tumors with distinct metastatic potential. Using intravital microscopy, they showed that cells from these distinct clones phenocopy their migratory behavior through EV exchange. They then showed that EVs which are shed into the tumor microenvironment, contain thousands of different proteins and RNAs, and many of these biomolecules are from interconnected signaling networks involved in cellular processes such as migration (*EMBO*, August 2018).

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 2007-2018 IN MILLION EUROS.



* EXCLUDED ARE THE REIMBURSEMENTS FOR INTEREST AND DEPRECIATION OF BUILDINGS

Kinetics and fidelity of repair of DNA double-stranded breaks

Eva Brinkman from the lab of Bas van Steensel developed a strategy to measure the kinetics of DSB repair for single loci in human cells. Using quantitative modeling of repaired DNA she could resolve the kinetics and fidelity of repair at specific sites in the human genome. Her data showed that repair of the DSBs tends to be error prone, due to classical and microhomology-mediated end joining pathways contribute to the erroneous repair. Estimation of their individual rate constants indicates that the balance between these two pathways changes over time and can be altered by additional ionizing radiation (*Mol Cell*, August 2018).

New rationale for p53 loss in cancer cells

Bente Benedict and Tanja van Harn from the Te Riele lab showed that G_1/S checkpoint failure in mitogen-starved cells lacking the retinoblastoma proteins pRB, p107 and p130, causes severe replication stress manifested by slow fork progression, reduced origin firing, DNA breakage and proliferative arrest. Unexpectedly, disruption of *Tp53* or its downstream target $p21^{CIP1}$ restored origin firing, reduced DNA breakage and allowed mitogen-independent proliferation. Alleviation of replication-stress-induced DNA damage may thus explain the frequent co-occurrence of pRB and p53 pathway disruption in cancer (*Elife,* October 2018)

ERC Consolidator Grant for Benjamin Rowland

How are the meters of DNA arranged in our cell nucleus such that all individual genes can do their job? Chromosome biologist Benjamin Rowland started a new research project funded by the European Research Council (ERC) to find out how the minuscule cohesin ring ensures that the DNA is structured in the right way.

PRECISION MEDICINE

Exploiting drug resistance

Postdoc Liqin Wang et al. from Rene Bernards' lab searched for acquired vulnerabilities of cancer cells when *BRAF* mutant melanomas become resistant to the combination of BRAF and MEK inhibitors. They found that drug resistance is associated with increased levels of reactive oxygen species (ROS). Subsequent treatment of BRAF-inhibitor resistant melanoma cells with the histone deacetylase inhibitor vorinostat leads to a lethal increase in the already elevated ROS levels in drug-resistant cells. This causes selective apoptotic death of only the drug-resistant tumor cells. Treatment of BRAF inhibitor-resistant melanoma with vorinostat in mice resulted in dramatic tumor regression. In collaboration with Jos Beijnen and Jan Schellens a clinical study was performed, in which patients with advanced BRAF + MEK inhibitor-resistant melanoma were treated with vorinostat. Preliminary results indicate that vorinostat can indeed selectively ablate BRAF inhibitor-resistant tumor cells, providing clinical proof of concept for a novel therapy identified in the lab (*Cell*, May 2018).

Targeting tumor heterogeneity

Julia Boshuizen in the laboratory of Daniel Peeper developed, for the first time, an approach to target different cancer cell groups within tumors, based on their distinct treatment susceptibilities. She showed that such a rational combinatorial treatment, comprising an AXL antibody-drug conjugate with BRAF + MEK inhibitors, resulted in more durable responses in patient-derived melanomas (*Nature Medicine*, January 2018).

New insight into resistance to PARP inhibitors

PARP inhibitors have recently entered the clinic for the treatment of homologous recombination-deficient cancers. Despite their success, drug resistance is a clinical hurdle and the mechanisms of resistance are poorly understood. By combining genetic screens with multi-omics analysis of matched PARPi-sensitive and PARP-resistant BRCA2-mutated mouse mammary tumors, the Jos Jonkers group identified loss of PAR glycohydrolase (PARG) as a major resistance mechanism. Importantly, PARG inactivation exposes vulnerabilities that can be exploited therapeutically (*Cancer Cell*, June 2018).

Triple therapy prioritized

The American medicines agency FDA assigned the Breakthrough Therapy Designation to a combination therapy that has its roots in the Netherlands Cancer Institute, where René Bernards and colleagues discovered why colon cancer cells are resistant to BRAF inhibitors. This knowledge lies at the root of an international clinical study with promising interim results, based upon which the FDA announced to speed up the approval process of the used drug combination.

ERC Advanced Grant for Rene Bernards

Rene Bernards received an ERC Advanced Grant of 2.5 million euros for his research into a new approach to the treatment of cancer. This is based on a "one-two punch" sequential strategy in which a first drug is used to induce a state of senescence, a stable proliferation arrest, in the cancer cells. The second drug then selectively kills the senescent cancer cells. Bernards will identify drugs that can induce senescence in cancer cells and search for drugs that kill senescent cancer cells. These drugs will then be validated experimentally in pre-clinical cancer models to test their efficacy.

IMMUNOTHERAPY

Improving cisplatin response of breast cancer by targeting macrophages

Macrophages are frequently infiltrating human cancers, and their presence is associated with poor chemotherapy response. Camilla Salvagno in the laboratory of Karin de Visser revealed that targeting macrophages by CSF-1 receptor blockade enhances the anti-cancer efficacy of platinum-based chemotherapeutics in a transgenic mouse model for breast cancer. She mechanistically uncovered that CSF-1R inhibition stimulates intratumoral type I interferon signaling, which is essential for the therapeutic synergy between cisplatin and CSF-1R blockade. She also discovered that further elimination of immunosuppressive neutrophils was required to engage an efficacious anti-tumor immune response (*Nature Cell Biology*, in press 2018).

How CD4 T cells help killer T cells

The group of Jannie Borst published an authoritative review on how CD4 T cell help the cytotoxic T cell response to cancer, and discovered (with collaborators at Sanquin) a unique constellation of signaling pathways in regulatory CD4 T cells (*Nature Reviews Immunology*, July 2018)

'Exhausted' T cells are not so exhausted after all

Researchers in the Ton Schumacher lab showed in a number of studies that "exhausted" or dysfunctional T cells actually form a highly active and dynamic group within the tumor. These cells, which are unable to kill tumor cells, do have the capacity to multiply. Their presence in the tumor helps the immune system better recognize tumor cells, which is an essential prerequisite for a good response to immunotherapy (*Nature*, June 2018; *Cell*, December 2018).

Training T cells in tumor organoids

Tumor organoids can now be used as a platform for studying the interaction between immune cells and tumor cells outside the patient's body. Krijn Dijkstra and Chiara Cattaneo from the group of Emile Voest have shown that it is possible to obtain T cells from the bloodstream of a patient and expand them in a dish together with a tumor organoid from the same patient. The immune cells develop the ability to kill the tumor cells and reduce organoid size, while leaving healthy control tissue of the same patient untouched (*Cell*, August 2018).

IMAGE-GUIDED INTERVENTIONS

First patient treated with MR-Linac

In September 2018, the NKI treated its first patient on the Elekta Unity MR-Linac system, a radiotherapy device in which an MRI scanner is integrated. This makes the Netherlands Cancer Institute the third hospital in the Netherlands to work with an MRI-guided radiation technique. Thanks to the integrated MRI scanner in the MR-Linac, MRI images can be made before and during radiation so that the tumor remains clearly visible. The image quality of the device is high. As a result, radiation can be more accurately focused on the tumor, resulting in less damage to the surrounding healthy tissue. This means that the radiation dose can be significantly increased or that patients less often need radiotherapy.

Prostate cancer: boosted EBRT therapy safe and feasible

Prostate cancer is the most frequently diagnosed cancer in men and the second most common cause of death due to cancer. External beam radiotherapy (EBRT) is the therapy of choice in the treatment of high-risk disease but there is a significant chance of local relapse.
The FLAME trial, a multi-center phase III trial randomized between 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. Toxicity analysis showed that the focal boost did not result in an increase in GU and GI toxicity when compared to the standard treatment.

SURVIVORSHIP

Second malignancies after cisplatin

Harmke Groot and Michael Schaapveld in the group of Flora van Leeuwen studied the second malignancy risk in a large Dutch cohort of testicular cancer survivors (n=5,848), treated in the cisplatin era (1976-2006). They showed, for the first time, that cisplatin is associated with a dose-dependent three- to five-fold increased risk of colorectal cancer and other gastrointestinal cancers. Cisplatin was also associated with increased risks of cancers of the lung, thyroid and urinary bladder (*Journal of Clinical Oncology*, 2018).

Online therapy alleviates menopausal symptoms

Vera Atema in the Neil Aaronson group demonstrated in a randomized controlled trial that an internet-based cognitive behavioral therapy (CBT) program, in both a self-managed and a guided form, significantly reduces cardinal menopausal symptoms in women with breast cancer who have experienced treatment-induced menopause. Compared with a usual care control group, the CBT groups showed significant clinical improvement over time in the perceived impact of hot flushes and night sweats and in the frequency of hot flushes, and in sleep quality. Such an internet-based intervention offers a convenient, accessible and relatively inexpensive means of addressing troublesome treatment side effects (*Journal of Clinical Oncology*, 2019).

Genetic susceptibility to radiation-induced breast cancer

Hodgkin lymphoma (HL) survivors have a strongly increased risk of breast cancer after chest radiotherapy (RT). Annemieke Opstal-van Winden in the Flora van Leeuwen group now demonstrated that genetic susceptibility contributes to radiation-induced breast cancer. A BC-PRS, consisting of 77 SNPs previously associated with breast cancer in the general population, also substantially increases the risk of breast cancer in chest-irradiated HL survivors. In addition, the researchers identified 9 SNPs interacting with chest RT and the risk of breast cancer after HL and showed a statistically significant association of a PRS composed of these interaction SNPs with breast cancer risk after chest RT for HL. These results imply that the absolute risk of breast cancer due to irradiation would be even larger among women at high genetic risk, which is relevant for clinical risk prediction (*Blood*, 2018).

QUALITY OF RESEARCH

The quality of our research can be monitored in several ways. First of all, objective bibliometric parameters such as citations and impact of scientific articles published by NKI staff demonstrate that our scientific productivity has been steadily increasing over time (table 1). It is 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 frequent invitations of our staff members to present at international meetings and in the awards and grants that they obtain. We score high on all these accounts. See the 'honors and appointments' section for the most prestigious grants and awards our researchers have received in the past year. The NKI is also part 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 does not award university degrees, but many of our staff members hold part-time chairs at Dutch universities, which allows them to award PhD degrees to graduate students who received their training at the Netherlands Cancer Institute. Currently, 49 staff members have professorships at one of the Dutch universities.
In 2018, our researchers and clinicians won several prestigious awards. Epidemiologist Floor van Leeuwen was awarded the 17th Rosalind E. Franklin Award for Women in Science by the American National Cancer Institute in Maryland. Biologist Rene Bernards was elected Fellow of the American Association for Cancer Research. Junior group leader Tineke Lenstra was awarded the NVBMB-prize 2018 by the Netherlands Society for Biochemistry and Molecular Biology, for her work on DNA transcription. This is a prize for highly talented young researchers. PhD student Lindy Visser received the PALGA Award for her research on DCIS. PALGA is the national network and registry of pathology in the Netherlands. Clinician Wanda de Kanter won the GLCC Journalism Award 2018 for her anti-tobacco campaign in the media. Junior group leaders Leila Akkari and Tineke Lenstra have been selected to join Oncode Institute as junior investigators. Together with five other

TABLE 1
SHORT TERM CITATIONS AND IMPACT OF SCIENTIFIC ARTICLES PUBLISHED BY THE NETHERLANDS CANCER INSTITUTE RESEARCH STAFF 2004-2018

PUBLICATION YEAR	PUBLICATIONS*	CITATIONS	CITATIONS/ PUBLICATIONS	IMPACT
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	793	15087	19,0	5344
2017	740			5927
2018	780**			6090**

* 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 MARCH 2019. 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

1. Dikken JL et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC Cancer 2011;11:329

2. Trip AK et al. Preoperative chemoradiotherapy in locally advanced gastric cancer, a phase I/II feasibility and efficacy study. Radiother Oncol. 2014;112:284-8

3. Trip AK et al. IMRT limits nephrotoxicity after chemoradiotherapy for gastric cancer. Radiother Oncol. 2014;112:289-94

4. Van de Vaart PJ et al. Intraperiton eal cisplatin with regional hyperthermia in advanced ovarian cancer: pharmacokinetics and cisplatin-DNA adduct formation in patients and ovarian cancer cell lines. Eur J Cancer 1998;34:148-154

5. Verwaal VJ et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737-3743

6. Van Driel WJ et al. The role of hyperthermic intraperitoneal intraoperative chemotherapy in ovarian cancer. Curr Treat Options Oncol 2015;16:14

7. Duijts SFA et al. Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: Results of a randomized controlled multicenter trial. J Clin Oncol 2012;30:4124-33

8. Mewes JC et al. Cost-effectiveness of cognitive behavioral therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients. J Cancer Surviv 2015;9:126-35

9. Wevers MR et al. Impact of rapid genetic counselling and testing on the decision to undergo immediate or delayed prophylactic mastectomy in newly diagnosed breast cancer patients: Findings from a randomized controlled trial. Br J Cancer 2014;110:1081-7

10. Van der Leij F et al. Target volume delineation in external beam partial breast irradiation: less inter-observer variation with preoperative- compared to postoperative delineation. Radiother Oncol. 2014;110:467-70

11. Rodenhuis S et al. Efficacy of high-dose alkylating chemotherapy in HER2/neu-negative breast cancer. Ann Oncol. 2006;17:588-96

12. Vollebergh MA et al. An aCGH classifier derived from BRCA1-mutated breast cancer and benefit of high-dose platinum-based chemotherapy in HER2-negative breast cancer patients. Ann Oncol. 2011;22:1561-70

13. Vollebergh MA et al. Genomic patterns resembling BRCA1- and BRCA2-mutated breast cancers predict benefit of intensified carboplatin-based chemotherapy. Breast Cancer Res. 2014;16:R47

14. Van Waart H et al. Effect of low intensity physical activity and high intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue and chemotherapy completion rates: Results of the PACES randomized clinical trial. J Clin Oncol. 2015;33:1918-27

15. Van Elmpt W et al. The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. Radiother Oncol. 2012;104:67-71

16. De Vreeze RS et al. Effectiveness of radiotherapy in myxoid sarcomas is associated with a dense vascular pattern. Int J Radiat Oncol Biol Phys. 2008;72:1480-7

17. Verheij M et al. Novel therapeutics in combination with radiotherapy to improve cancer treatment: Rationale, mechanisms of action and clinical perspective. Drug Resist Updat 2010;13:29-43

18. Heukelom J et al. Adaptive and innovative Radiation Treatment FOR improving Cancer treatment outcomE (ARTFORCE); a randomized controlled phase II trial for individualized treatment of head and neck cancer. BMC Cancer 2013;13:84

19. Peulen H et al. Mid-ventilation based PTV margins in Stereotactic Body radiotherapy (SBRT): a clinical evaluation. Radiother Oncol. 2014;110:511-6

20. Eijzenga W et al. Effect of routine assessment of specific psychosocial problems on personalized communication, referrals and distress levels in cancer genetic counseling practice: A randomized controlled trial. J Clin Oncol. 2014;32:2998-3004

21. Eijzenga W et al. Routine assessment of psychosocial problems after cancer genetic counseling: Results from a randomized controlled trial. Clin Genetics. 2015;87:419-27

22. Gomez-Eerland R et al. Manufacture of gene-modified human T-cells with a memory stem/central memory phenotype. Hum GeneTher Methods. 2014;25:277-87

23. Prahallad A et al. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. Nature 2012;483:100-3

24. Van Kesteren Z et al. A practical technique to avoid the hippocampus in prophylactic cranial irradiation for lung cancer. Radiother Oncol. 2012;102:225-7

25. Grills IS et al. A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. J Thorac Oncol. 2012;7:1382-93

26. Spliethoff JW et al. Monitoring of tumor response to Cisplatin using optical spectroscopy. Transl. Oncol. 2014;7:230-9

27. Buckle et al. Tumor bracketing and safety margin estimation using multimodal marker seeds: a proof of concept. J Biomed Opt. 2010;15:056021

28. Sun C et al. Intrinsic resistance to MEK inhibition in KRAS mutant lung and colon cancer through transcriptional induction of ERBB3. Cell Rep. 2014;7:86-93

29. Rottenberg S et al. Impact of intertumoral heterogeneity on predicting chemotherapy response of BRCA1-deficient mammary tumors. Cancer Res 2012;72:2350-2361

30. Wessels LF et al. Molecular classification of breast carcinomas by comparative genomic hybridization: a specific somatic genetic profile for BRCA1 tumors. Cancer Res 2002;62:7110-7117

31. Van Beers EH et al. Comparative genomic hybridization profiles in human BRCA1 and BRCA2 breast tumors highlight differential sets of genomic aberrations. Cancer Res 2005;65:822-827

32. Joosse SA et al. Prediction of BRCA1-association in hereditary non-BRCA1/2 breast carcinomas with array-CGH. Breast Cancer Res Treat 2009;116:479-489

33. Lips EH et al. Quantitative copy number analysis by Multiplex Ligation-dependent Probe Amplification (MLPA) of BRCA1-associated breast cancer regions identifies BRCAness. Breast Cancer Res 2011;13:R107

34. Van der Poel et al. Intraoperative laparoscopic fluorescence guidance to the sentinel lymph node in prostate cancer: clinical proof of concept of an integrated functional imaging approach using a multimodal tracer. Eur Urol. 2011;60:826-33

35. KleinJan GH et al. Optimisation of fluorescence guidance during robot-assisted laparoscopic sentinel node biopsy for prostate cancer. Eur Urol. 2014;66:991-8

36. Kvistborg P et al. TIL therapy broadens the tumor-reactive CD8(+) T cell compartment in melanoma patients. Oncoimmunology 1:409-418

37. Rottenberg S et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc. Natl. Acad. Sci. USA 2008;105:17079-84

38. Fong PC et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med. 2009;361:123-34

39. Oonk AM et al. Clinical correlates of 'BRCAness' in triple-negative breast cancer of patients receiving adjuvant chemotherapy. Ann Oncol. 2012;23:2301-5

40. Beelen K et al. PIK3CA mutations, phosphatase and tensin homolog, human epidermal growth factor receptor 2, and insulin-like growth factor 1 receptor and adjuvant tamoxifen resistance in postmenopausal breast cancer patients. Breast Cancer Res. 2014;16:R13

41. Beelen K et al. Phosphorylated p-70S6K predicts tamoxifen resistance in postmenopausal breast cancer patients randomized between adjuvant tamoxifen versus no systemic treatment. Breast Cancer Res. 2014;16:R6

42. Kenter GG et al. Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. N Engl J Med. 2009;361(19):1838-47

43. Bins AD et al. A rapid and potent DNA vaccination strategy defined by in vivo monitoring of antigen expression. Nat Med. 2005;11:899-904

44. Nachabé R et al. Diagnosis of breast cancer using difuse optical spectroscopy from 500 to 1600 nm: comparison of classification methods. J Biomed Opt. 2011;16:087010

45. Larkin J et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373:23-34

46. Bosch TM et al. Rapid detection of the DPYD IVS14+1G→A mutation for screening patients to prevent fluorouracil-related toxicity. Mol Diagn Ther. 2007;11:105-8

47. Deenen MJ et al. Upfront Genotyping of DPYD*2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis. J Clin Oncol. 2016;34:227-34

48. Brouwer OR et al. Lymphoscintigraphy and SPECT/CT in multicentric and multifocal breast cancer: does each tumour have a separate drainage pattern? Results of a Dutch multicentre study (MULTISENT) Eur J Nucl Med Mol Imaging. 2012;39:1137-43

49. Collarino A et al. The use of SPECT/CT for anatomical mapping of lymphatic drainage in vulvar cancer: possible implications for the extent of inguinal lymph node dissection. Eur J Nucl Med Mol Imaging. 2015;42:2064-71

50. Van den Berg NS et al. Multimodal surgical guidance during sentinel node biopsy for melanoma: combined gamma tracing and fluorescence imaging of the sentinel node through use of the Hybrid Tracer indocyanine green-(99m)Tc-nanocolloid. Radiology. 2015;275:521-9

51. Brouwer OR et al. A hybrid radioactive and fluorescent tracer for sentinel node biopsy in penile carcinoma as a potential replacement for blue dye. Eur Urol. 2014;65:600-9

52. Kraaijenga SA et al. Effects of Strengthening Exercises on Swallowing Musculature and Function in Senior Healthy Subjects: a Prospective Effectiveness and Feasibility Study. Dysphagia. 2015;30:392-403

53. Weeber F et al. Preserved genetic diversity in organoids cultured from biopsies of human colorectal cancer metastases. Proc Natl Acad Sci U S A. 2015;112:13308-11

54. Schermers et al. Feasibility of magnetic marker localization for non-palpable breast cancer. Breast 2017;33:50-56

55. Haas RL. Present and future of radiotherapy before and after surgery for sarcoma patients. Eur J Surg Oncol. 2014;40:1595-7

56. Haas RL et al. Preoperative radiotherapy for extremity soft tissue sarcoma; past, present and future perspectives on dose fractionation regimens and combined modality strategies. Radiother Oncol. 2016;119:14-21

57. Hodzic J et al. A cell-based high-throughput screening assay for radiation susceptibility using automated cell counting. Radiat Oncol. 2015;10:55

58. Moes et al. Pharmaceutical development and preliminary clinical testing of an oral solid dispersion formulation of docetaxel (ModraDoc001) Int J Pharm. 2011;28;420(2):244-50

59. Lips IM et al. Single blind randomized phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial); study protocol for a randomized controlled trial. Trials 2011;12:55

60. Sparidans RW et al. Liquid chromatography-tandem mass spectrometric assay for therapeutic drug monitoring of the tyrosine kinase inhibitor pazopanib in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci. 2012;905:137-40

talented female scientists, they were selected out of 56 applicants, based on their track record, research focus and potential to contribute to the mission of Oncode.

Several NKI researchers were awarded prestigious research grants in 2018. In December, the Dutch Cancer Society (KWF) awarded a subsidy of 2.8 million euros to professor Winette van der Graaf and dr. Olga Husson for research into the treatment and counselling of young adults with cancer. In total, 17 new research projects received financial support of the Dutch Cancer Society in 2018. Professors Rene Bernards and Emile Voest received a one million dollar grant to join the new Pancreatic Cancer Collective, a strategic partnership of the Lustgarten Foundation and Stand Up To Cancer (SU2C). Rene Bernards received an ERC Advanced Grant for research into drug resistance and Benjamin Rowland received an ERC consolidator grant. Julia Houthuijzen and Ineke Brouwer both received a VENI grant from the Dutch Society for Scientific Research (NWO), and Faria da Silva and Abdelghani Mazouzi were both awarded an EMBO fellowship.

Next to the special grants mentioned above several other NKI postdocs and group leaders have received several 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.

OUTLOOK AND ACKNOWLEDGEMENTS

For the last decades, our Institute has been at the international forefront of cancer research and innovative cancer treatments. It has been able to maintain that position, despite the difficult economic situation of the last few years. We have been very successful in obtaining external research grants 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 genetic and/or immunological fingerprinting of the tumor is extensively used in making clinical decisions of how to treat the individual patient. Success in this area will critically depend on a close collaboration between basic and clinical research and 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 its 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 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 who supported us. Since its foundation 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) for their institutional support and the Ministry of Health, Welfare and Sport, which provides a substantial core grant to our Institute and has provided the funds to renovate our research facilities. I also want to thank the many individuals that provide us with financial, moral and practical support. 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.

René Medema
Director of Research

Board members

Chairman of Board of Governors
T de Swaan

Patron
Her Royal Highness Princess Beatrix of the Netherlands

Board of Directors

RH Medema
Chairman and Director of Research

EE Voest
Medical Director

M van der Meer
Director of Organisation, Operations and Management

Scientific Advisory Council

RH Medema
Chairman

LFA Wessels
Secretary

ACJ van Akkooi

TR Brummelkamp

HGAM van Luenen

MK Schmidt

EE Voest

Board of Governors

T de Swaan
President

EH Swaab
Vice-president

GH Blijham

LJ Hijmans van den Bergh

JHJ Hoeijmakers

AM Jongerius

JMJM van Krieken

International Scientific Advisory Board

A Ashworth
Director of the UCSF Helen Diller Family Comprehensive Cancer Center, at the University of California, San Francisco

T de Lange
Leon Hess Professor, The Rockefeller University, New York, USA

SM Gasser
Director Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland

SP Jackson
Head of Cancer Research UK Laboratories, The Gurdon Institute, University of Cambridge, United Kingdom

A Musacchio
Honorary Professor, Max-Planck Institute of Molecular Physiology, Dortmund, Germany

R Nusse
Professor of Developmental Biology, Stanford University, Stanford, USA

HL Ploegh
Professor of Immunology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

SN Powell
Chairman, Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, USA

IF Tannock
Daniel Bergsagel Professor of Medical Oncology, Princess Margaret Hospital and University of Toronto, Toronto, Canada

K Vousden
Professor at The Francis Crick Institute, London, UK

National Scientific Advisory Board

DD Breimer
Professor of Pharmacology, Leiden University

JL Bos
Professor of Molecular Cancer Research, Utrecht University

EGE De Vries
Professor of Medical Oncology, University of Groningen

JHF Falkenburg
Professor of Experimental Hematology, Leiden University

CG Figdor
Professor of Experimental Immunology, Radboud University Nijmegen

P Lambin
Professor of Radiation Oncology, Maastricht University

A van Oudenaarden
Professor of Quantitative Biology of Gene Regulation, Utrecht University

CJH van de Velde
Professor of Surgical Oncology, Leiden University

A

Neil Aaronson

Group leader
Division Psychosocial Research and Epidemiology

Neil Aaronson PhD Senior group leader
Jacobien Kieffer MSc Senior statistical analyst
Marieke van Leeuwen PhD Post-doc
Carla Agasi-Idenburg MSc PhD student
Vera Atema MSc PhD student
Lisanne Hummel MSc PhD student
Marie-Anne van Stam MSc PhD student
Marieke ten Tusscher MSc Project manager
Evalien Veldhuijzen MSc Project manager

Selected publications

Atema V, van Leeuwen M, Kieffer JM, Oldenburg HSA, van Beurden M, Gerritsma MA, Kuenen MA, Plaisier PW, Lopes Cardozo AMF, van Riet YEA, Heuff G, Rijna H, van der Meij S, Noorda EM, Timmers GJ, Vrouenraets BC, Bollen M, van der Veen H, Bijker N, Hunter MS, Aaronson NK. Efficacy of Internet-Based Cognitive Behavioral Therapy for Treatment-Induced Menopausal Symptoms in Breast Cancer Survivors: Results of a Randomized Controlled Trial. J Clin Oncol (in press)

Hummel SB, van Lankveld JJDM, Oldenburg HSA, Hahn DEE, Kieffer JM, Gerritsma MA, Kuenen MA, Bijker N, Borgstein PJ, Heuff G, Cardozo AMFL, Plaisier PW, Rijna H, van der Meij 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 Ther 2018;44(5):485-496

Van Stam MA, Aaronson NK, et al. Patient-reported outcomes following treatment of localised prostater cancer and their association with regret about treatment choices. Eur Urol Oncol 2018 (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.

Efficacy of internet-based cognitive behavioral therapy (iCBT) on treatment-Induced menopausal symptoms in breast cancer survivors

In this randomized, controlled trial, we randomly assigned 254 BC survivors to a therapist guided or a self-managed iCBT group or a waiting-list control group. Compared with the control group, both iCBT groups reported a significant decrease in the perceived impact of HF/NS ($p<.001$, ES=.63 and.56) and improvement in sleep quality ($p<.001$, ES=.57 and .41). The guided group also reported significant improvement in overall levels of menopausal symptoms ($p=.003$, ES=.33), and night sweats frequency ($p<.0012$, ES=.64). At longer-term (6-month) follow-up, the effects remained significant with smaller ES, and also included significantly reduced frequency of hot flushes. iCBT, with or without therapist support, has salutary effects on the perceived impact and frequency of HF/NS, overall levels of menopausal symptoms and sleep quality.

Sustained effects of Internet-based cognitive behavioral therapy (iCBT) on sexual functioning of breast cancer survivors

We evaluated the long-term efficacy of iCBT) for sexual dysfunctions in 84 breast cancer survivors (BCS). The positive immediate post-intervention effects of the intervention observed in our randomised controlled trial on overall sexual functioning, sexual desire, sexual arousal, vaginal lubrication, discomfort during sex, sexual distress and body image at immediate post-treatment were maintained at 3- and 9-month follow-up. Although sexual pleasure decreased during follow-up, it did not return to baseline levels. Our findings provide evidence that iCBT has a sustained, positive effect on sexual functioning and body image of BCS with a sexual dysfunction.

Patient-reported outcomes following treatment of localized prostate cancer and their association with regret about treatment choices

In this prospective, observational study we documented: (1) differences in physical and psychosocial patient-reported outcomes (PROs) following radical prostatectomy, external beam radiotherapy, brachytherapy, and active surveillance; and (2) how these PROs and other factors are associated with treatment decision regret. The sample included 434 men who completed validated PRO measures at baseline (pre-treatment) and 3, 6 and 12 months post-treatment. At one year follow-up, those men who had received: (1) radical prostatectomy reported significantly ($p<0.01$) more urinary incontinence, worse sexual function, more hormonal/masculinity-related symptoms, and less emotional distress; (2) external beam radiotherapy reported significantly worse sexual function, more hormonal/masculinity-related symptoms, and more physical distress; and (3) brachytherapy reported significantly more urinary obstruction and irritation symptoms, compared to patients under active surveillance. Decision regret was not significantly different across treatment groups. At one year follow-up 23% of the patients reported clinically relevant decision regret, which was associated with hormonal-related symptoms, educational level, and positive surgical margins.

Reuven Agami

Division head, group leader Division of Oncogenomics

Reuven Agami PhD Group leader
Gözde Korkmaz PhD Senior post-doc
Fabricio Loayza Puch PhD Senior post-doc
Alejandro Piñeiro Ugalde PhD Post-doc
Julien Champagne PhD Post-doc
Yuval Malka PhD Post-doc
Abhijeet Pataskar PhD Post-doc
Ruiqi Han PhD student
Itamar Kozlovski PhD student
Li Li PhD student
Rui Lopez PhD student
Behzad Mombeini PhD student
Jane Sun PhD student
Remco Nagel PhD Technical staff

Selected publications

Han R, Li L, Ugalde AP, Tal A, Manber Z, Barbera EP, Chiara V, Elkon R and Agami R. Functional CRISPR screen identifies AP1-associated enhancer regulating FOXF1 to modulate oncogene-induced senescence. Genome Biol 2018;19(1):118

Li L, van Breugel P, Loayza-Puch F, Ugalde AP, Korkmaz G, Messika-Gold N, Han R, Lopes R, Barbera EP, Teunissen H, de Wit E, Soares R, Nielsen B, Holmstrom K, Martinez-Herrera D, Huarte M, Louloupi A, Drost J, Elkon R and Agami R. LncRNA-OIS1 regulates DPP4 activation to modulate senescence induced by RAS. Nucleic Acids Res 2018:46(8):4213-4227

Lopes R, Korkmaz G, Revilla S, van Vliet R, Nagel R, Custers L, Kim Y, van Breugel P, Zwart W, Moumbeini B, Manber Z, Elkon R, Agami R. CUEDC1 is a primary target of ERalpha essential for the growth of breast cancer cells. Cancer Lett. 2018;436:87-95

Uncovering novel vulnerabilities of cancer

Introduction

Our main research objective is to identify novel cellular vulnerabilities that can be exploited for cancer therapies. For this purpose, we developed, and are still developing, innovative genomic and genetic tools. Key targets are non-coding RNAs, mRNA translation, and regulatory DNA elements such as enhancers and chromatin domains. In particular, we employ novel and 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 2018:

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

Treating cancer with amino acid deprivation schemes showed limited success so far. Only in the case of acute lymphoblastic leukemia a combined treatment of L-Asparaginase with chemotherapy increased patient cure to ~95%. Attempts to broaden this treatment to solid cancer have failed up to now. In 2016, we have developed differential ribosome profiling technology (Diricore) to uncover treatment-induced cellular amino acid shortages. In 2018, we used this technology, in combination with a genome-wide CRISPR-Cas9 functional genetic screen, to uncover resistant mechanisms to L-Asparaginase treatment mechanisms. Blocking these resistant mechanisms leads to sensitization of solid tumors to L-Asparaginase treatment.

(B) Functional genetic screens of regulatory DNA elements

Functional characterization of non-coding elements in the human genome is a major genomic challenge and the maturation of genome-editing technologies is revolutionizing our ability to achieve this task. In 2016 we initiated a CRISPR-Cas9-based genetic approach to functionally annotate tumor suppressor and oncogenic regulatory DNA elements. In 2018 we continue to use this technology to identify key players in cellular senescence and ER-alpha driven breast cancers.
Oncogene-induced senescence (OIS), a cellular state of irreversible proliferation arrest that is enforced following excessive oncogenic activity, is a major barrier against cancer transformation; therefore, bypassing OIS is a critical step in tumorigenesis. By applying genome-wide profiling of enhancers we identified the transcription factor AP-1 as a major regulator of the transcriptional program induced by OIS. Using CRISPR-Cas9 screening targeting senescence-induced AP-1-enhancers, we identified a novel genetic cascade mediated by AP-1 and FOXF1 genes that controls OIS.
Breast cancer is the most prevalent type of malignancy in women with ~1.7 million new cases diagnosed annually, of which the majority express ER-alpha, a ligand-dependent transcription factor. Genome-wide chromatin binding maps suggest that ERα may control the expression of thousands of genes, posing a great challenge in identifying functional targets. Using our CRISPR-Cas9 functional genetic screening approach we characterized novel key regulators of ER-alpha mitogenic pathway.

(C) A role for long non-coding RNAs in cellular senescence

Long non-coding RNAs (lncRNAs) are transcripts longer than 200 nt without a protein-coding capacity. Functional studies showed that deregulated lncRNA expression promote tumorigenesis and metastasis and that lncRNAs may exhibit tumor-suppressive and oncogenic function. We used a loss of function genetic screen targeting the differentially expressed lncRNAs in OIS, and identified lncRNA-OIS1 as a lncRNA required for OIS. Detailed studies indicated the associated mechanism of action. We showed that lncRNA-OIS1 links oncogenic induction and senescence with optimal induction of the tumor suppressor DPP4. This pathway may be important for cancer as well as aging.

A

Leila Akkari

Group leader
Division Immunology

Leila Akkari PhD Group leader
Luuk van Hooren PhD Post-doc
Serena Vegna PhD Post-doc
Christel Ramirez MSc PhD student
Jeremy Tessier MSc PhD student
Shanna Handgraaf MSc Technical staff

Macrophage dynamics in cancer progression and response to treatment

Our laboratory is interested in identifying vulnerabilities in the heterotypic communication between cancer cell and immune cell that can be targeted therapeutically. We study the microenvironment-mediated mechanisms of tumor maintenance, progression and resistance to therapeutic intervention.

Unraveling the function of myeloid cells during glioma therapeutic response to standard of care therapy

A main focus in our group is to study the role of tumor infiltrating bone marrow derived macrophages (BMDM) and tissue resident microglia (MG) in glioblastoma multiforme using multiple murine models of the disease. The genetically engineered mouse models we employ develop 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 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. We identified transcriptional changes in BMDM/MG macrophage subpopulations during the course of treatment, that we additionally validated using proteomics analyses of bulk gliomas pre and post treatment. These changes include acquisition of a neural degeneration phenotype, rewiring brain macrophages to support glioma relapse post treatment. Our current work now focuses on identifying which signaling pathway activation underlie these changes, in order to target them pharmacologically and genetically and enhance the effect of radio/chemotherapy in aggressive gliomas.

Optimizing the combination between radio- and immunotherapy in glioblastoma

Incorporating anti-PD1 T-cell immunotherapy (IT) to the current standard of care treatment in glioblastoma has not yielded promising results in clinical trials. The lack of insights into the optimal timing and sequence of IT in relation to radiotherapy (RT) may be the cause of these failed clinical trials so far. In collaboration with Dr Gerben Borst, we are investigating the efficacy of a concurrent as opposed to an adjuvant IT. Our preliminary results show a survival benefit in the adjuvant compared to the concurrent setting potentially due to the delayed appearance of immunosuppressive components in the adjuvant setting. Importantly, we collaborate with Dr Dieta Brandsma and neurosurgeons at the Slotervaart and VUMC hospitals to obtain primary and recurrent human GBM, to identify additional alterations in the immune contexture of recurrent disease, including macrophage and T cell phenotype.

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

We have developed multiple HCC murine models using the relevant oncogenic drivers of this disease, by taking advantage of hydrodynamic gene delivery and the Sleeping Beauty-mediated somatic integration in mouse hepatocytes *in vivo*. In collaboration with Dr Rene Bernards' lab, we have used a subset of these models to successfully test novel pro-senescence therapy. Our analyses of the tumor microenvironment showed that the cancer cell genetic background strongly influences the immune cell landscape and that macrophages showed the largest differences in content in these models of HCC. These findings are encouraging us to therapeutically target macrophage populations in liver cancer.

Cancer specific dependencies

Roderick Beijersbergen

Group leader Division Molecular Oncology

Roderick Beijersbergen PhD Group leader
Lorenzo Bombardelli PhD Post-doc
Kathy Jastrzebski PhD Post-doc
Hanneke van Eden PhD student
Cor Lieftink MSc Bioinformatician
Ben Morris Technical staff
Wouter Nijkamp Technical staff
Martin de Rooij Technical staff

Selected publications

Jastrzebski K, Thijssen B, Kluin RJC, de Lint K, Majewski IJ, Beijersbergen RL, Wessels LFA. Integrative modeling identifies key determinants of inhibitor sensitivity in breast cancer cell lines. Cancer Res. 2018;78(15):4396 -4410

Wang C, Jin H, Gao D, Lieftink C, Evers B, Jin G, Xue Z, Wang L, Beijersbergen RL, Qin W, Bernards R. Phospho-ERK is a biomarker of response to a synthetic lethal drug combination of sorafenib and MEK inhibition in liver cancer. J Hepatol. 2018;69(5):1057-1065

Wang C, Jin H, Gao D, Wang L, Evers B, Xue Z, Jin G, Lieftink C, Beijersbergen RL, Qin W, Bernards R. A CRISPR screen identifies CDK7 as a therapeutic target in hepatocellular carcinoma. Cell Res. 2018;28(6):690-692

Our research continues to evolve around the discovery of regulators of crucial pathways deregulated in cancer, genotype specific dependencies and synthetic lethal interactions that can be explored as drug targets in precision therapy. To achieve these goals, we develop and apply functional genomic technologies including large scale RNAi and CRISPR/CAS9 screening. Besides CRISPR-based gene-editing, we apply CRISPR-based transcriptional activation, -repression and -base-editing screening technologies. With the ability to efficiently manipulate genomes in mammalian cells, we have started to generate screening models based on sensors that report gene-transcription, protein activation or pathway regulation. These advanced tools will allow for the discovery of novel components and pathways involved in cancer relevant phenotypes.

Identification of synthetic lethal interactions with mutations in the SWI/SNF chromatin remodeling complex

CRISPR-based screening provides a powerful way to identify synthetic lethal interactions. We have screened a panel of cell lines characterized by different mutations in members of the SWI/SNF chromatin remodeling complex. Inactivating mutations in members of the SWI/SNF chromatin-remodeling complex have been identified in a variety of cancer types with a frequency of up to 50%. Genes frequently found mutated in these cancers are ARID1A, ARID1B, SMARCA2, SMARCA4 and PBRM1. It has been proposed that mutation or loss of a specific component can result in the formation of other SWI/SNF complexes that either compensate for the loss of specific subunits, or that the residual altered complex may have a direct role in tumorigenesis. The targeting of residual SWI/SNF complexes as therapeutic strategy has been demonstrated by the synthetic lethal interactions between ARID1A mutation and ARID1B loss and between SMARCA4 mutation and SMARCA2 loss. Synthetic lethal interactions can also be the consequence of compensation by other chromatin mechanisms with antagonistic action e.g. EZH2 up-regulation in the context of SMARCB1 loss and targeted inhibition of EZH2 may therefore present a therapeutic opportunity for SMARCB1 mutant cancers. We have performed CRISPR drop-out screen in this panel of cell lines using an sgRNA library targeting ~500 genes involved in chromatin modification. In addition, we have used a set of MCF10A isogenic cell lines with the different SWI/SNF mutations. From these screens we have identified a number of potential synthetic lethal interactions and we are currently studying these novel interactions in more detail.

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 in which both genomic and non-genomic mechanisms cooperate to restore MAPK pathway output to sufficient levels to compensate for the effect of the BRAF and MEK inhibitors. However, MAPK pathway output levels need to be tightly controlled as too much leads to anti-proliferative signals. This is illustrated by the observation that resistant melanoma cells 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. Indeed, we have shown that hyperactivation of the MAPK pathway using Prostratin, a PKC and MAPK pathway activator, results in enhanced cell death after BRAF/MEK inhibitor withdrawal in resistant BRAF-mutant melanoma cells. Although prostratin can be explored for clinical application, we have set out to identify negative regulators such as phosphatases, which upon inhibition, also result in deregulation and hyperactivation of the MAPK pathway. With the identification of additional mechanisms, we aim to identify other means to control the level of MAPK pathway output under specific circumstances. This insight could to lead to potential targets that can be explored to kill resistant melanoma cells upon drug withdrawal with potentially a more preferable therapeutic window than MAPK pathway activators such as Prostratin.

B

Jos Beijnen

Group leader
Division Pharmacy
& Pharmacology

Jos Beijnen PhD Group leader
Joost van den Berg PhD Academic staff
Thomas Dorlo PhD Academic staff
Jeroen Hendrikx PhD Academic staff
Alwin Huitema PhD Academic staff
Bastiaan Nuijen PhD Academic staff
Cynthia Nijenhuis PhD Academic staff
Hilde Rosing PhD Academic staff
Bart Jacobs PhD Hospital pharmacist-in-training
Lotte van Andel MSc PhD Post-doc
Hedvig Arnamo MSc PhD student
Rene Boosman MSc PhD student
Maaike Bruin MSc PhD student
Maarten van Eijk MSc PhD student
Marie-Rose Flint-Crombag MSc PhD student
Steffie Groenland MSc PhD student
Maikel Herbrink MSc PhD student
Paniz Heydari MSc PhD student
Julie Jansen MSc PhD student
Eveline van Kampen MSc PhD student
Jonathan Knikman MSc PhD student
Sven de Krou MSc PhD student
Laura Kuijsten MSc PhD student
Merel van Nuland MSc PhD student
Semra Palic MSc PhD student
Jeroen Roosendaal MSc PhD student
Ignace Roseboom MSc PhD student
Luka Verrest MSc PhD student
Aurelia de Vries Schultink MSc PhD student
Joke Beukers Technical staff
Niels de Vries Technical staff
Abadi Gebretensae Technical staff
Michel Hillebrand Technical staff
Ciska Koopman Technical staff
Luc Lucas Technical staff
Lianda Nan Technical staff
Saskia Scheij Technical staff
Bas Thijsen Technical staff
Matthijs Tibben Technical staff
Joke Schol Technical staff
Maaike van Zon Technical staff
Nikkie Venekamp Technical staff
Rhianne Voogd MSc Technical staff

Pharmaceutical research: drug manufacturing – bioanalysis – pharmacokinetics

Our research programs focus on drug manufacturing including cellular immunotherapies, bioanalysis and pharmacokinetics of (anticancer) drugs for both preclinical and clinical projects.

Drug manufacturing

We support more than 20 mono- and (international) multi-center clinical trials (*e.g.* DRUP, POSEIDON, SUBITO, SENSOR) with drug manufacturing, packaging and distribution. In-house manufacturing of vorinostat capsules and oral solid dispersion tablet formulations of docetaxel (ModraDoc006) and paclitaxel (ModraPac005) is performed for ongoing clinical studies. Research to develop and/or to improve oral formulations of anticancer agents is continued by the introduction in 2019 of a new technique: *hot melt extrusion*. In 2018, we continued the production of Tumour Infiltrating Lymphocytes (TIL) infusions for metastatic melanoma patients treated in the first multi-center phase III trial with TIL therapy in the world. Previously produced DNA vaccines for HPV induced malignancies are currently tested by the Gynaecology department and promising results have been observed. ^{99m}Tc-PSMA radiopharmaceuticals for imaging of prostate cancer are under development in the department of Nuclear Medicine under our supervision.

Bioanalytical method development and implementation in pharmacokinetic studies

Plasma pharmacokinetics and tissue distribution of capecitabine, irinotecan, vinorelbine, ribociclib, palbociclib, abemaciclib and galunisertib were measured for preclinical studies. Less invasive sampling techniques, like Dried Blood Spots (DBS) and Volumetric Absorptive Microsampling (VAMS) were successfully developed for everolimus. In a mass balance study we found SGI-110, a prodrug of decitabine, to be rapidly metabolized and excreted in urine. The metabolic pathway of SGI-110 has now been elucidated and new metabolites have been identified. A metabolite profiling study with lurbinectedin (PM01183) with structural elucidation of metabolites revealed extensive metabolism of the drug. We analysed capecitabine and all its metabolites in a large, multi-centre, prospective genotyping study. Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) assays for the anti-hormonal drugs abiraterone, its active metabolite $\Delta(4)$-abiraterone, anastrozole, bicalutamide, endoxifen, enzalutamide and its active metabolite N-desmethyl enzalutamide, and exemestane were successfully developed, validated and implemented in our Therapeutic Drug Monitoring (TDM) program. This year we have received more than 5,000 samples for TDM analysis. New LC-MS/MS equipment including a hyphenated LC-MS Q-TOF platform is installed in the beginning of 2019.

Pharmacokinetic and Pharmacodynamics (PK/PD) modelling and simulation

For paclitaxel it was shown in a large retrospective study that older age does not have a relevant effect on its pharmacokinetics. A semi-mechanistic framework to predict the effects of pregnancy on the pharmacokinetics of selected anticancer agents has been developed and is currently validated. We implemented TDM for all novel tyrosine kinase inhibitor drugs in clinical practice. In this program we reported patients with severe toxicity on the standard dose of pazopanib who could safely and effectively be treated with pazopanib with an up to 8-fold lower dose based on measured plasma levels. Furthermore, it has been shown that elderly treated with kinase inhibitors do not have relevantly higher plasma concentration or lower dose intensity. Our program on treatment optimization of the repurposed anticancer PI3K/Akt inhibitor miltefosine for the neglected tropical parasitic disease leishmaniasis has been largely extended, with various clinical PK/PD studies initiated in 2018 in India, Bangladesh, Sudan and Kenya, funded partially through H2020. For ^{177}Lu-dotatate, a PK/PD model is under development in collaboration with the department of Nuclear Medicine. PK/PD modelling was also the basis for the introduction of fixed dosing of all monoclonal antibodies in our clinical practice.

André Bergman

Group leader
Division
Oncogenomics

André Bergman MD PhD Group leader
Sushil Badrising MD PhD student
Bianca Cioni MSc PhD student
Jeroen Kneppers MSc PhD student
Simon Linder MSc PhD student
Rebecca Louhanepessy MD PhD student
Suzan Stelloo MSc PhD student
Marit Vermunt MD PhD student
Anniek Zaalberg MSc PhD student
Yanyun Zu MSc PhD student

Selected publications

Cioni B, Nevedomskaya E, Melis MHM, van Burgsteden J, Stelloo S, Hodel E, Spinozzi D, de Jong J, van der Poel H, de Boer JP, Wessels LFA, Zwart W, Bergman AM. Loss of androgen receptor signaling in prostate cancer-associated fibroblasts (CAFs) promotes CCL2- and CXCL8-mediated cancer cell migration. Mol Oncol. 2018;12(8):1308-1323

Stelloo S, Nevedomskaya E, Kim Y, Hoekman L, Bleijerveld OB, Mirza T, Wessels LFA, van Weerden WM, Altelaar AFM, Bergman AM, Zwart W. Endogenous androgen receptor proteomic profiling reveals genomic subcomplex involved in prostate tumorigenesis. Oncogene. 2018;37(3):313-322

Stelloo S, Nevedomskaya E, Kim Y, Schuurman K, Valle-Encinas E, Lobo J, Krijgsman O, Peeper DS, Chang SL, Feng FY, Wessels LFA, Henrique R, Jerónimo C, Bergman AM, Zwart W. Integrative epigenetic taxonomy of primary prostate cancer. Nat Commun. 2018;9(1):4900

How the microenvironment affects prostate carcinogenesis

Our lab has an interest in the the interaction between normal prostate cells and prostate cancer. The prostate cancer microenvironment consists of stromal 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 Cancer Associated Fibroblasts (CAFs). 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. Immunohistochemical studies showed co localization of AR and the pan-macrophage marker CD68 in human prostate cancer samples suggesting that macrophages express AR. Moreover, single cell mRNA sequencing of myeloid (CD14+) cells isolated from human prostate cancer biopsies showed AR expression. Further studies showed that AR in macrophages regulates the expression of multiple cytokines that stimulate prostate cancer cell migration and invasion. AR in macrophages also stimulated differentiation into M2. These results suggest that inhibition of AR in macrophages is 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. A significant number of metastases did not originate from the largest prostate cancer lesion, but from smaller lesions.

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.

René Bernards

Group leader
Division Molecular Carcinogenesis

René Bernards PhD Group leader
Katrien Berns PhD Academic staff
Begona Diosdado MD PhD Post-doc
Haojie Jin PhD Post-doc
Rodrigo Leite de Oliveira PhD Post-doc
Sara Mainardi PhD Post-doc
Arnout Schepers PhD Post-doc
Cun Wang PhD Post-doc
Zheng Xue PhD Post-doc
Fleur Jochems MSc PhD student
Josephine Kahn MSc PhD student
Antonio Mulero Sanchez MSc PhD student
Joao Neto MSc PhD student
Ziva Pogacar MSc PhD student
Tonci Sustic MSc PhD student
Liqin Wang MSc PhD student
Annemiek Bes-Gennissen Technical staff
Astrid Bosma Technical staff
Marielle Hijmans MSc Technical staff

Selected publications

Mainardi S, Mulero-Sánchez A, Prahallad A, Germano G, Bosma A, Krimpenfort P, Lieftink C, Steinberg JD, de Wit N, Gonçalves-Ribeiro S, Nadal E, Bardelli A, Villanueva A, Bernards R. SHP2 is required for growth of KRAS-mutant non-small-cell lung cancer in vivo. Nat Med. 2018;24(7):961-967

Wang C, Jin H, Gao D, Wang L, Evers B, Xue Z, Jin G, Lieftink C, Beijersbergen RL, Qin W, Bernards R. A CRISPR screen identifies CDK7 as a therapeutic target in hepatocellular carcinoma. Cell Res. 2018;28:690-2

Wang L, Leite de Oliveira R, Huijberts S, Bosdriesz E, Pencheva N, Brunen D, Bosma A, Song J-Y, Zevenhoven J, Los-de Vries GT, Horlings H, Nuijen B, Beijnen JH, Schellens JHM, Bernards R. An Acquired Vulnerability of Drug-Resistant Melanoma with Therapeutic Potential. Cell. 2018;173:1413-25

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 aim to bring our discoveries to the clinic quickly in close collaboration with the clinicians in our affiliated hospital.

Pro-senescence therapies for the treatment of cancer

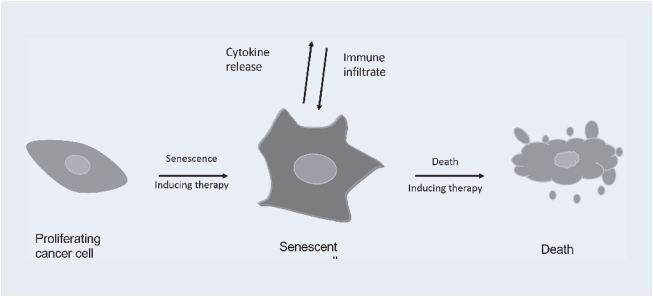
Induction of senescence represents a promising strategy for the treatment of cancer, especially when such pro-senescence therapy is combined with a second drug that selectively kills senescent cancer cells (senolytic agent). Through a genetic screen identifying pro-senescence effectors, we found that inhibition of CDC7 induces senescence selectively in *TP53* mutant liver cancer cells. Using a chemical screen, we found that inhibition of mTOR is effective in causing apoptotic cell death only in senescent HCC cells. In multiple in vivo liver cancer models we found that a combination of CDC7 and mTOR inhibitors results in dramatic synergistic inhibition of tumor growth. Our data indicate that a pro-senescence therapy combined with a senolytic drug can be effective for treatment of liver cancer (see figure).

Collateral sensitivity of drug resistant cancers

Drug resistance comes at a fitness cost that can lead to novel vulnerabilities of the drug resistant cancer cells. We searched for acquired vulnerabilities when *BRAF* mutant melanomas become resistant to the combination of BRAF and MEK inhibitors. We found that treatment drug resistant melanoma cells with the histone deacetylase inhibitor vorinostat resulted in a lethal increase in the already elevated levels of Reactive Oxygen Species in drug-resistant cells, causing apoptotic death of only the drug resistant tumor cells. Treatment of BRAF inhibitor-resistant melanoma with vorinostat in mice results in a dramatic tumor regression. In collaboration with professors Beijnen and Schellens a clinical study was performed in which patients with advanced BRAF+MEK inhibitor resistant melanoma were treated with vorinostat. Preliminary results from this study indicate that vorinostat can indeed selectively ablate BRAF inhibitor-resistant tumor cells, providing clinical proof of concept for the novel therapy identified in the laboratory. More generally, these 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.

PTPN11 as a drug target in RAS mutant cancers

It is well-established that *KRAS* mutant tumors are insensitive to inhibition of upstream growth factor receptor signaling. Indeed, inhibition of the protein tyrosine phosphatase PTPN11, which links receptor tyrosine kinase signaling to the RAS-RAF-MEK-ERK pathway, was shown to be ineffective in *KRAS* mutant cancer cell lines. Our data indicate that PTPN11 inhibition in *KRAS* mutant NSCLC cells 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. We aim to test a combination of PTPN11 and MAPK inhibitors in *KRAS* mutant tumors in the clinic in the course of 2019.



A one-two punch model for cancer therapy based on induction of senescence.
A first drug induces senescence in cancer cells, followed by a second drug that selectively kills senescent cancer cells.

Mouse models of thoracic cancers

Anton Berns

Group Leader
Division Molecular Genetics

Anton Berns PhD Group Leader
Paul Krimpenfort PhD Staff member
Jitendra Badhai PhD Post-doc
Rajith Bhaskaran PhD Post-doc
Giustina Ferone PhD Post-doc
Ekaterina Semenova PhD Post-doc
Hilda de Vries PhD Post-doc
Jan Paul Lambooij Technical staff
Jan van der Vliet Technical staff
John Zevenhoven Technical staff

Selected publications

Adami H-O, Berns A, Celis JE, de Vries E, Eggermont A, Harris A, et al. European Academy of Cancer Sciences - position paper. Mol Oncol. 2018;12(11):1829-37

Kas SM, de Ruiter JR, Schipper K, Schut E, Bombardelli L, Wientjens E, Drenth AP, de Korte-Grimmerink R, Mahaken S, Philips C, Smith PD, Klarenbeek S, van de Wetering K, Berns A, Wessels LF, and Jonkers J. Transcriptomics and Transposon Mutagenesis Identify Multiple Mechanisms of Resistance to the FGFR Inhibitor AZD4547. Cancer Res. 2018;78:5668-79

Nagel R, Avelar AT, Aben N, Proost N, van de Ven M, van der Vliet J, Cozijnsen, M, de Vries H, Wessels L, and Berns A. Inhibition of the replication stress response is a synthetic vulnerability in SCLC that acts synergistically in combination with cisplatin. Mol. Cancer Therapeutics, 2019 (in press)

We use the mouse as a model organism to study the role of oncogenes and tumor suppressor genes in lung cancer and mesothelioma development. By utilizing recombination-mediated switching and taking advantage of somatic gene transfer methods and genome editing techniques we alter the expression of multiple oncogenes and tumor suppressor genes in a tissue-specific fashion permitting accurate modeling of tumorigenesis as it is observed in man.

Small Cell Lung Cancer

We identified several SCLC subtypes in mouse models in which *Mycl* or *Nfib* was overexpressed with concomitant loss of *Rb* and *Trp53* in lung epithelial cells. These include CDH1-high peripheral primary and aggressive CDH1-negative centrally located secondary tumor lesions. Cisplatin treatment preferentially eliminates the latter, thus revealing a striking differential response. Using a combined transcriptomic and proteomic approach, we observed a marked reduction in proliferation and metabolic rewiring following cisplatin-treatment, and found evidence for a unique metabolic and structural profile defining intrinsically cisplatin-resistant populations. This offers perspectives for new combination therapies that might also hold promise for treating human SCLC, given the very similar response of both mouse and human SCLC to cisplatin. In a functional genome-wide screen in which all individual genes were knocked out to identify novel vulnerabilities of SCLC. The stress response machinery appeared particularly important in SCLC. By the use of Chk1 and ATR inhibitors we showed that SCLC cells are more sensitive to these inhibitors than non-transformed cells. Furthermore, these inhibitors acted synergistically with either etoposide and cisplatin. VE822 mediated inhibition of ATR in combination with cisplatin also outperforms the combination of cisplatin with etoposide *in vivo*.

Malignant Mesothelioma

Malignant Mesothelioma (MM) is one of the most lethal human malignancies of the thoracic cavity that can present as three different subtypes: epithelioid, sarcomatoid and biphasic. We have developed a mouse model of malignant mesothelioma (MM) based on the disruption of the *Bap1*, *Nf2*, and the *Cdkn2ab*, tumour suppressor loci that are also frequently mutated in human MM. Inactivation of all three genes loci in the mesothelial lining of the thoracic cavity leads to a highly aggressive primarily epithelioid MM with a modest response to frontline therapy similar as observed in man. *Bap1* deletion alone does not cause MM but dramatically accelerates MM development when combined with *Nf2* and *Cdkn2ab* disruption. The accelerated tumour development is accompanied by increased Polycomb repression and EZH2-mediated redistribution of H2K27me3 towards promoter sites, with concomitant activation of the PI3K, MAPK, and Hippo pathways. Early passage MM cells with inactivated BAP1 from these mice are hypersensitive to EZH2 inhibition. Moreover, dual inhibition of EZH2(GSK126) and FGFR(AZD4547) leads to strong synergistic lethality in these cells. Therefore, the autochthonous mouse model described here is particularly suited to explore and validate new treatment regimens for MM.

To assess whether the cell-of-origin is an important determinant of the mesothelioma subtype we inactivated *Nf2* and *Trp53* in cells of the mesothelial lining of *Cdkn2a*-deficient mice cells *in vitro* and *in vivo*. Cloned *in vitro* switched mesothelial cells showed distinct protein profiles reminiscent of the three tumor subtypes and gave rise to the distinct tumor subtypes upon *in vivo* grafting. Their expression profiles align with the cognate mesothelioma subtypes of human patients. We also showed that restricting tumor suppressor inactivation to subsets of cells in the mesothelial lining *in vivo* using lentiviral vectors expressing iCre from distinct promoters did give rise to a distinct MM subtype distribution supporting the notion that the cell-of-origin is a critical factor in dictating the tumor subtype of MM.

B

Christian Blank

Group leader Division Molecular Oncology & Immunology

Christian Blank MD PhD Group leader
Trieu Van My PhD Post-doc
Esmee Hoefsmit MSc PhD student
Ruben Lacroix MSc PhD student
Disha Rao MSc PhD student
Irene Reijers MD PhD student
Lisette Rozeman MD PhD student
Mesele Valenti Technical staff

Understanding resistance upon 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. Also, their spatial relationship within the tumor will be crucial to determine the relevance of individual immune inhibitory cell infiltrates. 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 to improve the outcome upon checkpoint inhibition

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, NCT02625337), that was presented as late braking abstract at this year's ESMO annual meeting.

Currently, we are testing new approaches to alter the skewing towards low regulatory T cell content in tumors, more resistant T cells in the hostile tumor environment and improving the presence of antigen presenting cells within the tumor.

Biomarker identification for personalized immunotherapy

Immunotherapies like CTLA-4 or PD-1/PD-L1 blockade have revolutionized the treatment of late stage melanoma. 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, and confirmed in a second larger cohort of patrients, that an interferon-gamma RNA signature, 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 and subsequent testing of alternative combinations in signature unfavorable patients.

Selected publications

Blank CU, Rozeman EA, Fanchi LF, Sikorska K, van de Wiel B, Kvistborg P, Krijgsman O, van den Braber M, Philips D, Broeks A, van Thienen JV, Mallo HA, Adriaansz S, Ter Meulen S, Pronk LM, Grijpink-Ongering LG, Bruining A, Gittelman RM, Warren S, van Tinteren H, Peeper DS, Haanen JBAG, van Akkooi ACJ, Schumacher TN. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med. 2018;24(11):1655-1661

Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, Haydon A, Lichinitser M, Khattak A, Carlino MS, Sandhu S, Larkin J, Puig S, Ascierto PA, Rutkowski P, Schadendorf D, Koornstra R, Hernandez-Aya L, Maio M, van den Eertwegh AJM, Grob JJ, Gutzmer R, Jamal R, Lorigan P, Ibrahim N, Marreaud S, van Akkooi ACJ, Suciu S, Robert C. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma N Engl J Med. 2018;378(19):1789-1801

Lacroix R, Rozeman EA, Kreutz M, Renner K, Blank CU. Targeting tumor-associated acidity in cancer immunotherapy. Cancer Immunol Immunother. 2018;67(9):1331-1348

Eveline Bleiker

Group leader Division Psychosocial Research and Epidemiology

Eveline Bleiker PhD Group leader
Jacobien Kieffer PhD Technical staff
Ellen Engelhardt PhD Post-doc
Aleksandra Berezowska PhD Post-doc
Annelies Boekhout PhD Post-doc
Jacqueline ter Stege MSc PhD student
Danielle Starreveld MSc PhD student
Kasper Overbeek MD PhD student
Pernilla Scheelings MSc Jr researcher
Marianne Kuenen Research assistant
Miranda Gerritsma MSc Research assistant
Jessie de Geus MSc Research assistant

Selected publications

Brédart A, [...], Bleiker E, Kulis D, Bonnetain F, Aaronson NK; EORTC Quality of Life Group. et al. Phase III study of the European Organisation for Research and Treatment of Cancer satisfaction with cancer care core questionnaire (EORTC PATSAT-C33) and specific complementary outpatient module (EORTC OUT-PATSAT7). Eur J Cancer Care. 2018;27(1)

Menko, FH, Stege JA ter, Kolk L van der, Jeanson K, Schats W, Ait Moha D, Bleiker EMA. The uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome: a systematic review of the literature and implications for clinical practice. Fam Cancer. 2019;18(1):127-135

Starreveld DEJ, Daniels LA, Valdimarsdottir HB, Redd WH, Geus J de, Ancoli-Israel S, Lutgendorf S, Korse CM, Kieffer JM, Leeuwen FE van, Bleiker EMA. Light therapy as a treatment of cancer-related fatigue in (non-)Hodgkin lymphoma survivors (SPARKLE trial): study protocol of a multicenter randomized controlled trial. BMC Cancer 2018;18(1):880

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 of developing cancer because of a family history of cancer or an inherited gene mutation. The overall aim of the research is to improve the quality of life and quality of care.

Clinical genetics

Whole body-MRI for carriers of a *TP53* mutat-ion

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, and leukemia 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). In the initial round of our annual surveillance program, including 56 *TP53* mutation carriers, malignancies were detected in approximately 7% of patients. This detection rate comes at the expense of many false-positives and increased levels of distress. However, almost all (97%) reported that the benefits of the annual screening outweigh the burden.

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 women who have to decide on breast surgery and reconstruction. Decisions about breast reconstruction are complex and largely depend on patients' personal preferences. We developed the online pDA, consisting 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. Currently, a randomized controlled trial runs in eight hospitals and has enrolled 209 women being treated for breast cancer or ductal carcinoma in situ, undergoing ablative surgery. In 2019, when 250 women are enrolled, data on the effectiveness of the decision aid will be analyzed.

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%). This fatigue impacts on the quality of life, even years after diagnosis. 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 every morning for 30 minutes. The SPARKLE-study (financially supported by the KWF) is a multi-center RCT which investigates the efficacy of this intervention in (non-)Hodgkin survivors. We also 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. In 2018 we have included 93 participants in the study, stemming from 10 hospitals. In 2019, we will continue to recruit patients until 160 participants are enrolled in the study.

B

Gerben Borst

Group leader
Division Cell Biology

Gerben Borst MD PhD Group leader
Beatriz Gomez Solsona MSc PhD student
Eline Hessen MD PhD student
Paul Slangen MSc PhD student
Mariska van Geldorp Technical staff

Selected publications

Barazas M, Gasparini A, Huang Y, Küçükosmanoğlu A, Annunziato S, Bouwman P, Sol W, Kersbergen A, Proost N, de Korte-Grimmerink R, van de Ven M, Jonkers J*, Borst GR*, Rottenberg S*. Radiosensitivity is an acquired vulnerability of PARPi-resistant BRCA1-deficient tumors, Cancer Res. 2018
*shared senior and corresponding authorship

Bibault JE, Franco P, Borst GR, Van Elmpt W, Thorwhart D, Schmid MP, Rouschop KMA, Spalek M, Mullaney L, Redalen KR, Dubois L, Verfaillie C, Eriksen JG. Learning radiation oncology in Europe: Results of the ESTRO multidisciplinary survey. Clin Transl Radiat Oncol. 2018

Jelvehgaran P, de Bruin DM, Salguero FJ, Borst GR, Song JY, van Leeuwen TG, de Boer JF, Alderliesten T, van Herk M. Feasibility of using optical coherence tomography to detect acute radiation-induced esophageal damage in small animal models. J Biomed Opt. 2018;23(4):1-12

Optimizing treatment strategies for brain tumors, and uncovering irradiation escapes mechanisms

Optimizing the timing and duration of targeted agents in relation to the RT

Immunotherapy

Local radiation causes significant alterations in the tumor microenvironment that are thought to boost immunity. However, the working mechanism, optimal timing and sequence of immunotherapy (IT) in relation to radiotherapy (RT) are still unknown. In collaboration with the Akkari group we are investigating the efficacy of concurrent versus the adjuvant IT approach in a pro-neural glioblastoma mouse model.

Cell cycle interfering agents

Mitotic enrichment has previously been clinically tested as radiosensitizing strategy with cytotoxic agents (e.g. high dose vincristine). However, both the compound(s) used and the application strategy were inappropriate and we want to revive mitotic enrichment as radiosensitizing strategy for glioblastoma patients with better agents and scheduling. In collaboration with the van Tellingen group we are currently evaluating the feasibility to introduce one of the candidate drugs in a clinical trial.

Uncovering and exploiting new interphase effects of Tumor Treating Fields (TTF)

Tumor Treating Fields (TTF) is an FDA approved modality of anticancer treatment for glioblastoma (GBM) patients. TTF is a local treatment using alternating electric fields that are delivered via insulated transducers. These electric fields are thought to specifically target dividing cells by interfering in various processes that regulate the mitotic progression. Our preliminary data uncovered additional effects of TTF in the interphase that appear to significantly contribute to the antineoplastic effects of TTF in GBM cells. Importantly, these effects are targetable with different small molecule inhibitors. We are currently studying the outcome in vitro combining TTF with interphase interfering drugs.

Optimizing of the MRI guided imaging in patients with brain metastases and primary tumors

Previously, we observed that brain metastases can undergo significant shifts and target volume changes in short time intervals. What the effect is of these shifts is unknown and we are currently studying the dose coverage changes due to these shifts and volume changes.
Radiotherapy is also the mainstay treatment for glioblastoma patients and for these patients even less is known about tumor shifts and target volume changes during fractionated radiotherapy. This information is of paramount importance because dose escalation studies are ongoing defining the target volume on the MRI that is made after surgery and before radiotherapy. Also for this group of patients we study the effect of changes on the dose coverage of the tumor to optimize the timing of the MRI.

Characterizing effects of radiotherapy in BCRA1-deficient mammary tumors

The Rottenberg group has previously shown that the K14cre;Brca1F/F;p53F/F (KB1P) mouse model for BRCA1-mutated breast cancer is useful to study basic mechanisms of drug resistance. Interestingly, we found that this model escapes radiotherapy by acquiring resistance and formation of metastases. In collaboration with the van Rheenen, Jonkers and Rottenberg groups we are using state of the art assays and tools (e.g. single cell sequencing, cell cycle analysis, intra-vital microscopy) to further elucidate the underlying mechanisms of radioresistance.

Molecular mechanisms that govern the T-cell response

Jannie Borst

Division head, group leader Division Immunology

Jannie Borst PhD Group leader
Inge Verbrugge PhD Associate staff scientist
Yanling Xiao MD PhD Associate staff scientist
Victoria Iglesias Guimarais PhD Post-doc
Sander de Kivit PhD Post-doc
Jara Palomero Gorrindo PhD Post-doc
Tomasz Ahrends MSc PhD student
Nikolina Bąbała MSc PhD student
Julia Busselaar MSc PhD student
Elselien Frijlink MSc PhD student
Mark Mensink MSc PhD student
Andryi Volkov MSc PhD student
Xin Lei MD Research Associate
Astrid Bovens MSc Technical staff
Irene van der Haar Àvila MSc Technical staff
Paula Kroon PhD Technical staff
Evert de Vries BSc Technical staff
Tom de Wit MSc Technical staff

Selected publications

Bąbała N, Bovens A, de Vries E, Iglesias-Guimarais V, Ahrends T, Krummel MF, Borst J°, Bins AD°. Subcellular localization of antigen in keratinocytes dictates delivery of CD4+ T cell help for the CTL response upon therapeutic DNA vaccination into the skin. Cancer Immunol Res. 2018;6:835-847

Borst J, Ahrends, T, Bąbała N, Melief CJ, and Kastenmuller W. CD4+ T-cell help in cancer immunology and immunotherapy. Nat Rev Immunol. 2018;18: 635-647

Cuadrado E, van den Biggelaar M*, de Kivit S*, Chen Y, Slot M, Doubal I, Meijer A, van Lier RAW, Borst J°, Amsen D°. Quantitative proteomics reveals mechanisms to protect cellular identity in human regulatory T cells. Immunity. 2018;48:1046-1059

Our work is inspired by the desire to improve immunotherapy 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*.

CD4 T cell help for the CTL response

We have recently put forward a model in which cytotoxic T lymphocyte (CTL) priming in lymphoid organs takes place in two steps. In the first step of priming, CD4 T cells and CD8 T cells are activated separately by different (migratory) DC types that have been activated by innate stimuli. In the second step of priming, CD4 T cells and CD8 T cells find their respective antigens on the same, lymph node resident DC. In this cellular interaction, CD4 T-cell help for the CTL response is delivered, which optimizes CTL effector and memory differentiation. The CD27/CD70 costimulatory system is key in "help" delivery (Ahrends et al., Cancer Res. 2016, Immunity 2017). We argue that "help" for the CTL response can be exploited to optimize anti-tumor immunity by a variety of strategies (Borst et al., Nat. Rev. Immunol 2018). We are translating our findings in mouse models to the human situation currently.

In collaboration with Aduro Biotech Europe and Merck, we have brought an agonistic antibody to the CD27 costimulatory receptor into clinical phase 1-2 testing in the beginning of 2018, including at our own clinic at the AVL. This is the result of over a decade of preclinical work with dr. Hans van Eenennaam and his team, who also developed Pembrolizumab.

Human DC function

Associate staff scientist Dr Yanling Xiao drives a research line on the homeostatic development of mouse and human DCs from hematopoietic progenitors. She has developed protocols to generate human DCs from these progenitor populations in good yield. The team has developed an *in vitro* DC-T cell culture system, which proves that these *in vitro* generated DCs can crosspresent cell-associated tumor antigen and crossprime tumor specific CTL responses. With this system, we can identify tumor-specific CD8 T cells in human blood. We aim to develop this assay into a tool for clinical diagnostics.

In collaboration with the team of Dr Ron Kerkhoven at the Genomics Core Facility, Dr Xiao has pioneered TotalSeq single cell sequencing (Biolegend) at the NKI to study the composition of the *in vitro* generated DC population and to compare it to defined and functionally distinct DC subsets isolated from human blood or bone marrow.

Understanding regulatory T cells

Regulatory CD4 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. A large proteomics study has revealed that human Treg identity is defined by adaptations in multiple signaling pathways that act downstream of the TCR, costimulatory- and cytokine receptors (Cuadrado et al. Immunity 2018). We have recently completed a study in collaboration with prof Celia Berkers (Utrecht University) that includes metabolomic analysis. We have found that human thymic Tregs and conventional CD4 T cells differentially respond to CD28 and TNF receptor family costimulation. Specifically, we find that thymic Tregs can make a glycolytic switch to support rapid proliferation, but require specific costimulatory input to do so and handle glycolytic intermediates in a different way than conventional CD4 T cells do.

Thijn Brummelkamp

Group leader
Division Biochemistry

Experimental Biomedical Genetics

Using a classical genetic approach, we mutate the DNA of an organism and study the consequences. We use two 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 link new genes to human disease.

Regulators of Molecular Phenotypes

As key executers of biological processes, the activity and abundance of proteins is subjected to extensive regulation. Using mutagenesis in haploid human cells we have developed an approach to couple genomic mutations to protein measurements within individual cells. Using this approach, which is both sensitive and scalable, genes can be identified that regulate any quantifiable protein phenotype in haploid human cells. Besides known regulators this also points out new genetic connections: the E3 ligase subunit KCTD5 was identified as new regulator of the AKT signaling pathway, CMTM6 as a new component of the PD1-PDL1 axis and Vasohibins were recognized as the long-sought tubulin detyrosinating enzymes.

In the future the ability to link genes to protein phenotypes using deep sequencing will enable us to build a genetic wiring map for haploid human cells. To better understand how genes collaborate we also study two types of genetic interactions that: synthetic lethality and genetic suppression.

Pathogen Portals

Our group studies viral families that cause the most-deadly human infections (Filovirus [e.g. Ebola virus], Arenavirus [e.g. Lujo virus], Bunyavirus [e.g. Hanta virus] as well as the most frequent human infections (Picornavirus [e.g. rhinovirus]). We use haploid genetics to gain insight into the entry tactics of these pathogens into human cells.

Genetic screens revealed that our mechanistic understanding of virus entry was incomplete, notably at the step that involves escape from the endo-lysosomal compartment. For Ebola and Lassa virus we revealed a 'receptor switch' to an intracellular transmembrane protein, recognized deep in the endo-lysosomal compartment. For Picornaviruses we identified PLA2G16 and demonstrated recruitment of this host factor to the perforated endosomal membrane. Loss of PLA2G16 led to a virus-resistance phenotype that could be reverted by ablation of a pathway previously linked 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.

Studies on Coxsackie A and New World Hanta viruses identified new virus entry receptors at the cell surface. Haploid genetic screens identified the WNT-pathway component Kremen-1 as a critical host factor for infection, a finding that could be validated in mouse models deficient for KREMEN. Remarkably, Kremen-1 functions as entry receptor for a large subgroup of Coxsackie A viruses for which entry receptors remained unknown. In collaboration with other research groups PCDH1 was identified as entry receptor for New World Hantaviruses, a finding for which the relevance could be shown using blocking antibodies and PCDH1-deficient hamsters generated using CRISPR-CAS9.

Thijn Brummelkamp PhD Group leader
Astrid Fauster PhD Post-doc
Lisa Landskron Post-doc
Abdelghani Mazouzi PhD Post-doc
Gian-Luca McLelland Post-doc
Danielle Bianchi PhD student
Joppe Nieuwenhuis PhD student
Jacqueline Staring PhD student
Elmer Stickel PhD student
Nicolaas Boon Technical staff
Lisa van den Hengel Technical staff

Selected publications

Bigenzahn JW, Collu GM, Kartnig F, Pieraks M, Vladimer GI, Heinz LX, Sedlyarov V, Schischlik F, Fauster A, Rebsamen M, Parapatics K, Blomen VA, Müller AC, Winter GE, Kralovics R, Brummelkamp TR, Mlodzik M, Superti-Furga G. LZTR1 is a regulator of RAS ubiquitination and signaling. Science, 2018;362(6419):1171-1177

Jangra RK, Herbert AS, Li R, Jae LT, Kleinfelter LM, Slough MM, Barker SL, Guardado-Calvo P, Román-Sosa G, Dieterle ME, Kuehne AI, Muena NA, Wirchnianski AS, Nyakatura EK, Fels JM, Ng M, Mittler E, Pan J, Bharrhan S, Wec AZ, Lai JR, Sidhu SS, Tischler ND, Rey FA, Moffat J, Brummelkamp TR, Wang Z, Dye JM, Chandran K. Protocadherin-1 is essential for cell entry by New World hantaviruses. Nature, 2018;563(7732):559-563

Staring J, van den Hengel LG, Raaben M, Blomen VA, Carette JE, Brummelkamp TR. KREMEN1 Is a Host Entry Receptor for a Major Group of Enteroviruses. Cell Host Microbe. 2018;23(5):636-643.e5

Karin de Visser

Group leader
Division Tumor Biology & Immunology

Karin de Visser PhD Group leader
Ewald van Dyk PhD Post-doc
Hannah Garner PhD Post-doc
Anni Laine PhD Post-doc
Lorenzo Spagnuolo PhD Post-doc
Antoinette van Weverwijk PhD Post-doc
Noor Bakker MSc PhD student
Olga Blomberg MSc PhD student
Danique Duits MSc PhD student
Kevin Kos MSc PhD student
Camilla Salvagno MSc PhD student
Max Wellenstein MSc PhD student
Tisee Hau BSc Technical staff
Chris Klaver MSc Technical staff
Lisanne Raeven MSc Technical staff
Kim Vrijland MSc Technical staff

Selected publications

Salvagno C, Ciampricotti M, Tuit S, Hau C-S, van Weverwijk A, Coffelt SB, Kersten K, Vrijland K, Kos K, Ulas T, Song J-Y, Ooi C-H, Rüttinger D, Cassier PA, Jonkers J, Schultze JL, Ries CH and de Visser KE. Therapeutic targeting of macrophages enhances chemotherapy efficacy by unleashing type I interferon response. Nat Cell Biol 2018 (provisionally accepted)

Blomberg OS, Spagnuolo L, de Visser KE. Immune regulation of metastasis: mechanistic insights and therapeutic opportunities. Dis Model Mech. 2018;11(10)

Wellenstein MD, de Visser KE. Cancer-Cell-Intrinsic Mechanisms Shaping the Tumor Immune Landscape. Immunity. 2018;48(3):399-416

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 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.

Improving response to platinum-based chemotherapy by targeting macrophages

Poor chemotherapy response is a major obstacle to successful cancer treatment. There is a growing realization that the immune system influences the success of chemotherapy, however, the exact underlying mechanisms are largely unknown. Utilizing mouse tumor models that faithfully recapitulate human breast tumorigenesis, we discovered that targeting macrophages by CSF-1 receptor (CSF-1R) blockade enhances the anti-cancer efficacy of platinum-based chemotherapeutics. We mechanistically uncovered that CSF-1R inhibition stimulates intratumoral type I interferon signaling which is essential for the therapeutic synergy between cisplatin and CSF-1R blockade. Further elimination of immunosuppressive neutrophils was required to engage an efficacious anti-tumor immune response that further improved therapeutic benefit of cisplatin (Salvagno et al. accepted for publication in Nature Cell Biology). These findings illustrate the importance of breaching multiple layers of immunosuppression during cytotoxic therapy to engage anti-tumor immunity in breast cancer.

Impact of the genetic makeup of breast cancer on pro-metastatic inflammation

Cancer-associated systemic inflammation is strongly linked with poor disease outcome in cancer patients. For example, high neutrophil-to-lymphocyte ratios in blood of cancer patients are associated with increased metastasis, and we (Coffelt et al. Nature 2015) and others have previously demonstrated that neutrophils promote metastasis formation in mouse tumor models. Given the emerging interest in immunomodulatory therapies for cancer, it is crucial to understand the mechanisms by which tumors shape the systemic immune landscape. In collaboration with Jos Jonkers (Division of Molecular Pathology), we uncovered the impact of the genetic makeup of breast cancer on pro-metastatic inflammation. We have revealed a novel role for p53 as a key regulator of systemic inflammation in breast cancer. Mechanistically, p53 loss in cancer cells induces paracrine stimulation of tumor-associated macrophages, which elicits an inflammatory cascade leading to the systemic accumulation of neutrophils, which facilitates metastasis formation (Wellenstein et al. in revision). These insights illustrate the importance of the genetic makeup of cancer cells in dictating pro-metastatic systemic inflammation, and set the stage for personalized immune intervention strategies for cancer patients.

Translating our findings to breast cancer patients

In collaboration with medical oncologist Marleen Kok (NKI) we have established an extensive immunomonitoring program to perform in-depth profiling of the immune landscape in fresh blood samples of patients with different subtypes of breast cancer. Through these analyses, we validate the findings from our pre-clinical studies in patients, and we hope to gain a deeper understanding of the complex cancer-immune crosstalk in breast cancer patients.

D

Elzo de Wit

Group leader
Division Gene Regulation

Elzo de Wit PhD Group leader
Luca Braccioli PhD Post-doc
Koen Flach PhD Post-doc
Ningqing Liu PhD Post-doc
Teun van den Brand MSc PhD student
Michela Maresca MSc PhD student
Marijne Schijns MSc PhD student
Robin van der Weide MSc PhD student
Hans Teunissen BSc Technical staff

Selected publications

Kaaij LJT, van der Weide RH, Ketting RF, de Wit E. Systemic Loss and Gain of Chromatin Architecture throughout Zebrafish Development. Cell Rep. 2018;24(1):1-10.e4

Allahyar A, Vermeulen C, Bouwman BAM, Krijger PHL, Verstegen MJAM, Geeven G, van Kranenburg M, Pieterse M, Straver R, Haarhuis JHI, Jalink K, Teunissen H, Renkens IJ, Kloosterman WP, Rowland BD, de Wit E, de Ridder J, de Laat W. Enhancer hubs and loop collisions identified from single-allele topologies. Nat Genet. 2018;50(8):1151-1160

Geeven G, Teunissen H, de Laat W, de Wit E. peakC: a flexible, non-parametric peak calling package for 4C and Capture-C data. Nucleic Acids Res. 2018;46(15):e91

Genome dynamics and function

Our research centers around the question: how are genes regulated within the context of the three-dimensional genome? We use a combination of genetic and acute perturbation experiments in combination with genomics tools to understand how distal regulatory elements (e.g. enhancers) contribute to the regulation of genes. In addition to implementing and developing genomics methods we also develop software for the analysis of chromosome conformation capture data. Last year we published peakC, which is a non-parametric peak caller for 4C and Capture-C data. In addition, we are actively developing a user-friendly package for the analysis of Hi-C data, called GENOVA. With it, users can generate publication quality figures. These and other computational biology methods assist us into answering fundamental questions with respect to 3D genome organization and expression.

An unexpected link between the 3D genome and epigenome

Together with the Rowland lab we have analyzed how loss of architectural proteins affect the 3D genome. Importantly, we have found that a change in 3D genome architecture is associated with a strong change in the epigenetic landscape. For instance, by knocking out MED12 we find a loss of chromatin loops and a concomitant increase in heterochromatin. On the other hand, an increase in chromatin loops, resulting from the knock-out the cohesin release factor WAPL, is associated with an almost complete loss of heterochromatin domains. The increase of heterochromatin is associated with an expected loss of expression. However, in the absence of WAPL, MED12 is no longer required for the expression of these genes. We have therefore uncovered how chromatin loops can contribute to the regulation of gene expression.

Cohesin cooperates with pluripotency factors to maintain pluripotency

In order to better understand the order of events upon loss of factors that affect chromatin loop formation, we have generated an acute depletion line for Wapl in mouse embryonic stem cells. Upon depletion of Wapl, these cells start to differentiate, suggesting that the 3D genome plays an important role in the maintenance of pluripotency. We find that the cohesin complex, which is regulated by Wapl, is bound at the same sites as pluripotency transcription factors, such as Nanog and Sox2. Paradoxically, upon the stabilization of cohesin on chromatin, these cohesin binding sites are lost. This is accompanied by a loss of small self-interacting chromatin domains. Our results show that dynamic cohesin cooperates with lineage-specific transcription factors in the maintenance of the pluripotent state.

The 3D cancer genome

An exciting new avenue of research that we are pursuing is the organization of the 3D genome in cancer. Until now detailed information about the 3D genome in tumor samples is lacking. Together with the Zwart lab we have started to investigate the 3D genome in metastatic breast cancer samples. We have found that there is considerable diversity in the 3D genome between different tumors. We are now trying to understand how this relates to gene expression, chromatin landscape, treatment outcome and survival.

William Faller

Group leader
Division
Oncogenomics

William Faller PhD Group leader
Joana Silva PhD Post-doc
Ferhat Alkan PhD Post-doc
Eric Pinto Barbera MSc PhD student
Rob van der Kammen BSc Technical staff

Publication

Huels DJ, Bruens L, Hodder MC, Cammareri P, Campbell AD, Ridgway RA, Gay DM, Solar-Abboud M, Faller WJ, Nixon C, Zeiger LB, McLaughlin ME, Morrissey E, Winton DJ, Snippert HJ, van Rheenen J, Sansom OJ. Wnt ligands influence tumour initiation by controlling the number of intestinal stem cells. Nat Commun. 2018;9(1):1132

RNA translation and mTOR signaling in mouse models of cancer

The main interest of our lab is the role that mTOR signaling and RNA translation play in normal and cancer cells. In particular we are focused on the stem cell populations in the intestine, and cancers of the same organ. We study this using genetically modified mouse models (GEMMS), and 3d organoid culture, which allow us to maintain the complexity of the organ, while still providing tractable systems to study. In particular, these tools allow us to genetically modify our genes of interest, providing an opportunity to delineate the role of various signaling pathways in normal cells, and how they are corrupted by the oncogenic process.

RNA translational elongation in colon cancer

The Adenomatous polyposis coli (Apc) gene is lost in around 80% of human colorectal cancers (CRCs), and acts to drive Wnt signaling. We have previously shown that in a mouse model of CRC, translation elongation is increased following Apc deletion. Furthermore, this increase is required for the cancer cells to proliferate. We are now trying to understand what RNAs are regulated like this, and what determines whether an RNA is regulated in this manner or not.
For example, we have seen that after Apc deletion, Cyclin D2 is decreased by translation elongation, while Cyclin D3 is increased. When we delete these genes in the mouse intestine using the VillinCre^{ERT2}, they have opposing effects, with loss of Cyclin D2 promoting Wnt-driven proliferation, and loss of Cyclin D3 inhibiting it. This suggests that these highly homologous proteins have opposite roles after Apc deletion, with Cyclin D2 acting as a tumour suppressor, and Cyclin D3 acting as an oncogene. This surprising finding also seems to be recapitulated in human data, with high expression of Cyclin D2 or Cyclin D3 correlating with good and poor prognosis respectively. We are now confirming this hypothesis in a cancer model, and working to understand why and how these proteins are regulated in such an opposing manner.

mTOR and RNA translation in intestinal stem cells

Stem cells are the drivers of CRC development and resistance to therapy, and understanding this population of cells is a major focus of the lab. We have shown that following inhibition of mTOR we get a change in stem cell populations, with the appearance of a rare population with distinct characteristics. These characteristics include alterations in metabolism, protein synthesis and proliferation. Strikingly, it appears that these cells maintain the ability to activate mTOR signaling, even in the presence of mTOR inhibitors. This resistance to mTORC1 silencing is reminiscent of *in vivo* colonic adenomas that are driven by Kras activation, suggesting that MAPK signaling may result in the appearance of this stem cell population, which is inherently resistant to mTOR inhibition.
We are now working to understand the function of these cells in the normal intestine and cancer, and the role that they play in the resistance to therapy.

H

John Haanen

Group leader
Division Immunology

John Haanen MD PhD Group Leader
Joost van den Berg PhD Academic staff
Raquel Gomez MSc Technical staff
Saskia Scheij Technical staff
Rhianne Voogd MSc Technical staff
Maaike van Zon Technical staf

Publications

Dijkstra KK, Cattaneo CM, Weeber F, Chalabi M, van de Haar J, Fanchi LF, Slagter M, van der Velden DL, Kaing S, Kelderman S, van Rooij N, van Leerdam ME, Depla A, Smit EF, Hartemink KJ, de Groot R, Wolkers MC, Sachs N, Snaebjornsson P, Monkhorst K, Haanen J, Clevers H, Schumacher TN, Voest EE. Generation of tumor-reactive T cells by co-culture of peripheral blood lymphocytes and tumor organoids. Cell. 2018;174(6):1586-1598

Rohaan MW, van den Berg JH, Kvistborg P, Haanen JBAG. Adoptive transfer of tumor-infiltrating lymphocytes in melanoma: a viable treatment option. J Immunother Cancer. 2018;6(1):102

Scheper W, Kelderman S, Fanchi LF, Linnemann C, Bendle G, de Rooij MAJ, Hirt C, Mezzadra R, Slagter M, Dijkstra K, Kluin RJC, Snaebjornsson P, Milne K, Nelson BH, Zijlmans H, Kenter G, Voest EE, Haanen JBAG, Schumacher TN. Low and variable tumor reactivity of the intratumoral TCR repertoire in human cancers. Nat Med. 2018

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 Tumor Infiltrating Lymphocytes (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 Schumacher, Kvistborg and Blank lab at the NKI-AVL and with national and international collaborators.

Highlights 2018

In collaboration with Sanquin and one European cancer center in Copenhagen, Denmark, we are continuing our international, randomized controlled phase III trial in stage IV melanoma patients, comparing Tumor Infiltrating Lymphocytes (TIL) with standard of care for second line treatment. Enrollment of patients started in October 2014. Up to date 67 patients have been randomized. Materials (liquid and tumor biopsies) are being collected for translational research. We have established additional funding from KWF to open new clinical centers to increase recruitment.

In pre-clinical 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 been tested in a phase I clinical trial (Prof G 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, and vaccine induced E6 and E7 directed T cell responses have been detected directly *ex vivo* in blood to monitor the immunogenicity of these therapeutic vaccines.

Together with a third party and the Voest lab, we are working on strategies to extract tumor reactive cells from the blood as novel treatment option.
In addition, we have an exciting collaboration with NEON therapeutics (Cambridge, MA), in which we develop new T cell therapies directed against patient specific neo-antigens. For this collaboration, large scale optimization runs are currently ongoing.

Biostatistics

Michael Hauptmann

Group leader
Division Psychosocial Research and Epidemiology

Michael Hauptmann PhD Group leader
Katarzyna Jóźwiak PhD Academic staff
Sander Roberti MSc PhD student
Doug Stram MSc PhD student
John Zavrakidis MSc Junior researcher

Selected publications

Groot HJ, Lubberts S, de Wit R, Witjes JA, Kerst JM, de Jong IJ, Groenewegen G, van den Eertwegh AJM, Poortmans PM, Klumpen H, van den Berg HA, Smilde TJ, Vanneste BGL, Aarts MJB, Incrocci L, van den Bergh ACM, Jóźwiak K, van den Belt-Dusebout AW, Horenblas S, Gietema JA, van Leeuwen FE, Schaapveld M. Risk of solid cancer after treatment for testicular germ cell cancer in the platinum era. J Clin Oncol, 2018;36(4):2504-2513

Lubin JH, Hauptmann M, Blair A. Indirect adjustment of relative risks of an exposure with multiple categories for an unmeasured confounder. Ann Epidemiol 2018;28(11):801-807

Meulepas JM, Ronckers CM, Smets AMJB, Nievelstein RAJ, Gradowska P, Lee C, Jahnen A, van Straten M, de Wit MY, Zonnenberg B, Klein WM, Merks JH, Visser O, van Leeuwen FE, Hauptmann M. Radiation Exposure From Pediatric CT Scans and Subsequent Cancer Risk in the Netherlands. J Natl Cancer Inst 2018

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 basic, pre-clinical, clinical and epidemiological research.

Cancer risk after diagnostic medical radiation exposure

Computed tomography (CT), a strong diagnostic tool, delivers higher radiation doses than most imaging modalities. As CT use has increased rapidly, radiation protection is important, particularly among children. For a nationwide retrospective cohort of 168 394 children who received one or more pediatric CT scans in a Dutch hospital between 1979 and 2012, we obtained cancer incidence, vital status, and confounder information by record linkage with external registries. The estimated annual number of pediatric CT scans in the Netherlands increased from 7,731 in 1990 to 26,023 in 2012. Mean cumulative bone marrow doses were 9.5 mGy at the end of follow-up, and leukemia risk (excluding myelodysplastic syndrome) was not associated with cumulative bone marrow dose (44 cases). Cumulative brain dose was on average 38.5 mGy and was statistically significantly associated with risk for malignant and nonmalignant brain tumors combined (ERR/100 mGy: 0.86, 95% confidence interval = 0.20 to 2.22, P = 0.002, 84 cases). These results indicate that CT-related radiation exposure increases brain tumor risk, and we estimate that the approximately 10,000 annual head CT scans among Dutch children lead to one brain tumor case annually attributed to radiation. Careful justification of pediatric CT scans and dose optimization, as are customary in many hospitals, are essential to minimize risks (Meulepas et al, JNCI in press). Johanna Meulepas received her PhD in 2018 for this work.

Indirect adjustment of relative risks for unmeasured confounders

In observational epidemiologic studies, there is often concern that an unmeasured variable might confound an observed association. Investigators can assess the impact from such unmeasured variables on an observed relative risk (RR) by utilizing externally sourced information and applying an indirect adjustment procedure. Although simple and easy to use, this approach applies to exposure and confounder variables that are binary. Other approaches eschew specific values and provide only bounds on the potential bias. For both multiplicative and additive RR models, we developed formulae for indirect adjustment of observed RRs for unmeasured potential confounding variables when there are multiple categories. In addition, we suggest an alternative strategy to identify the characteristics that the confounder must have to explain fully the observed association. We use examples involving studies of pediatric computer tomography scanning and leukemia and nuclear radiation workers and smoking to demonstrate that with externally sourced information, an investigator can assess whether confounding from unmeasured factors is likely to occur (Lubin et al, Am J Epidemiol 2018).

Statistical collaboration

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.

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.

H

Hugo Horlings

Group leader
Division of Molecular Pathology

Hugo Horlings MD PhD Clinical group leader
Iris Nederlof PhD student
Michiel de Maaker Technical staff

Selected publications

Li H, van der Leun AM, Yofe I, Lubling Y, Gelbard-Solodkin D, van Akkooi ACJ, van den Braber M, Rozeman EA, Haanen JBAG, Blank CU, Horlings HM, David E, Baran Y, Bercovich A, Lifshitz A, Schumacher TN, Tanay A, Amit I. Dysfunctional CD8 T Cells Form a Proliferative, Dynamically Regulated Compartment within Human Melanoma. Cell. 2018

Sobral-Leite M, Van de Vijver K, Michaut M, van der Linden R, Hooijer GKJ, Horlings HM, Severson TM, Mulligan AM, Weerasooriya N, Sanders J, Glas AM, Wehkamp D, Mittempergher L, Kersten K, Cimino-Mathews A, Peters D, Hooijberg E, Broeks A, van de Vijver MJ, Bernards R, Andrulis IL, Kok M, de Visser KE, Schmidt MK. Assessment of PD-L1 expression across breast cancer molecular subtypes, in relation to mutation rate, BRCA1-like status, tumor-infiltrating immune cells and survival. Oncoimmunology. 2018;7(12)

Wang L, Leite de Oliveira R, Huijberts S, Bosdriesz E, Pencheva N, Brunen D, Bosma A, Song JY, Zevenhoven J, Los-de Vries GT, Horlings HM, Nuijen B, Beijnen JH, Schellens JHM, Bernards R. An Acquired Vulnerability of Drug-Resistant Melanoma with Therapeutic Potential. Cell. 2018;173(6):1413-1425. e14

Computational pathology

Last year, I finished my translational and applied cancer research fellowship from the Dutch Cancer Society (KWF 2014-2018). During this fellowship I focused on the use of molecular biomarkers in daily practice of pathology to refine the diagnosis and treatment of breast and ovarian cancer. This fellowship gave me opportunities to obtain extensive skills in the application of large scale and high throughput genomics technologies in clinical settings, which will be essential for a pathologist to empower precision medicine. This fellowship has been in collaboration with; 1) the Department of Pathology of Antoni van Leeuwenhoek; 2) laboratory of professor René Bernards at the Netherlands Cancer institute; 3) laboratory of professor David Huntsman at the Centre for Translational and Applied Genomics (CTAG), British Columbia Cancer Agency in Vancouver and 4) laboratory of professor Howard Chang at Stanford University, USA.

Together with professor Huntsman's team we investigated the impact of *FOXL2* mutation testing in a large cohort of Adult Granulosa Cell Tumor of the ovary (AGCT) diagnosed previously by conventional histology and immunohistochemistry. *FOXL2* mutation is a pathognomonic defining feature of AGCT and is not seen in other tumors, in particular other ovarian cancers. FOXL2 mutation testing was used to stratify 336 AGCTs from three European centers into three categories: 1) FOXL2 mutant molecularly defined AGCT (MD-AGCT) (n = 256 of 336), 2) FOXL2 wild-type AGCT (n = 17 of 336), 3) misdiagnosed other tumor types (n = 63 of 336). The overall and disease-specific survival of the misdiagnosed cases was lower than in the MD-AGCTs ($P < .001$). The historical, pre-molecular data underpinning our clinical understanding of AGCT was likely skewed by inclusion of misdiagnosed cases, and future management strategies should reflect the potential for surgical cure and long survival even after relapse [JNCI, 2016 Jun 13;108(11)].

Computational Pathology to empower precision medicine

I was recruited as a "junior" clinical group leader at the Netherlands Cancer Institute. My lab will have a strong translational theme and we will focus on the development of Computational Pathology approaches that combines clinical, pathology and genomics data with image analysis of the tumor to study cancer-immune interactions and their consequences modulating therapeutic sensitivity and tumor progression in breast and ovarian cancer patients. We will train powerful computers to recognize tumor and their microenvironment by annotating pathology samples from the clinic. We will analyze different regions within tumor samples from time of diagnosis, relapse and metastasis and combine it with data describing RNA, DNA and protein sequences of single cells to explore the impact of intra-tumor heterogeneity upon cancer immunity and progression. Combining these image-based quantitative results with genetic analysis of the cancer-immune interactions can be complementary or offer entirely new explanations to identity biomarkers to predict response to conventional chemotherapy, targeted or immunotherapy in women with breast and ovarian cancer.

Translational research in Immunotherapy Trials

We will collaborate with medical oncologists and basic scientist to perform translational research in clinical trials with the goal to discover and validate biomarkers that will empower personalized predictions concerning response to treatment. For example, last year in collaboration with the group of Marleen Kok we performed translational research of an Adaptive phase II randomized non-comparative trial of nivolumab after induction treatment in Triple-Negative Breast Cancer (TNBC) patients: *TONIC-trial*. We also support basic scientist to translate their fundamental research into clinical applications. For example, we contributed in 2017 to the discovery of CMTM6/4 as protein regulators of PD-L1 and last year we assessed CMTM6 expression in melanoma and lung cancer patients treated with immunotherapy to evaluate CMTM6 and PD-L1 expression as potential biomarker for response to immunotherapy.

Heinz Jacobs

Group leader
Division Immunology

Heinz Jacobs PhD Group leader
Mir Farshid Alemdehy PhD Post-doc
Muhammad Assad Aslam MSc PhD student
Alessandra Buoninfante MSc PhD student
Daniel de Groot MSc PhD student
Bas Pilzecker MSc PhD student
Ronak Shah MSc PhD student
Aldo Spanjaard MSc PhD student
Paul van den Berk BSc Technical staff

Selected publications

Aslam MA, Alemdehy MF, Pritchard CEJ, Song J-Y, Muhaimin FI, Wijdeven RH, Huijbers IJ, Neefjes J, and Jacobs H. Towards an understanding of C9orf82 protein/CAAP1 function. PLoS One. 2019; 14:e0210526

Buoninfante OA, Pilzecker B, Aslam MA, Zavrakidis I, van der Wiel R, van de Ven M, van den Berk PCM, and Jacobs H. Precision Cancer Therapy: Profiting from Tumor Specific Defects in the DNA Damage Tolerance System. Oncotarget. 2018; 9:18832-18843

Buoninfante OA. Physiological and Pharmacological Relevance of DNA Damage Tolerance. PhD Thesis, University of Amsterdam, July 5th 2018

Programming Mutagenesis and Epigenetics in Lymphocyte Biology

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 defects uncover a novel early erythroid-committed progenitor

DNA damage tolerance (DDT) enables DNA replication in the presence of replication roadblocks. DDT is regulated by $PCNA^{K164}$ ubiquitination and REV1. We now discovered that DDT is an essential capacity of the DNA damage response network. By intercrossing PcnaK164R mutant and Rev1KO mice, DDT was found essential for mammalian life. A compound mutation rendered hematopoietic stem cells (HSCs) and their precursors genetically unstable, instigating a pathological premature ageing process where the associated HSC depletion culminated in a severe, embryonic-lethal anemia. Single cell RNA-sequencing of the remaining HSCs and progenitors identified the earliest erythroid-committed progenitor (ECP). In line, this novel subset strictly depends on the erythroid transcription factor Klf1. In conclusion, DDT is an essential activity within the DNA damage response network that co-determines central biological processes like stem cell fitness, tissue homeostasis, and ageing.

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.

J

Jacqueline Jacobs

Group leader
Division
Oncogenomics

Jacqueline Jacobs PhD Group leader
Aurora Cerutti PhD Post-doc
Santiago Hernández Pérez PhD Post-doc
Inge de Krijger MSc PhD student
Zeliha Yalçin MSc PhD student
Judit Serrat MSc Technical staff

Telomere and Genome Integrity

Tight control of DNA repair is critical in maintaining genome integrity and in preventing or treating pathology, but the underlying processes are not well understood. As a consequence, we lack important knowledge about the causes underlying cancer development and the consequences of DNA-damaging anti-cancer therapies. Our work focuses on (erroneous) DNA damage response and repair activities at telomeres and DNA double-strand breaks (DSBs) and how they contribute to cancer and aging by causing cell death, cell senescence, loss of genome integrity or genomic instability. Our research is in large part directed by functional genetic screens or proteomics-based approaches aimed at identifying critical new factors, complemented with in-depth mechanistic follow-up and candidate-driven approaches.

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. A few years ago, we performed a functional genetic screen that helped us identify MAD2L2, a.k.a. REV7, as an unexpected factor that promotes NHEJ and inhibits HDR at telomeres and DSBs by inhibiting 5' DNA end-resection downstream of 53BP1/RIF1. Thereby MAD2L2 contributes to DNA repair pathway choice between NHEJ and HDR and to the synthetic lethality of BRCA1-deficient cancer cells treated with PARP inhibitors, with MAD2L2-loss causing PARP inhibitor resistance by restoring HR. How MAD2L2, lacking known enzymatic activities itself, acts to inhibit resection was unclear.

We therefore further investigated how MAD2L2 operates in DNA repair control by investigating the protein complexes that MAD2L2 engages in. We identified a previously uncharacterized protein, SHLD2 (FAM35A), as a novel interactor of MAD2L2 that we found to functionally resemble MAD2L2 with respect to its role in DNA repair pathway choice. In a collaborative effort with other research groups we established that SHLD2 and another previously uncharacterized protein SHLD1, together with MAD2L2, form a complex called Shieldin. Shieldin protects DNA ends against excessive resection, thereby promoting repair by NHEJ and counteracting HDR.

Loss of Shieldin factors makes BRCA1-deficient cells resistant to PARP inhibitors, but increases their sensitivity to cisplatin, suggesting how defining the SHLD1/2 status of BRCA1-deficient tumours might aid patient stratification and yield new treatment opportunities. In collaborative work with the Jonkers and Rottenberg labs at the NKI we also implicated the CST complex in DNA repair pathway choice and PARP-inhibitor sensitivity.

Furthermore, we addressed how DNA repair pathway choice is controlled in concert with the DNA replication machinery, such that during S-phase, when NHEJ and HR pathways are both active and un-replicated and replicated DNA regions co-exist, HR only operates on replicated regions of the genome. We found that replication-associated dilution of H4K20me2 distinguishes pre-replicative from post-replicative chromatin to locally direct the NHEJ-promoting 53BP1/RIF1 complex to pre-replicative chromatin and the HR-promoting BRCA1 protein to post-replicative chromatin.

Selected publications

Dev H, Chiang TW#, Lescale C#, de Krijger I#, Martin AG, Pilger D, Coates J, Sczaniecka-Clift M, Wenming Wei, Ostermaier M, Herzog M, Lam J, Shea A, Demir M, Wu Q, Yang F, Fu B, Lai Z, Balmus G, Belotserkovskaya R, Serra V, O'Connor MJ, Bruna A, Beli P, Pellegrini L, Caldas C, Deriano L*, Jacobs JJL*, Galanty Y* and Jackson SP*. Shieldin complex promotes DNA end-joining and counters homologous recombination in BRCA1-null cells. Nat Cell Biol. 2018;20(8):954-965
#these authors contributed equally
*co-corresponding authors

Barazas M, Annunziato S, Pettitt SJ, de Krijger I, Ghezraoui H, Roobol SJ, Lutz C, Frankum J, Song F, Brough R, Evers B,Gogola E, Bhin J, van de Ven M, van Gent DC, Jacobs JJL, Chapman R, Lord CJ, Jonkers J and Rottenberg S. The CST complex mediates end-protection at double-strand breaks and promotes PARP inhibitor sensitivity in BRCA1-deficient cells. Cell Rep. 2018;23(7):2107-2118

Simonetta M, de Krijger I, Serrat J, Moatti N, Fortunato D, Hoekman L, Bleijerveld OB, Altelaar AFM, Jacobs JJL. H4K20me2 distinguishes pre-replicative from post-replicative chromatin to appropriately direct DNA repair pathway choice by 53BP1-RIF1-MAD2L2. Cell Cycle. 2018;17(1):124-136

Kees Jalink

Division head (ad int.), group leader Division Cell Biology

Kees Jalink PhD Group leader
Bram van den Broek PhD Academic staff
Rolf Harkes PhD Post-doc
Leila Nahidi PhD Post-doc
Jeffrey Klarenbeek MSc Technical staff

Selected publications

Argenzio E, Klarenbeek J, Kedziora KM, Nahidiazar L, Isogai T, Perrakis A, Jalink K, Moolenaar WH, Innocenti M. Profilin binding couples chloride intracellular channel protein CLIC4 to RhoA-mDia2 signaling and filopodium formation. J Biol Chem. 2018;293(50):19161-19176

Kamermans A, Planting KE, Jalink K, van Horssen J, de Vries HE. Reactive astrocytes in multiple sclerosis impair neuronal outgrowth through TRPM7-mediated chondroitin sulfate proteoglycan production. Glia. 2019;67(1):68-77

Kuipers AJ, Middelbeek J, Vrenken K, Pérez-González C, Poelmans G, Klarenbeek J, Jalink K, Trepat X, van Leeuwen FN. TRPM7 controls mesenchymal features of breast cancer cells by tensional regulation of SOX4. Biochim Biophys Acta Mol Basis Dis. 2018;1864(7):2409-2419

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 like FRET, FLIM and FCCS aim to provide information about the **function** of molecules, rather than just static images of their position within the cell. We also develop methods, hard- and software for various advanced microscopy applications. These techniques are used in research projects in our group as well as in collaborations within and outside our institute.

High-content screening

Conventional microscopy screens typically entail low-resolution, static images of a treatment endpoint. In high content screening, we aim to bring the full power of live-cell confocal microscopy to the screens. We have completed a screen of 300 candidate genes that have been selected for playing a possible role in determining the dynamics of the intermediate filament network. High-quality time-lapse recordings of HaCaT cells expressing YFP-tagged keratin-14 were obtained and analyzed for a number of morphometric and dynamic parameters. An analysis method capable of detecting the peculiar continuous inward movement of tangential keratin fibers was devised, and the most interesting candidates were followed up upon in collaboration with Dr. R. Windoffer at Aachen University.

FLIM imaging on wide-field and confocal microscopes

This year saw important progress in fast Fluorescence Lifetime Imaging (FLIM) in our lab. FLIM records the fluorescence lifetime of a fluorophore, i.e. the average time that a fluorophore remains in the excited state following excitation and is an intrinsically quantitative method to detect molecular interactions in living cells. Collaborating with industry and with leading laboratories in Delft and Amsterdam, an innovative toggling camera was constructed and integrated on a wide-field microscope in the lab. We also developed the necessary new paradigms and algorithms to operate it. FLIM 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, IP_3 and ERK signaling.In May we completed a 2-year intense collaboration with Leica, a leading manufacturer of advanced microscopy equipment. In response to our analysis of certain shortcomings in previous generation instrumentation, Leica developed the FALCON system, capable of detecting FLIM much faster, and virtually free of detection artifacts. We intensely α- and β-tested hardware and algorithms and provided valued feedback. As a result, we now have an extremely advanced confocal FLIM microscope at our disposal, which – due to our feedback – possesses exactly the functionality we need for our work.

Marrying functional imaging with high-content screening

This year we hope to finish setting up the FLIM microscope for screening purposes. This will allow us to study cell dynamic cellular events, such as signaling, metabolism and chromosome segregation efficiently using genetic (either genome-wide or gene subsets) or small-molecule screening.
We conduct screens to identify gene products involved in receptor desensitization by reading out signals in the *Galpha-q* and *Galpha-s* pathways. Screening of the effects of dynamic perturbations is also automated, both implemented by flexible micro-fluid administration of agonists and by optogenetic perturbations.

J

Jos Jonkers

Division head,
Senior group leader
Division of Molecular Pathology

Jos Jonkers PhD Group leader
Jinhyuk Bhin PhD Post-doc
Peter Bouwman PhD Senior post-doc
Julia Houthuijzen PhD Post-doc
Arne Nedergaard Kousholt PhD Post-doc
Frank Rolfs Post-doc
Daniel Zingg PhD Post-doc
Stefano Annunziato MSc PhD student
Chiara Brambillasca MSc PhD student
Lisette Cornelissen MSc PhD student
Julian de Ruiter MSc PhD student
Stefan Hutten PhD student
Sjors Kas MSc PhD student
Catrin Lutz PhD student
Ana Moises Da Silva PhD student
Sarah Moser PhD student
Mariana Paes Dias PhD student
Emilia Pulver PhD student
Koen Schipper MSc PhD student
Roebi de Bruijn MSc Bioinformatician
Hanneke van der Gulden Technical staff
Ingrid van der Heijden Technical staff
Ellen Wientjens Technical staff
Madelon Badoux Research assistant
Anne Paulien Drenth Research assistant
Anna Gandaglia Research assistant
Eva Schut-Kregel Research assistant
Eline van der Burg Research assistant
Julia Yemelyanenko Research assistant

Selected publications

Barazas M, [...], Jonkers J, Rottenberg S. The CST complex mediates end protection at double-strand breaks and promotes PARP inhibitor sensitivity in BRCA1-deficient cells. Cell Rep. 2018;23(7):2107-2118

Gogola E, [...], Jonkers J, Rottenberg S. Selective loss of PARG restores PARylation and counteracts PARP inhibitor-mediated synthetic lethality. Cancer Cell. 2018;33(6):1078-1093

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) study tumor cell-intrinsic and -extrinsic mechanisms of breast cancer development and progression; (2) develop novel therapeutic strategies for prevention and treatment of breast tumors; (3) study mechanisms of acquired resistance to targeted therapeutics.

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.

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 shown that PARPi resistance can be induced by 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.

Therapy resistance in ILC

We used *in vivo* Sleeping Beauty (SB) transposon mutagenesis to screen for genes conferring *in vivo* resistance to the FGFR inhibitor AZD4547 in ILC. This approach 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 the utility of *in vivo* insertional mutagenesis for identifying therapy resistance mechanisms.

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 rodent 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.

Marleen Kok

Group leader Division Molecular Oncology & Immunology

Marleen Kok MD PhD Group Leader
Iris Nederlof MD PhD student
Leonie Voorwerk MD PhD student
Marieke Bruggeman MSc Technical staff
Chris Klaver MSc Technical staff

Selected publications

Agahozo A, Hammerl D, Debets R, Kok M, van Deurzen C. Tumor infiltrating lymphocytes and ductal carcinoma in situ of the breast: friends or foes? Mod Pathol, 2018;31(7):1012-1025

Kok M, Winer E, Loi S. Passion for immune checkpoint blockade in breast cancer? Comments on Impassion 130. Ann Oncol, 2018

Sobral-Leite M, Van de Vijver K, Michaut M, van der Linden R, Hooijer G, Horlings H, Severson T, Mulligan A, Weerasooriya N, Sanders J, Glas A, Wehkamp D, Mittempergher L, Kersten K, Cimino-Mathews A, Peters D, Hooijberg E, Broeks A, Andrulis I, van de Vijver M, Bernards R, Kok M, de Visser K, Schmidt M. PD-L1 expression and the immune landscape of breast cancer molecular subtypes. Oncoimmunology 2018;7(12)

Improving breast cancer immunotherapy

Cancer immunotherapy, especially PD1-blockade, has resulted in durable anti-tumor responses in a subgroup of breast cancer patients. However, the overall response rates are still modest and more clinical and translational research is vital to bring this treatment strategy to the clinic. Using innovative clinical trial approaches as well as applying state-of-the-art knowledge from fundamental cancer immunology and biology, we work on i) the identification of those breast cancer patients that will benefit from immunotherapy, and ii) a better understanding of the interactions between breast cancer and tumor-associated as well as circulating immune cells in order to develop novel immunomodulatory strategies.

Modulation of the tumor microenvironment to improve response to PD-1 blockade

The response rate of triple negative breast cancer (TNBC) patients to PD-1 blockade is low, highlighting an urgent clinical need for strategies that render the TNBC tumor microenvironment (TME) more sensitive to PD-1 blockade. Immunomodulatory mechanisms have been proposed for both chemotherapy and irradiation, but it has not been established whether these therapies may improve efficacy of PD-1 blockade by favorably changing the TME. Patients with metastatic TNBC were randomized to anti-PD1 without induction or to one of four induction treatments, consisting of irradiation or a two-week low-dose regimen of cyclophosphamide, cisplatin or doxorubicin, all followed by anti-PD-1. The majority of clinical responses were observed on anti-PD1 in the cisplatin and doxorubicin induction cohorts. After doxorubicin and cisplatin induction, we detected an upregulation of immune-related genes, involved in PD-1/PD-L1, and T-cell cytotoxicity pathways. This was supported by enrichment among upregulated genes related to inflammation, JAK-STAT and TNFα-signaling after doxorubicin. In addition, we observed a trend towards increased T-cell infiltration, measured using T-cell receptor (TCR) sequencing, after doxorubicin. Together, the data suggest that short-term doxorubicin and cisplatin may induce a more favorable TME and increase the likelihood of response to PD-1 blockade in TNBC. Results have been presented at ASCO 2018 (J Clin Oncol 36, no. 15_suppl, 1012).

Immune-related invasive lobular breast cancer

Recently, genomic profiling showed that within invasive lobular breast cancer (ILC) an 'immune-related' subtype exists. Besides, in a previously established mouse model for mILC, a synergistic effect of platinum and checkpoint inhibitors was observed (dr Karin de Visser group). Currently we are investigating the efficacy and immunomodulatory capacity of PD-1 blockade in combination with platinum agents in patients with metastatic ILC.

Systemic immune characteristics in breast cancer patients

There is now substantial evidence from preclinical studies that suppressive immune cells and soluble immune mediators can blunt the anti-cancer T cells response. Right now the key question is whether this immunosuppressive phenomenon is present in breast cancer patients and whether it is important for response to immunotherapy. In collaboration with the group of dr Karin de Visser we have set up a pipeline for comprehensive analyses of these systemic immunosuppressive components using high-dimensional flow cytometry combined with functional assays on fresh material from breast cancer patients.

Pia Kvistborg

Group leader
Division Molecular Oncology and Immunology

Pia Kvistborg PhD Group leader
Anastasia Gangaev PhD student
Steven Ketelaar PhD student
Kelly Hoefakker MSc Technical staff
Sanne Patiwael Technical staff

Selected publications

Blank CU, Rozeman EA, Fanchi LF, Sikorska K, van de Wiel B, Kvistborg P, Krijgsman O, van den Braber M, Philips D, Broeks A, van Thienen JV, Mallo HA, Adriaansz S, Ter Meulen S, Pronk LM, Grijpink-Ongering LG, Bruining A, Gittelman RM, Warren S, van Tinteren H, Peeper DS, Haanen JBAG, van Akkooi ACJ, Schumacher TN. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med. 2018;24(11):1655-1661

Kvistborg P, Yewdell JW. Enhancing responses to cancer immunotherapy. Science. 2018;359(6375):516-517

Schumacher TN, Scheper W, Kvistborg P. Cancer Neoantigens. Annu Rev Immunol. 2018

T cells in cancer

Immunocompetence in cancer

It is well known that the tumor microenvironment can be highly immunosuppressive and render intra-tumor T cells dysfunctional. Furthermore, there is evidence suggesting that this suppression is not restricted to the tumor site but can also occur systemically. Such immune deviation has for instance been demonstrated by looking at dendritic cells isolated from peripheral blood of cancer patients with various types of solid tumors. However, we currently lack knowledge regarding systemic dysfunction of T cells in cancer patients. We are investigating this issue by comparing the state of T cells from stage IV, stage III melanoma patients and healthy donors. To allow this direct comparison between a similar set of T cell reactivities, we will focus on virus-specific T cells specific for EBV, CMV and Influenza A. Our experimental approach is to conjugate our in-house made pMHC multimers with oligo-barcodes so that we can obtain information regarding TCR sequence, gene expression profiles and antigen-specificity on a single cell level.

T cell functionality and antigen-specificity

A main research line in our group is to investigate the functional difference between T cells specific for e.g., self-antigens and tumor-specific mutated 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. Such imprinted differences in T cell states are likely to influence the responsiveness to immunotherapies such as checkpoint targeting therapies. Therefore, we are investigating the change in T cell states upon checkpoint targeting therapies focusing on T cell responses with different antigen-specificities. Such knowledge can be utilized 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.

Tineke Lenstra

Group leader
Division Gene Regulation

Tineke Lenstra PhD Group leader
Ineke Brouwer PhD Post-doc
Biljana Atanasovska PhD Post-doc
Heta Patel BSc PhD student
Gert-Jan Kuijntjes PhD student
Aleksandra Balwierz PhD Technical staff
Wim Pomp Technical specialist

Publication

Van Welsem T, Korthout T, Ekkebus R, Morais D, Molenaar TM, van Harten K, Poramba-Liyanage DW, Sun SM, Lenstra TL, Srivas R, Ideker T, Holstege FCP, van Attikum H, El Oualid F, Ovaa H, Stulemeijer IJE, Vlaming H, van Leeuwen F. Dot1 promotes H2B ubiquitination by a methyltransferase-independent mechanism. Nucleic Acids Res. 2018;46(21):11251-11261

Transcription dynamics in single cells

Gene expression is tightly regulated to ensure that genes are transcribed in the right cell at the right time. Single-cell studies have shown that cells in a population can show considerable heterogeneity in gene expression, and 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 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. However, the origin and regulators of bursting remain largely unknown. Our lab uses a single-molecule RNA labeling technique to directly visualize and measure transcriptional bursts in both yeast and mammalian cells to understand how different levels of regulation control bursting.

Transcription factor dwell time controls burst size

Using a combination of *in vitro* and *in vivo* single-molecule imaging approaches, we directly correlated binding of a transcription factor (TF) with the transcriptional bursting kinetics of its target genes in living yeast cells. We find that the TF dwell times depends on the affinity of the binding site and sets the transcriptional burst size. Using a novel imaging platform, we simultaneously tracked TF binding and transcription at one locus, revealing the timing and correlation between TF binding and transcription. Our data support a model where multiple polymerases initiate during a burst as long as the TF is bound to DNA, and a burst terminates upon TF dissociation.

The effect of chromatin on bursting

Nucleosome binding in the promoter region of genes can affect the accessibility and binding dynamics of transcriptional regulators to DNA binding sites, which may regulate bursting. We have setup assays to conditionally change the nucleosome promoter structure by dynamically depleting nucleosome remodeling complexes from the nucleus. Several complexes were identified that influence transcriptional bursting, which we are currently characterizing further. 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.

Bursting of neighboring genes

Closely positioned genes may affect each other's transcription, for example by propagation of supercoils generated by transcription. We have setup an dual-color imaging assay technique to simultaneously monitor bursting of divergent and tandem gene pairs in the same cell. We showed that transcriptional bursts of divergent genes are correlated, and that transcription of one gene increases transcription of its divergent neighbour. We are currently using different perturbation approaches to determine the mechanism of this correlation.

L

Sabine Linn

Group leader
Division Molecular Pathology

Sabine Linn MD PhD Group leader
Leonora de Boo MD PhD student
Vincent de Jong MD PhD student
Dinja Kruger MD PhD student
Annelot van Rossum MD PhD student
Sonja Vliek MD PhD student
Mark Opdam Technical Staff

Selected publications

Dackus G, Jozwiak K, Sonke GS, van der Wall E, van Diest PJ, Hauptmann M, Siesling S and Linn SC. Optimal adjuvant endocrine treatment of ER+/HER2+ breast cancer patients by age at diagnosis: A population-based cohort study. Eur J Cancer 2018;90:92-101

Kruger DT, Beelen KJ, Opdam M, Sanders J, van der Noort V, Boven E and Linn SC. Hierarchical clustering of activated proteins in the PI3K and MAPK pathways in ER-positive, HER2-negative breast cancer with potential therapeutic consequences. Br J Cancer 2018;119(7):832-839

Van Rossum A, Kok M, van Werkhoven E, Opdam M, Mandjes I, van Leeuwen-Stok A, van Tinteren H, Imholz A, Portielje J, Bos M, van Bochove A, Wesseling J, Rutgers E, Linn S, Oosterkamp H; MATADOR Trialists' Group. Adjuvant dose-dense doxorubicin-cyclophosphamide versus docetaxel-doxorubicin-cyclophosphamide for high-risk breast cancer: First results of the randomised MATADOR trial (BOOG 2004-04). Eur J Cancer 2018;102:40-48

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 and develop tests that will 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 groups of Jos Jonkers and Jacco van Rheenen, who use genetically engineered mouse models for breast cancer, to study differential chemo sensitivity 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 prognostic molecular classifiers for adjuvant systemic treatment advice in breast cancer.

Differential benefit of adjuvant taxanes

The MATADOR trial (ISRCTN61893718) randomized 664 patients between 6 cycles adjuvant docetaxel-doxorubicin-cyclophosphamide ($T_{75}A_{50}C_{500}$) and 6 cycles dose-dense AC ($ddA_{60}C_{600}$). We employed RNA-sequencing data of pretreatment tumor samples to investigate the association between expression levels and recurrence-free survival via a data-driven and a biology-driven approach using hallmark gene sets and tumor cell deconvolution. The data-driven approach did not yield predictive information, while the biology-driven approach did. Overall, both treatments were equally effective. However, specific phenotypes fared better after either TAC, or ddAC. These findings require validation.

Molecular mechanisms underlying sensitivity to high dose alkylating agents

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 CNAs. We are currently exploring the predictive potential of these genomic scars in several clinical trials utilizing DNA damaging agents. In addition, we are collecting more data on putative resistance modifiers, such as XIST and 53BP1.

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.
We have recently generated RNA-sequencing data for ±450 triple negative breast cancers of women aged 40 years or younger at diagnosis. All were node-negative. Median follow-up is 17 years. In the Netherlands, before 1999, N0 patients did not receive adjuvant chemotherapy. Hence, these patients are all systemic treatment naïve. We shall develop a prognostic classifier for this group of patients.

Rene Medema

Group leader
Division Cell Biology

Rene Medema PhD Group leader
Lenno Krenning PhD Research associate
Jonne Raaijmakers PhD Research associate
Femke Feringa PhD Post-doc
Apostolos Menegakis PhD Post-doc
Jeroen van den Berg MSc PhD student
Anoek Friskes MSc PhD student
Anna Gonzalez Manjon MSc PhD student
Louise Janssen MSc PhD student
Lisa Koob MSc PhD student
Mar Soto MSc PhD student
Xabier Vergara MSc PhD student
Rob Klompmaker Technical staff
Chantal Vaarting Technical staff

Selected publications

Feringa FM, Raaijmakers JA, Hadders MA, Vaarting C, Macurek L, Heitink L, Krenning L, Medema RH. Persistent repair intermediates induce senescence. Nat Commun. 2018;9:3923

Janssen LME, Averink TV, Blomen VA, Brummelkamp TR, Medema RH, Raaijmakers JA. Loss of Kif18A Results in Spindle Assembly Checkpoint Activation at Microtubule-Attached Kinetochores. Curr Biol. 2018;28:2685-96

Van den Berg J, A GM, Kielbassa K, Feringa FM, Freire R, Medema RH. A limited number of double-strand DNA breaks is sufficient to delay cell cycle progression. Nucleic Acids Res. 2018;46:10132-44

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. The group uses the knowledge that is generated to define and experimentally test new anti-cancer strategies.

In our work on the DNA damage response we have been trying to understand how the fate of a cell with damaged DNA is determined. We would like to obtain answers to questions like: how many breaks are required to impose a cell cycle arrest, how many breaks are required to produce a permanent cell cycle arrest, and does it matter where in the genome these breaks occur? The answers to these important questions might help us understand and predict the response of a tumor to DNA damaging agents that are commonly used in the treatment of cancer.

In 2018 we published our first paper using a new tool we have developed in the lab that consists of a CRISPR/Cas9-based system that permits us to efficiently introduce DSBs at defined sites in the genome. Using this system, we can ask how many breaks are needed to produce a cell cycle arrest, and resolve if it matters where in the genome such breaks occur. In this first paper we showed that a guide RNA targeting only a single site in the human genome is sufficient to trigger a checkpoint response that is potent enough to delay cell cycle progression. Abrogation of this checkpoint leads to aneuploid progeny (van den Berg et al., Nucleic Acids Res, 2018).

In addition, using ionizing radiation, we showed that the decision to withdraw from the cell cycle in G2 is induced through delayed processing of double strand breaks. We showed that stalled HR-mediated repair results in high levels of resected DNA and enhanced ATR-dependent signaling, allowing p21 to rise to levels at which it drives cell cycle exit (Feringa et al., Nat Commun, 2018). These data imply that cells have the capacity to discriminate breaks that can be repaired from breaks that are difficult to repair at a time when repair is still ongoing.

In our work addressing the process of chromosome segregation we made use of the haploid genetic screens developed by the Brummelkamp lab to identify synthetic lethal and synthetic viable interactions with spindle assembly checkpoint components Mad1 and Mad2. This allowed us to show that Bub1 is required for chromosome alignment and only has a minor contribution in checkpoint signaling (Raaijmakers et al., Cell Reports, 2018). In addition, we were able to resolve a longstanding debate in the field, namely that lack-of-tension across the kinetochores is sufficient to directly activate the spindle assembly checkpoint (Janssen et al., Curr. Biol., 2018).

Gerrit Meijer

Group leader
Division Diagnostic Oncology

Gerrit Meijer MD PhD Group leader
Beatriz Carvalho PhD Principal investigator
Remond Fijneman PhD Principal investigator
Janneke van Denderen PhD Academic staff
Linda Bosch PhD Senior post-doc
Meike de Wit PhD Senior post-doc
Sanne Martens-de Kemp PhD Post-doc
Gosia Komor MSc PhD student
Meta van Lanschot MD PhD student
Iris van 't Erve PhD student
Mariska Bierkens PhD Senior technical staff
Anne Bolijn Technical staff
Pien Delis-van Diemen Technical staff
Alex Henneman PhD Technical staff
Annemieke Hiemstra MSc Technical staff
Brenda Hijmans PhD Technical staff
Margriet Lemmens Technical staff
Pauline van Mulligen MA Technical staff
Brian Severins Technical staff
Marianne Tijssen Technical staff
Menno de Vries MSc Technical staff

Selected publications

Komor MA, et al. Consensus molecular subtype classification of colorectal adenomas. J Pathol. 2018;246(3):266-276

Van den Broek E, et al. MACROD2 expression predicts response to 5-FU-based chemotherapy in stage III colon cancer. Oncotarget. 2018;9(50):29445-2945

Van Lanschot MCJ, et al. Molecular profiling of longitudinally observed small colorectal polyps: A cohort study. EBioMedicine. 2019;39:292-300

Translational Gastrointestinal Oncology

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

The current Dutch population-wide screening program uses the immunochemical fecal occult blood screening test (FIT). Although efficient, FIT still misses approximately 30% of carcinomas and 70% of pre-malignant lesions. We aim to unravel the biology of adenoma to carcinoma progression, identify biomarkers and clinically validate new biomarker-based tests.
We gained more insight into the relation between morphologically-defined advanced adenomas and molecularly-defined high-risk adenomas, which are likely to progress to cancer. Candidate biomarkers for early detection were validated in large collections of clinically well-characterized tumor and stool/FIT samples. Within the MOCCAS (MOlecular stool testing for Colorectal CAncer Surveillance) study, an interim analysis on the performance of molecular markers supports the notion that use of these markers could lead to less surveillance colonoscopies.

Patient stratification

Cancer is a heterogeneous disease. By DNA-, RNA-, and protein-profiling it becomes feasible to stratify patients according to their molecular tumor profile, and to optimize treatment for individual patients. The minute amounts of tumor material in liquid biopsies (i.e. blood samples), which can be obtained longitudinally and more easily compared to tissue biopsies, are also amenable to these assays.

Knowledge about the prevalence of chromosomal breakpoints in CRC is limited, and the impact of these genomic aberrations on patient outcome is poorly understood. MACROD2 is frequently affected by chromosomal breaks. We determined its predictive value in stage II and III CRC. In parallel, we collect blood samples in several nation-wide CRC studies, to investigate whether DNA mutation analysis of circulating cell-free DNA can be applied as biomarkers to better determine who to treat, how to treat, and when to treat CRC patients.

Translational research infrastructure

To improve translation 'from bench to bedside', logistics and data stewardship of clinical studies need to be optimized: data must be FAIR (Findable, Accessible, Interoperable and Reusable).
The Health Research Infrastructure (Health-RI) offers services for sustainable management of research data. Locally, we are loading clinical, biobanking, and molecular data from multiple TGO studies in the data integration platforms tranSMART and cBioPortal. Internationally, we align our data management with initiatives such as Cancer Core Europe and AACR GENIE.

Daniel Peeper

Division head, group leader Division Molecular Oncology & Immunology

Daniel Peeper PhD Group leader
Oscar Krijgsman PhD Senior post-doc
Thomas Kuilman PhD Senior post-doc
Astrid Alflen Post-doc
Xiangjun Kong PhD Post-doc
Pierre Lévy PhD Post-doc
Maarten Ligtenberg PhD Post-doc
Alexandra Terry Post-doc
Tushar Tomar PhD Post-doc
Georgi Apriamashvili MSc PhD student
Julia Boshuizen MD MSc PhD student
Juliana De Carvalho Neme Kenski MSc PhD student
Xinyao Huang MSc PhD student
Sofía Ibáñez Molero PhD student
Chun-Pu Lin PhD student
Sebastiaan Schieven PhD student
Alex van Vliet PhD student
David Vredevoogd MSc PhD student
Beaunelle de Bruijn MSc Technical staff
Nils Visser BSc Technical staff

Selected publications

Kluin RJC, Kemper K, Kuilman T, de Ruiter JR, Iyer V, Forment JV, Cornelissen-Steijger P, de Rink I, Ter Brugge P, Song JY, Klarenbeek S, McDermott U, Jonkers J, Velds A, Adams DJ, Peeper DS, Krijgsman O. XenofilteR: computational deconvolution of mouse and human reads in tumor xenograft sequence data. BMC Bioinformatics. 2018;19(1):366

Boshuizen J, Koopman LA, Krijgsman O, Shahrabi A, van den Heuvel EG, Ligtenberg MA, Vredevoogd DW, Kemper K, Kuilman T, Song JY, Pencheva N, Mortensen JT, Foppen MG, Rozeman EA, Blank CU, Janmaat ML, Satijn D, Breij ECW*, Peeper DS* (*co-corresponding), Parren PWHI. Cooperative targeting of melanoma heterogeneity with an AXL antibody-drug conjugate and BRAF/MEK inhibitors. Nature Med. 2018 ;24(2):203

Functional genomics for cancer and immune cell therapy

Introduction

We use function-based, genome-wide experimental strategies to develop rational combinatorial cancer treatment, targeting both cancer and immune cells. By screening for novel therapeutic targets and predictive biomarkers, we aim to achieve more durable clinical responses for patients. On the one hand, we are increasing our understanding of how cancer cells rewire their signaling networks, to expose and exploit new pharmacologically tractable tumor susceptibilities, also in the context of immunotherapy. On the other hand, we are manipulating various cell types from the patient's own immune system to boost their specific cytotoxicity towards tumor cells. With these function-based approaches, we develop new rational combinatorial therapies, which simultaneously eliminate the patients' tumors and harness their immune system.

Targeting tumor heterogeneity

Intratumor heterogeneity is a key factor contributing to therapeutic failure and, hence, cancer lethality. Heterogeneous tumors commonly show partial therapy responses, allowing for the emergence of drug-resistant clones that often express high levels of the receptor tyrosine kinase AXL. In melanoma, AXL-high cells are resistant to MAPK pathway inhibitors, whereas AXL-low cells are sensitive to these inhibitors, rationalizing a differential therapeutic approach. In collaboration with Genmab, which developed an AXL antibody-drug conjugate (Enapotamab vedotin, comprising a human AXL antibody linked to a microtubule-disrupting agent), we demonstrated that Enapotamab vedotin and MAPK pathway inhibitors cooperatively inhibited melanoma growth. Furthermore, by inducing AXL transcription, BRAF/MEK inhibitors potentiated the efficacy of Enapotamab vedotin. These findings provide proof of concept for the premise that rationalized combinatorial targeting of distinct populations in heterogeneous tumors may improve therapeutic effect, and merit clinical validation of Enapotamab vedotin in both treatment-naive and drug-resistant cancers in mono- or combination therapy.

Xenofilter

Mouse xenografts from (patient-derived) tumors (PDX) or tumor cell lines are widely used as models to study various biological and preclinical aspects of cancer. However, analysis of their RNA and DNA profiles is challenging, because they comprise sequencing reads not only from the grafted human cancer but also from the murine host. Therefore, we developed the open-source R-package XenofilteR, which separates mouse from human sequence reads based on the number of discordant base pairs between the reads and the reference genome. XenofilteR removes >99.9% of mouse reads from the sequence profiles while retaining SNPs and somatic mutations of human origin, thereby outperforming currently available tools. Therefore, XenofilteR is a very useful tool for all studies utilizing PDX, facilitating translational research.

Developing systems to integrate targeted and immunotherapy

Notwithstanding 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, we have built *in vitro* and *in vivo* systems to study interactions between tumor cells and T cells. We use these systems to perform function-based screens to develop combinatorial targeted and immunotherapy regimens to achieve more durable clinical responses. These screens have identified several unexpected targets that may be of therapeutic interest, and that are currently being characterized. 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.

Anastassis Perrakis

Group leader
Division Biochemistry

Structural biology

We aim to provide molecular insight to macromolecular interactions and structures, understanding how these regulate specific biological activities in space and in time. In parallel we develop concepts, algorithms, and software improving the methods for this work. Our work enables the development of new specific drugs and biologics.

Structural studies of Autotaxin

ATX produces the signalling phospholipid LPA; LPA and ATX are involved in cancer metastasis and other pathogenic situations. Previously, we found a new allosteric site at ATX. This prompted a detailed evaluation of the kinetics of the enzymatic activity of ATX, analysing kinetic data with a global modelling approach. This revealed a product activation mechanism, whereas hydrolysis of various LPC species is activated by various LPAs. Our focus since has been to understand the catalysis-independent signalling of ATX in different contexts.

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. A module in the N-terminus of Mps1, the NTE-TPR, as well as a C-terminal extension (CTE) and a Middle Region (MR) are important localizing of Mps1 to the kinetochores, competing with microtubules for binding to the NDC80 complex in the outer kinetochores, and is a major regulator of the SAC. Studying interactions of the NTE, CTE, MR, and the TPR, allowed progress in understanding how the Mps1 modules interact with the outer kinetochore complexes, modulating microtubule attachment.

We also contributed to the study of the dynein adaptor Spindly and the RZZ complex, which drive kinetochore expansion in a dynein-independent manner. We showed that C-terminal farnesylation and MPS1 kinase activity causes conformational changes of Spindly: dynamic kinetochore size regulation in mitosis is coordinated by a single, Spindly-based mechanism that promotes initial microtubule capture and subsequent correct maturation of attachments.

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. Well into the second decade since its discovery by Piet Borst and colleagues, we found a function of base J in non-telomeric regions, showed how 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, demonstrated that full-length JBP1 binding to DNA takes place in two distinct steps, and have characterised the low-resolution shape of the J-DNA complex with JBP1. Excitingly, we recently established a mass spectrometry based assay for JBP1 function and have done the groundwork towards an EM structure for the JBP1 protein.

Methods for X-ray crystallography

PDB-REDO is a project we lead together with Robbie Joosten in my group. We strive to make better crystallographic structure models by improving published structures and making them available through the PDB_REDO data bank, while providing a web-server that allows practicing crystallographers to take full advantage of the PDB_REDO procedure.

PDB_REDO is a decision-making system that makes rational decisions for the best crystallographic model optimization protocols. This year we continued our focus on using structural homology as a tool to create better structures, especially at low resolution. Using homology information we created a new algorithm to "transfer" flexible un-modelled loops from one structure to another, allowing us to build about 25,000 loops that were not previously in the PDB.

Anastassis Perrakis PhD Group leader
Robbie Joosten PhD Senior post-doc
Misbha Ud Din Ahmad PhD Post-doc
Yoshitaka Hiruma PhD Post-doc
Krista Joosten PhD Post-doc
Athanassios Adamopoulos PhD student
Bart van Beusekom PhD student
Fernando Salgado-Polo PhD student
Tatjana Heidebrecht Technical staff
Foteini Tsakou Technical staff
George Damaskos Software engineer
Maarten Hekkelman Software engineer

Selected publications

Sacristan C, Ahmad MUD, Keller J, Fermie J, Groenewold V, Tromer E, Fish A, Melero R, Carazo JM, Klumperman J, Musacchio A, Perrakis A, Kops GJ. Dynamic kinetochore size regulation promotes microtubule capture and chromosome biorientation in mitosis. Nat Cell Biol. 2018;20(7):800-810

Salgado-Polo F, Fish A, Matsoukas MT, Heidebrecht T, Keune WJ, Perrakis A. Lysophosphatidic acid produced by autotaxin acts as an allosteric modulator of its catalytic efficiency. J Biol Chem. 2018;293(37):14312-14327

Van Beusekom B, Joosten K, Hekkelman ML, Joosten RP, Perrakis A. Homology-based loop modeling yields more complete crystallographic protein structures. IUCrJ. 2018;5(Pt 5):585-594

Therapy escape of cancer

Sven Rottenberg

Group leader
Division Molecular Pathology

Sven Rottenberg DVM PhD Dipl ECVP Group leader
Christina Andronikou MSc PhD student
Marco Barazas MSc PhD student
Ewa Gogola MSc PhD student
Alexandra Duarte Technical staff

Selected publications

Duarte A, Gogola E, Sachs N, Barazas M, Annunziato S, de Ruiter J, Velds A, Blatter S, Houthuijzen J, van de Ven M, Clevers H, Borst P, Jonkers J*, Rottenberg S*. BRCA-deficient mouse mammary tumor organoids to study cancer drug resistance. Nat Methods. 2018;15:134-140

Barazas M, Annunziato S, Pettitt SJ, de Krijger I, Ghezraoui H, Roobol SJ, Lutz C, Frankum J, Song FF, Brough R, Evers B, Gogola E, Bhin J, van de Ven M, van Gent DC, Jacobs JJL, Chapman R, Lord CJ, Jonkers J*, Rottenberg S*. The CST complex mediates end protection at double-strand breaks and promotes PARP inhibitor sensitivity in BRCA1-deficient cells. Cell Rep. 2018;23:2107-2118

Gogola E, Duarte AA, de Ruiter JR, Wiegant WW, Schmid JA, de Bruijn R, James DI, Guerrero Llobet S, Vis DJ, Annunziato S, van den Broek B, Barazas M, Kersbergen A, van de Ven M, Tarsounas M, Ogilvie DJ, van Vugt M, Wessels LFA, Bartkova J, Gromova I, Andújar-Sánchez M, Bartek J, Lopes M, van Attikum H, Borst P, Jonkers J*, Rottenberg S*. Selective loss of PARG restores PARylation and counteracts PARP inhibitor-mediated synthetic lethality. Cancer Cell. 2018;33:1078-1093

* Corresponding authors

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 (NKI). Using our mouse models, we are also investigating the escape from local radiotherapy control (4) in collaboration with the NKI-AVL radiotherapist Gerben Borst.

Identification of the shieldin and CST complexes that counteract DNA end resection and cause PARP inhibitor resistance when lost

The synthetic lethal interaction between BRCA1 or BRCA2 deficiency and poly(ADP-ribose) polymerase (PARP) inhibition is a well-established therapeutic paradigm with encouraging clinical response rates. Despite this success, long-lasting clinical response rates in patients with advanced disease are limited by the development of resistance, the mechanisms of which have not been fully elucidated. Using the *K14cre;Brca1/2*$^{F/F}$*;p53*$^{F/F}$ (KB1P or KB2P) mouse models of hereditary breast cancer, we have identified PARPi resistance mechanisms that are independent of functional BRCA1/2 restoration. The BRCA1-independent resistance mechanisms predominantly involved the partial restoration of homologous recombination (HR) through re-wiring of the DNA damage response (DDR); for example, by loss of 53BP1. Although this loss partially restores end resection of DNA double-strand breaks (DSBs), the precise underlying mechanism was elusive. In collaboration with the groups of Dan Durocher (Lunenfeld-Tanenbaum Research Institute, Toronto), Ross Chapman (University of Oxford) and Chris Lord (ICR, London), we identified the RPA-like shieldin (SHLD1-SHLD2-SHLD3-REV7/MAD2L2) and CST (CTC1-STN1-TEN1) complexes as resection antagonists that act downstream of 53BP1. These findings might also have clinical implications, because loss-of-function mutations in the CST- or shieldin-encoding genes are predicted to cause clinical PARPi resistance. Moreover, we expect that these alterations provide new therapeutic vulnerabilities, because we recently found that depletion of the 53BP1-dependent DNA repair pathway enhances sensitivity to radiotherapy.

Loss of PARG restores PARylation and counteracts PARP inhibitor-mediated synthetic lethality

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. Our finding highlights an important aspect of PARPi therapy: the endogenous PARG activity in tumor cells is crucial for therapy success. 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.

Benjamin Rowland

Group leader
Division Gene Regulation

Benjamin Rowland PhD Group leader
Ahmed Elbatsh PhD Post-doc
Judith Haarhuis PhD Post-doc
Alberto García Nieto MSc PhD student
Claire Hoencamp MSc PhD student
Roel Oldenkamp MSc PhD student
Marjon van Ruiten MSc PhD student
Ángela Sedeño Cacciatore MSc PhD student
Laureen Willems BSc Technical staff

Publications

Allahyar A, Vermeulen C, Bouwman BAM, Krijger PHL, Verstegen MJAM, Geeven G, van Kranenburg M, Pieterse M, Straver R, Haarhuis JHI, Jalink K, Teunissen H, Renkens IJ, Kloosterman WP, Rowland BD, de Wit E, de Ridder J, de Laat W. Enhancer hubs and loop collisions identified from single-allele topologies. Nat Genet. 2018;50:1151-1160

Van Ruiten MS, Rowland BD. SMC complexes: Universal DNA looping machines with distinct regulators. Trends Genet. 2018;34:477-487

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 ring-shaped SMC complexes that can entrap DNA and build loops to provide structure to 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? How does cohesin contribute to the formation of the often megabase-sized loops that shape interphase chromosomes? And how does loop formation by these complexes affect nuclear organization and gene expression? We are addressing these questions using a multi-disciplinary approach that covers genetics, genomics, biochemistry and imaging, and through our fruitful collaborations also includes biophysics and crystallography.

Chromosome organization by cohesin

The cohesin complex is essential for the formation of chromatin loops across the genome. We recently discovered that the interphase genome is structured through a highly dynamic process that involves a continuous cycle of formation, loss and re-formation of loops by cohesin. We also found that the cohesin release factor WAPL limits the degree by which loops can be enlarged. Together, our findings support the model that cohesin structures chromosomes through the processive enlargement of DNA loops (Haarhuis et al., Cell 2017).

Cohesin is required for the formation of loops between CTCF sites along chromosomes. In collaboration with the laboratories of Wouter de Laat, Jeroen de Ridder and Elzo de Wit we have revealed that distant CTCF sites can be brought together in rosette-like structures that form through the collision of CTCF-bound loop anchors, and that cohesin release by WAPL counteracts the formation of these structures (Allahyar et al., Nat. Genet. 2018).

Chromosome condensation by condensin

Cohesin and condensin are enzymes with highly conserved ABC-like ATPases at their basis. These ATPase machineries each contain two distinct ATPase sites. In collaboration with the lab of Kim Nasmyth, we recently found that cohesin's ATPase sites have distinct roles, as only one of these sites controls DNA release (Elbatsh et al., Mol Cell, 2016 and Beckouët et al., Mol Cell, 2016). Acetylation proximal to this release ATPase site locks cohesin on DNA to establish enduring sister chromatid cohesion.

This year, we collaborated with the labs of Cees Dekker, Christian Haering and Elzo de Wit, and found that specifically one of condensin's ATPase sites drives loop formation, while the other site rather controls what type of DNA structures are formed. Condensin's ATPase thus controls condensation in a dual manner. We find that this mechanism is conserved from yeast to humans. Asymmetric ATPases with distinct roles for each ATPase site are likely to reflect a universal principle for SMC complexes that enables these ancient molecular machines to intricately control chromosome architecture.

Sanne Schagen

Group leader Division Psychosocial Research and Epidemiology

Sanne Schagen PhD Group leader
Michiel de Ruiter PhD Research associate
Joost Agelink van Rentergem PhD Post-doc
Heleen Feenstra PhD Post-doc
Kete Klaver PhD student
Emmie Koevoets PhD student
Philippe Lee Meeuw Kjoe PhD student
Kimberly van der Willik PhD student
Lenja Witlox PhD student
Jacobien Kieffer MSc Senior statistical analyst
Marianne Kuenen Research assistant

Selected publications

Stouten-Kemperman MM, de Ruiter MB, Boogerd W, Kerst JM, Kirschbaum C, Reneman L, Schagen SB. Brain Hyperconnectivity >10 Years After Cisplatin-Based Chemotherapy for Testicular Cancer. Brain Connect. 2018;8(7):398-406

Van der Willik KD, Koppelmans V, Hauptmann M, Compter A, Ikram MA, Schagen SB. Inflammation markers and cognitive performance in breast cancer survivors 20 years after completion of chemotherapy: a cohort study. Breast Cancer Res. 2018;20(1):135

Van der Willik KD, Ruiter R, Wolters FJ, Ikram MK, Stricker BH, Hauptmann M, Compter A, Schagen SB, Ikram MA. Mild Cognitive Impairment and Dementia Show Contrasting Associations with Risk of Cancer. Neuroepidemiology. 2018;50(3-4):207-215

Cognitive function in cancer patients

The projects constituting our lines of research center around the characterization of the incidence, pattern and course of cognitive problems associated with cancer and cancer therapies, the risk factors for cognitive problems and the pathophysiological mechanisms that underlie cognitive problems in patients with tumours either inside or outside the CNS. Our research is also directed to develop, evaluate and implement interventions to minimize and manage cognitive problems and to enhance quality of life and increase functional independence.

Trajectories of cognitive function prior to cancer diagnosis

Research suggests that non-central nervous system cancer may negatively impact the brain apart from cancer treatment. However, studies assessing cognitive function in newly diagnosed cancer patients cannot exclude psychological effects of diagnosis. To overcome these limitations, we investigated trajectories of cognitive function of patients before cancer diagnosis.

Between 1989-2013, 2,185 participants from the population-based Rotterdam Study were diagnosed with non-CNS cancer. Cognitive assessments were performed every three-five years using a neuropsychological battery from which the general cognitive factor was derived, assessing global cognitive function. We evaluated 1) whether shared risk factors for both cancer and cognitive impairment influence cognitive function by excluding test results within two years preceding cancer diagnosis and 2) the impact of subclinical cancer, thereby including all test results up to cancer diagnosis. Using linear mixed models we compared cognitive trajectories prior to diagnosis between cancer cases and age-matched cancer-free controls (1:2).

We found no evidence that cognitive function declines differently over time among individuals who will be diagnosed with cancer prior to disease manifestation than among individuals who will remain cancer-free; The general cognitive factor declined from study entry up to two years before cancer diagnosis at a similar rate for cases and controls (*P* difference=.763). In addition, the change of the general cognitive factor over time did not differ between cases and controls after inclusion of all test results up to diagnosis (*P* difference=.669).

Our results do not support the idea that cancer itself or shared risk factors for cancer and cognitive impairment play a role in the origination of cognitive impairment in non-CNS cancer.

Online assessment of cognitive function

We developed and tested a neuropsychological test battery that can be completed online without supervision, the Amsterdam Cognition Scan. The ACS is available in the Dutch and English language. We are currently working on a Swedish, French, Spanish and German version. The ACS is at present used in various clinical trials, such as the SUBITO study on the efficacy of high-dose chemotherapy for high-risk BRCA1-like breast cancer, and will soon be incorporated in the SONIA trial on the efficacy of endocrine therapy plus CDK4/6 in first or second line for hormone positive advanced breast cancer. Several behavioral and life-style intervention trials with the aim to diminish cognitive problems in cancer patients also use the ACS. We expect that this instrument will facilitates the collection of cognitive data in research. It also allows for more in-depth analysis of patients' responses, thereby contributing to our insight into the nature of cognitive problems following cancer and cancer therapies.

Alfred Schinkel

Group leader
Division
Pharmacology

Alfred Schinkel PhD Group leader
Cristina Lebre PhD Academic staff
Changpei Gan MSc PhD student
Stéphanie van Hoppe MSc PhD student
Wenlong Li MSc PhD student
Alejandra Martínez MSc PhD student
Margarida Martins MSc PhD student
Jing Wang MSc PhD student
Yaogeng Wang MSc PhD student

Genes and proteins involved in anticancer drug resistance and pharmacokinetics

We study genes and proteins that cause drug resistance or drug susceptibility in tumors, or influence the pharmacological and toxicological behavior of (anticancer) drugs and toxins, including carcinogens. Of special interest are multispecific drug efflux and uptake transporters, as well as drug-metabolizing enzymes. Insight into these systems may: i) improve chemotherapy and 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 understand the physiological, pharmacological and toxicological roles of the proteins involved we generate and analyze knockout or transgenic mice lacking or overexpressing the relevant genes. Below we describe a few recent studies illustrating our approach.

P-glycoprotein restricts brain accumulation and cytochrome P450-3A limits oral availability of the ALK/ROS1 inhibitor lorlatinib

Lorlatinib is a recently approved oral anaplastic lymphoma kinase (ALK) inhibitor for treatment of non-small-cell lung cancer. It was designed to have high membrane and blood-brain barrier permeability. We investigated the roles of the multidrug efflux transporters ABCB1 and ABCG2, and the multispecific drug-metabolizing enzyme CYP3A in plasma pharmacokinetics and tissue distribution of lorlatinib using genetically modified mouse strains. Following oral lorlatinib administration, brain accumulation of lorlatinib was fourfold increased in Abcb1a/1b$^{-/-}$ and Abcb1a/1b;Abcg2$^{-/-}$ mice. Lorlatinib plasma levels were not altered. Oral coadministration of the ABCB1/ABCG2 inhibitor elacridar increased the brain accumulation of lorlatinib in wild-type mice fourfold. In Cyp3a$^{-/-}$ mice, the plasma exposure of lorlatinib was increased 1.3-fold, but was then twofold reduced upon transgenic overexpression of human CYP3A4 in liver and intestine, whereas relative tissue distribution of lorlatinib remained unaltered. Lorlatinib brain accumulation is thus limited by P-glycoprotein in the blood-brain barrier, which can be effectively reversed by elacridar coadministration. Moreover, oral availability of lorlatinib is restricted by CYP3A4 activity.

P-glycoprotein restricts brain penetration of the Bruton's tyrosine kinase inhibitor ibrutinib, while cytochrome P450-3A limits its oral bioavailability

Ibrutinib, an oral tyrosine kinase inhibitor (TKI) approved for treatment of B-cell malignancies, inhibits the Bruton's tyrosine kinase. We investigated whether ABCB1 and ABCG2 or the CYP3A enzyme family can affect the oral bioavailability and tissue disposition of ibrutinib and its metabolite ibrutinib-DiOH. In mice, Abcb1 markedly restricted the brain penetration of ibrutinib and ibrutinib-DiOH, either alone or in combination with Abcg2, resulting in 4.5- and 5.9-fold increases in ibrutinib brain-to-plasma ratios in Abcb1a/1b$^{-/-}$ and Abcb1a/1b;Abcg2$^{-/-}$ mice. Cyp3a deficiency increased the ibrutinib plasma AUC by 9.7-fold compared to wild-type mice. This increase was mostly reversed (5.1-fold reduction) by transgenic human CYP3A4 overexpression. Our results suggest that pharmacological inhibition of ABCB1 during ibrutinib therapy might benefit patients with malignancies or (micro)metastases positioned behind an intact blood-brain barrier. Moreover, inhibitors or inducers of CYP3A will likely strongly affect ibrutinib oral bioavailability and, thus, its therapeutic efficacy, as well as its toxicity risks.

Selected publications

Li W, Sparidans RW, Wang Y, Lebre MC, Wagenaar E, Beijnen JH, Schinkel AH. P-glycoprotein (MDR1/ABCB1) restricts brain accumulation and cytochrome P450-3A (CYP3A) limits oral availability of the novel ALK/ROS1 inhibitor lorlatinib. Int J Cancer. 2018;143(8):2029-2038

Van Hoppe S, Rood JJM, Buil L, Wagenaar E, Sparidans RW, Beijnen JH, Schinkel AH. P-Glycoprotein (MDR1/ABCB1) Restricts Brain Penetration of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib, While Cytochrome P450-3A (CYP3A) Limits Its Oral Bioavailability. Mol Pharm. 2018;15(11):5124-5134

Wang J, Gan C, Sparidans RW, Wagenaar E, van Hoppe S, Beijnen JH, Schinkel AH. P-glycoprotein (MDR1/ABCB1) and Breast Cancer Resistance Protein (BCRP/ABCG2) affect brain accumulation and intestinal disposition of encorafenib in mice. Pharmacol Res. 2018;129:414-423

Marjanka Schmidt

Group leader
Division of Molecular Pathology

Marjanka Schmidt PhD Group leader
Sander Canisius PhD Research associate
Susanne Rebers PhD Research associate
Sandra van den Broek PhD Post-doc, project manager
Delal Akdeniz MSc MD PhD student
Maria Escala Garcia MSc PhD student
Daniele Giardiello MSc PhD student
Iris Kramer MSc PhD student
Anna Morra MSc PhD student
Maartje Schreurs MSc PhD student
Marcelo Sobral-Leite MSc PhD student
Nikkie Aarts PhD Project staff
Aaike van Oort Project staff
Marjolein Timmers MSc Project staff
Proteeti Bhattacharjee MSc Project manager
Miriam Beusink MSc Research assistant
Renske Keeman MSc Data manager
Sten Cornelissen Technical staff

Selected publications

Escala-Garcia M, BCAC authors, [...] and Schmidt MK. Genome-wide association study of germline variants and breast cancer-specific mortality. Br. J. Cancer 2018 (in press)

Kramer I, Schaapveld M, Oldenburg H, Sonke G, McCool D, van Leeuwen F, van de Vijver K, Russell N, Linn S, Siesling S, Menke-van der Houven van Oordt W, Schmidt MK. The influence of adjuvant systemic regimens on contralateral breast cancer risk and receptor subtype. J Natl Cancer Inst. 2018 (in press)

Rebers S, Vermeulen E, Brandenburg AP, Aaronson NK, Schmidt MK. Recall and Retention of Consent Procedure Contents and Decisions: Results of a Randomized Controlled Trial. Public Health Genomics. 2018

Molecular breast cancer epidemiology

Our work spans the themes of precision medicine (and prevention) and survivorship. We investigate germline genetic variants for their role in breast cancer subtype development and prognosis. Where relevant, we translate and implement our findings in models and tools to facilitate shared decision-making by patients and physicians with the aim to prevent breast cancer (recurrence), reduce overtreatment, and improve outcome.

Huge efforts to identify hereditary variants relevant for breast cancer prognostication

Together with other researchers within the Breast Cancer Association Consortium, we examined the association between germline variants and breast cancer survival. We included data based on ~10.4 million variants for 96,661 women with breast cancer. While we did not find any variant associated with breast cancer survival at genome-wide significance, the most significant variants were located close to genes for which there is biological evidence related to breast cancer outcome. A major limitation of the studies to date is the relatively low number of breast cancer deaths, which determine the power of the statistical tests. To overcome this limited power, we are now using a network-based approach to detect genetic effects across multiple genes and proteins with similar biological functions.

Systemic adjuvant treatment prevents a second breast cancer

Contralateral breast cancer (CBC) is a rare event (10-year cumulative incidence 4%), with potential for poor outcome. We are developing a CBC risk model, using data of 132,756 patients with 4,682 CBC from 20 studies, to help clinical decision making for follow-up and risk-reducing surgery.
We also investigated the influence of adjuvant systemic regimens for the first breast cancer on subtype-specific CBC risk. Using data of 80,000 Dutch patients diagnosed between 2003-2010 and multivariable Cox regression analyses, we showed that adjuvant endocrine therapy, chemotherapy, and trastuzumab combined with chemotherapy were associated with overall 54%, 30%, and 43% risk reductions of CBC, respectively. Taxane-containing chemotherapy and aromatase inhibitors were associated with the largest CBC risk reduction. Subtype analyses revealed that endocrine therapy was only associated with a reduced risk of ER-positive CBC and did not protect against the development of ER-negative CBC.

Launch of ELSI (Ethical, Legal and Social issues) Servicedesk for precision medicine

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? In 2018, we launched a new national facility, the ELSI Servicedesk (www.elsi.health-ri.nl), which aims to provide researchers practical information and advice they need in implementing laws and guidelines in their work. Moreover, we aim to contribute to the harmonization of ELSI policies in the Netherlands, thereby facilitating multi-center collaborations and enabling responsible innovation. Although recently launched, the ELSI Servicedesk receives about 400 visitors per month and already received about 15 requests for tailored ELSI advice from one of our experts.

Ton Schumacher

Group leader Division Molecular Oncology & Immunology

Ton Schumacher PhD Group leader
Chong Sun PhD Senior post-doc
Marleen Kok MD PhD Post-doc
Wouter Scheper PhD Post-doc
Daniela Thommen MD PhD Post-doc
Kaspar Bresser MSc PhD student
Feline Dijkgraaf MSc PhD student
Lorenzo Fanchi MSc PhD student
Mirjam Hoekstra MSc PhD student
Lianne Kok MSc PhD student
Anne van der Leun MSc PhD student
Meike Logtenberg MSc PhD student
Riccardo Mezzadra MSc PhD student
Ali Can Sahillioglu MSc PhD student
Maarten Slagter MSc PhD student
Paula Voabil MSc PhD student
Marlous van den Braber Technical staff
Marjolein de Bruijn Technical staff
Mireille Toebes Technical staff
Jos Urbanus Technical staff

Selected publications

Blank CU, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med. 2018;24(11):1655-1661

Logtenberg MEW, et al. Glutaminyl cyclase is an enzymatic modifier of the CD47- SIRPa axis and target for immunotherapy. Nat Med. 2018 (in press)

Scheper W, et al. Low and variable tumor-reactivity of the intratumoral TCR repertoire in human cancers. Nat Med. 2019;25(1):89-94

Dissecting and manipulating tumor-specific immunity

The aim of our research is simple 1). To design novel technologies to examine and modify immune responses 2). To subsequently use these technologies to unravel and manipulate immune recognition of human cancer. Some of the highlights of the past year have been the following:

Dissecting and enhancing T cell recognition in human cancer

There is now widespread evidence for the clinical value of T cell-based immunotherapies, such as T cell checkpoint inhibitors, in a number of human cancers. However, activity of these therapies has to date been most prominent for tumor types with high numbers of DNA alterations, presumably reflecting T cell recognition of the cancer neoantigens that are formed as a consequence of this DNA damage. The low clinical activity of T cell checkpoint inhibitors in tumors with lower amounts of DNA damage begs the question what the role may be of the T cells that do infiltrate these tumor types. To address this question, we have developed technology to 'rescue' the intratumoral TCR repertoire, allowing one to analyze its quality in an unbiased manner. We have subsequently utilized this technology to assess whether the intratumoral TCR repertoire in ovarian cancer and colorectal cancer is commonly tumor reactive. Data obtained indicate that only a small and variable fraction of the intratumoral TCR pool shows autologous tumor reactivity in these tumor types, emphasizing that human tumors can be 'cold' in not only a quantitative but also in a qualitative manner. Parallel work in NSCLC and melanoma suggests that it may to some extent be feasible to predict which TCRs are likely to harbor tumor reactivity, as based on the phenotypic/ transcriptional profile of the T cells in which they are contained. From a therapeutic perspective, these data argue for the use of modalities that induce a broadening of the tumor-specific T cell response in tumors in which the quality of the intratumoral TCR repertoire is poor.

To understand whether T cell checkpoint blockade displays significant clinical activity in patients with an earlier disease stage, the group of Christian Blank and our group initiated the OpACIN study, aiming to evaluate the feasibility of neo-adjuvant and adjuvant checkpoint blockade in patients with stage III melanoma. Data obtained demonstrate a very high response rate – but also high toxicity – of neo-adjuvant T cell checkpoint blockade, and also demonstrate that neo-adjuvant checkpoint blockade leads to a superior expansion of tumor-resident T cell clones, as compared to adjuvant therapy. Data from the OpACIN study form a strong incentive for the broader evaluation of neo-adjuvant T cell checkpoint inhibition regimens in melanoma and beyond.

Targeting of the myeloid cell checkpoint CD47 through QPCTL

CD47 serves as a 'don't eat me' signal for myeloid cells by binding to the inhibitory receptor signal-regulatory protein alpha (SIRPα). Using a haploid genetic screen, we have identified glutaminyl-peptide cyclotransferase-like (QPCTL) as a major component of this myeloid cell checkpoint. Mechanistically, the pyroglutamate formation activity of QPCTL was shown to be required for formation of the SIRPα binding site of CD47. Notably, interference with QPCTL expression was shown to result in a major increase in tumor cell killing and neutrophil influx by tumor-opsonizing antibodies in vivo. These data provide an avenue for small molecule inhibition of the CD47 pathway to augment antibody therapy of cancer.

Structural biology

Titia Sixma

Division head, group leader
Division Biochemistry

Titia Sixma PhD Group leader
Roy Baas PhD Post-doc
Alex Fish PhD Post-doc
Xiaohu Guo PhD Post-doc
Luca Martinelli PhD Post-doc
Andrea Murachelli PhD Post-doc
Anu Priyanka PhD Post-doc
Ivette Aarsman MSc PhD student
Doreth Bhairosing-Kok MSc PhD student
Susanne Bruekner MSc PhD student
Shreya Dharadhar MSc PhD student
Niels Keijzer PhD student
Robbert Kim Msc PhD student
Michael Uckelmann MSc PhD student
Pim van Dijk Technical staff
Yvette Stijf-Bultsma Technical staff
Herrie Winterwerp Technical staff

Selected publications

Haahr P, Borgermann N, Guo X, Typas D, Achuthankutty D, Hoffmann S, Shearer R, Sixma TK, Mailand N. ZUFSP Deubiquitylates K63-Linked Polyubiquitin Chains to Promote Genome Stability. Mol Cell, 2018; 70:165-174

Morrow ME, Morgan MT, Clerici M, Growkova K, Yan M, Komander D, Sixma TK, Simicek M, Wolberger C. Active site alanine mutations convert deubiquitinases into high-affinity ubiquitin-binding proteins. EMBO Rep. 2018;19:e45680

Uckelmann M, Densham RM, Baas R, Winterwerp HHK, Fish A, Sixma TK, Morris JR. USP48 restrains resection by site-specific cleavage of the BRCA1 ubiquitin mark from H2A. Nat Commun. 2018;9:229

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 (MMR) 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). Interestingly, to load onto DNA, MutS needs to open its clamp domain by kinking the long 'lever' helices (Bhairosing-Kok, in revision). We use cryo-electron microscopy in collaboration Meindert Lamers and Rafael Fernandez-Leiro to study different states in MMR. This has generated structures in different MutS states that we are currently validating.

Ubiquitin conjugation

Ubiquitin conjugation is an important signal in cellular pathways, changing the fate of a target protein, by degradation, relocalisation or complex formation. Deregulation of ubiquitin-dependent processes often leads to cancer. Ubiquitin signals are balanced by deubiquitinating enzymes (DUBs), which antagonize ubiquitination of specific protein substrates. Because ubiquitination pathways are critically important, we focus on mechanisms of ubiquitin conjugation to aid the process of drug design.

DUB activity is often carefully controlled. We use a combination of biochemistry and kinetic modelling to study DUB mechanism. This revealed how a novel DUB, ZUFSP, is regulated by product inhibition (Haahr et al, Mol Cell, 2018). USP7 (or HAUSP) is one of the most abundant DUBs. It also allowed to follow all the steps in the reaction of USP7 and to define how the correct substrate can promote the reaction (Kim et al, Nat Comm. *in press*).

In the DNA damage response H2A 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. We use biochemistry and structural studies by cryo-EM to analyze these reactions. We found that USP48 reverses BRCA1-dependent H2A ubiquitination. In collaboration with Jo Morris we could show that this is relevant for genome stability (Uckelmann, Densham et al, Nat Comm, 2018).

Jan-Jakob Sonke

Division head (ad int.), group leader Division Radiation Oncology

Jan-Jakob Sonke PhD Group Leader
Roeland Dilz PhD Post-doc
Martin Fast PhD Senior post-doc
Matthew la Fontaine PhD Post-doc
Takahiro Kanehira PhD Post-doc
Artem Khmelinskii PhD Post-doc
Simon van Kranen PhD Post-doc
Barbara Stam PhD Post-doc
Jonas Teuwen PhD Post-doc
Chris Beekman MSc PhD student
Judi van Diessen MD PhD student
Zeno Gouw MSc PhD student
Jolien Heukelom MD PhD student
Natasja Janssen MSc PhD student
Celia Juan de la Cruz MSc PhD student
Tessa van de Lindt MSc PhD student
Kai Lønning MSc PhD student
Lukas Schroder MSc PhD student
Uros Stanković MSc PhD student
Maddalena Rossi MSc Technical staff

Selected publications

Fast M, van de Schoot A, van de Lindt T, Carbaat C, van der Heide U, Sonke JJ. Tumor trailing for liver SBRT on the MR-Linac, Int J Radiat Oncol Biol Phys. 2018

Van de Lindt TN, Fast MF, van der Heide UA, Sonke JJ. Retrospective self-sorted 4D-MRI for the liver, Radiother Oncol. 2018 Jun;127(3):474-480

Van Diessen J, De Ruysscher D, Sonke JJ, Damen E, Sikorska K, Reymen B, van Elmpt W, Westman G, Fredberg Persson G, Dieleman E, Bjorkestrand H, Faivre-Finn C, Belderbos J. The acute and late toxicity results of a randomized phase II dose-escalation trial in non-small cell lung cancer (PET-boost trial), Radiother Oncol. 2018

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 adapts 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.

4D MRI

Daily MRI-guided radiotherapy for moving targets requires four dimensional (4D) imaging sequences. The purpose of this study was therefore to develop a 4D-MRI strategy providing T2-weighting for non-contrast enhanced tumor visibility. Images were acquired using an axial multi-slice 2D Turbo Spin Echo (TSE) sequence, repeated a variable number of times (dynamics). A self-sorting signal (SsS) was retrieved from the data by computing correlation coefficients between all acquired slices. Images were sorted into 10 phases and missing data were interpolated. For 30 dynamics, acquisition-reconstruction time was <5 min and showed good image quality and tumor visibility in liver cancer patients.

Tumor Trailing

Drifts of the tumor position during treatment delivery limit the accuracy of radiotherapy delivery. Tumor trailing is a treatment delivery technique which continuously adjusts the beam aperture according to the last available time-averaged position of the target. This study investigates whether tumor trailing on the MR-Linac can improve target coverage in liver SBRT in the case of baseline motion. To that end, in 17 oligometastatic liver patients, treatment was simulated using an in-house developed delivery emulator. For imaging frequencies ≥ 1, tumor trailing restored target dose in liver SBRT in the case of baseline motion for the presented patient cohort. This approach was validated using phantom measurements on the MR-Linac.

Acute and late toxicity results the PET-boost trial

Dose escalation driven by biological imaging has the potential to improve treatment outcome in locally advanced lung cancer patients. The PET-boost randomized phase II trial (NCT01024829) investigated dose-escalation to the entire primary tumor or redistributed to regions of high pre-treatment FDG-uptake in inoperable non-small cell lung cancer (NSCLC) patients. The toxicity results of the PET-boost trial revealed that an iso-toxic hypofractionated dose-escalation to the primary tumour is associated with elevated acute and late toxicities compared to conventional chemoradiotherapy but within the limits of the pre-defined stopping rules.

Receptors for matrix adhesion

Arnoud Sonnenberg

Group leader
Division Cell Biology

Arnoud Sonnenberg PhD Group leader
Lisa te Molder MSc PhD student
Veronika Ramovs MSc PhD student
Wei Wang MSc PhD student
Alba Zuidema MSc PhD student
Maaike Kreft BSc Technical staff

Selected publications

Yazlovitskaya EM, Viquez OM, Tu T, De Arcangelis A, Georges-Labouesse E, Sonnenberg A, Pozzi A, Zent R.
The laminin binding α3 and α6 integrins cooperate to promote epithelial cell adhesion and growth. Matrix Biol. 2018

Zuidema A, Wang W, Kreft M, Te Molder L, Hoekman L, Bleijerveld OB, Nahidiazar L, Janssen H, Sonnenberg A.
Mechanisms of integrin αVβ5 clustering in flat clathrin lattices.
J Cell Sci. 2018;131(21)

Romagnoli M, Cagnet S, Chiche A, Bresson L, Baulande S, de la Grange P, De Arcangelis A, Kreft M, George-Labouesse E, Sonnenberg A, Deugnier M-A, Raymond K., Glukhova MA, and Faraldo MM. Deciphering the mammarry stem cell niche: a role for laminin binding integrins. Stem Cell Reports 2019 (in press)

Our main aim is to understand the molecular mechanisms that regulate the interaction of cells with components of the extracellular matrix and to establish the role of cell adhesion receptors in health and disease. A major class of cell adhesion receptors are formed by members of the integrin family. We would like to understand how integrins interact with their ligands and assemble multiprotein complexes at the cell-substratum site in normal and pathological conditions, define the interplay among different integrins and understand the underlying molecular mechanisms.

Assembly of different integrin-based adhesion structures

Integrins are obligate heterodimers composed of α and β subunits. In mammals 18 α and 8 β subunits have been characterized. We are investigating three integrins that are clustered in different adhesion structures and associate with distinct cytoskeletal elements. These are laminin-binding α3β1 and α6β4, and αVβ5, a receptor for vitronectin. While the integrins α3β1 and αVβ5 are connected to the actin cytoskeleton in focal adhesions, α6β4 associates with the intermediate filament system in hemidesmosomes. Additionally, integrins α3β1 and αVβ5 can localize to adhesion structures that are seemingly not connected with the actin cytoskeleton; αVβ5 can be found in flat clathrin lattices and α3β1, when in complex with CD151, resides in tetraspanin webs. We study the dynamic regulation of these adhesion structures, how cellular traction forces influence their assembly and the mechanisms underlying the ability of the integrins to regulate signalling transduction cascades.

Role of integrins in health and disease

Integrin α3β1, which mediates the adhesion of epithelial cells to laminin-332 and -511 in the basement membrane and plays a role in the maintenance of cell-cell contacts, has been implicated both as a promoter and suppressor of tumorigenesis and metastasis in different types of tumors. Among others, we observed such dual role in cancer in a model of chemically induced skin tumorigenesis (DMBA/TPA treatment) in mice, where α3β1 is required for the initiation and development of the disease. However, during the later stages of skin carcinogenesis, the loss of integrin α3β1 resulted in increased invasiveness and metastases formation. The correlation between α3β1 and breast cancer development is even less clear, as independent studies of human samples have reported all possible outcomes – positive, negative and lack of correlation between α3β1 and tumor formation and progression. This reflects the complex role of this integrin during the lifespan of cancer. Our current work focuses on understanding the often opposing function of α3β1 in cancer by studying its role in specific stages and types of tumors. Our primary focus is to determine the mechanisms behind α3β1-dependent onset of skin tumors induced by DMBA/TPA treatment. To this end we are investigating the role of α3β1 in the proliferation, differentiation and dynamics of different skin cell populations during homeostatic conditions and during skin tumorigenesis and are studying the related α3β1 dependent signalling pathways and interactors. Furthermore, we are trying to better define the role of α3β1 in breast cancer by looking into its function in a mouse model for human breast cancer, overexpressing the HER2 oncogene.

T

Hein te Riele

Group leader
Division Tumor
Biology & Immunology

Hein te Riele PhD Group leader
Chantal Stoepker PhD Post-doc
Bente Benedict MSc PhD student
Frank van Gemert MSc PhD student
Tim Harmsen MSc PhD student
Wietske Pieters MSc PhD student
Thomas van Ravesteyn MSc PhD student
Marleen Dekker BSc Technical staff
Elly Delzenne-Goette Technical staff

Selected publications

Benedict B, van Harn T, Dekker M, Hermsen S, Kucukosmanoglu A, Pieters W, Delzenne-Goette E, Dorsman JC, Petermann E, Foijer F, Te Riele H. Loss of p53 suppresses replication-stress-induced DNA breakage in G1/S checkpoint deficient cells. Elife 2018;7:e37868

Harmsen T, Klaasen S, Van de Vrugt H, Te Riele H. DNA mismatch repair and oligonucleotide end-protection promote base-pair substitution distal from a CRISPR/Cas9-induced DNA break. Nucleic Acids Res. 2018;46:2945-55

Wielders CLC, van Nierop P, Vormer TL, Foijer F, Verheij J, Lodder JC, Andersen JB, Mansvelder HD, Te Riele H. RNAi screening of subtracted transcriptomes reveals tumor suppression by taurine-activated GABAA receptors involved in volume regulation. PLoS One 2018;13:e0196979

Genomic instability and carcinogenesis

How does genomic instability develop and impact the initiation and progression of cancer? We study two causes of genomic instability: *(1)* loss of DNA mismatch repair (MMR) and *(2)* defective G_1/S control causing unscheduled S-phase entry and replication stress. We develop novel gene modification tools to induce and study genomic instability in cell culture and mouse models.

Unclassified variants of MMR genes

Carriers of a deleterious MMR gene variant (deletion, stop codon) are cancer prone (Lynch syndrome, LS) and need surveillance to reduce cancer risk. However, single codon variants are difficult to interpret and carriers of such 'Variants of uncertain significance' (VUS) cannot be properly counseled. We developed a functional test to study MMR VUS: "oligonucleotide-directed mutation screening" (ODMS) (Houlleberghs et al., PNAS 2016;113:4128, PLoS Genet 2017;13:e1006765). Briefly, the variant is introduced into mouse embryonic stem cells (ESCs), hemizygous for MMR genes, by oligonucleotide-directed gene modification (Van Ravesteyn et al., PNAS 2016;113:4122). This technique uses short (25 nt) single-stranded oligonucleotides (ssODN) to introduce the VUS into ±0.01% of cells. When the VUS is deleterious, modified cells survive exposure to 6-thioguanine (6TG) and form colonies. This protocol identified 64 deleterious VUS among 149 MMR gene variants.

To address extra-exonic variants (promoter, intron and 5'- and 3'-untranslated sequences), we optimized ODMS in human cells. To implement functional assays in clinical practice, we have created a nationwide KWF-sponsored consortium of preclinical laboratories, clinical genetics centers and gastroenterologists, termed IN*VUS*E (*"investigating variants of uncertain significance for use in clinical practice"*).

CRISPR/Cas9-assisted gene modification

ssODN-directed gene modification is stimulated by targeted DNA breakage using CRISPR/Cas9. Strikingly, we found DNA MMR impacts ssODN-directed gene modification *without* and *with* nuclease activity differently: while suppressing oligo targeting without nuclease, MMR was crucial for nucleotide substitution *distal* from the break and instructed by the 3'-half of the ssODN. 3'-end protection of the ssODN stimulated MMR-dependent gene editing. These findings imply gene editing is effectuated by templated break repair rather than oligonucleotide integration and guide gene editing strategies when a proximal nuclease site is lacking (Harmsen et al., NAR 2018;46:2945).

We corrected a disruptive mutation in the Fanconi anemia (FA) gene *Fancf* using CRISPR/Cas9 and a 120-nt ssODN template in mouse ESCs and fibroblasts. Although the frequency was low (3-6%) FA corrected ESCs rapidly overgrew non-corrected cells, which even allowed recovery of the very rare templated gene editing events obtained by using Cas9D10A nickase. Notably, nickase activity resulted in mono-allelic gene editing without undesired mutagenesis that is a drawback of wild-type Cas9 (Van de Vrugt et al., Sci Rep 2019; in press).

Replication stress

G_1/S checkpoint failure in mitogen-starved cells that lack the retinoblastoma proteins pRB, p107 and p130, causes replication stress, manifesting as slow fork progression, reduced origin firing, DNA breakage and proliferative arrest (Van Harn et al., Genes Dev 2010;24:1377). We found that disruption of Tp53 or its downstream target $p21^{CIP1}$ allowed mitogen-independent proliferation, not only by attenuating the DNA damage response, but rather by reducing the level of DNA breakage. While replication speed remained low, origin firing was restored, possibly reducing the fragility of stalled replication forks (Benedict et al., Elife 2018;7:e37868). Reduced DNA breakage upon Tp53 loss was seen in G_1/S-checkpoint-defective mouse fibroblasts, human retina pigment epithelial cells and in an *in vivo* teratoma model. Thus, loss of p53 may promote growth of incipient cancer cells by reducing replication-stress-induced DNA damage.

Uulke van der Heide

Group leader Radiation Oncology

Uulke van der Heide PhD Group leader
Petra van Houdt PhD Research associate
Ghazaleh Ghobadi PhD Post-doc
Rick Keesman PhD Post-doc
Rita Simoes PhD Post-doc
Catarina Dinis Fernandes MSc PhD student
Edzo Klawer MSc PhD student
Ernst Kooreman MSc PhD student
Roque Rodriguez-Outeiral MSc PhD student
Marcel van Schie MSc PhD student
Iban Torres-Xirau MSc PhD student

Selected publications

Dinis Fernandes C, van Houdt PJ, Heijmink SW, Walraven I, Keesman R, Smolic M, Ghobadi G, van der Poel HG, Schoots I, Pos PJ, van der Heide UA. Quantitative 3T multiparametric MRI of benign and malignant prostatic tissue in patients with and without local recurrent prostate cancer after external-beam radiation therapy. J Magn Res Imag. 2018 (in press)

Monninkhof EM, van Loon JWL, van Vulpen M, Kerkmeijer LGW, Pos FJ, Haustermans K, van den Bergh L, Isebaert S, McColl GM, Jan Smeenk R, Noteboom J, Walraven I, Peeters PHM, van der Heide UA. Standard whole prostate gland radiotherapy with and without lesion boost in prostate cancer: Toxicity in the FLAME randomized controlled trial. Radiother Oncol. 2018;127(1):74-80

Van Schie MA, Dinh CV, Houdt PJV, Pos FJ, Heijmink SWTJP, Kerkmeijer LGW, Kotte ANTJ, Oyen R, Haustermans K, van der Heide UA. Contouring of prostate tumors on multiparametric MRI: Evaluation of clinical delineations in a multicenter radiotherapy trial. Radiother Oncol. 2018;128(2):321-326

Imaging technology in radiation oncology

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. We analyzed the toxicity up to two years after treatment and found that the focal boost did not result in an increase in Genetourinary and gastrointestinal toxicity when compared to the standard treatment. This suggests that the described focal dose escalation technique is safe and feasible. The primary endpoint, 5-year biochemical failure free survival, will be reached in 2020.

To date no guidelines exist for contouring prostate cancer inside the gland, using multiparametric (mp-) MRI. We analyzed the clinical delineations of the FLAME study cohort. A logistic regression analysis of each institute's weighting of T2w, ADC and Ktrans intensity maps in the delineation of the cancer, reveiled considerably different interpretations. As reviewing of all delineations by an expert panel is not feasible, we selected outliers for further evaluation based on discrepancies between our earlier developed tumor probability (TP) model and each institute's clinical delineations using Areas Under the ROC Curve (AUC) analysis.

Quantitative MRI for radiotherapy

To improve target definition and tumor characterization for dose painting, strategies to integrate quantitative MRI in the radiotherapy workflow are designed and applied to a range of tumor sites.
In a series of test-retest studies, we investigated the impact of contrast injection duration on the quantification of tracer kinetics parameters in DCE-MRI. We observed a significantly lower peak height and increased width in the arterial input function (AIF) for injection durations of 15 s and longer. However, we did not find significant differences in tracer kinetic parameters. We found that the most reliable measurement of the AIF is obtained when the complex MRI signal (magnitude and phase) is used, rather than the signal magnitude alone. This resulted in the highest repeatability of tracer kinetic parameters determined in two subsequent DCE-MRI exams in patients with prostate cancer.
We applied quantitative MRI to characterize prostatic tissue after radiotherapy. By investigating patients after radiotherapy with and without a local recurrence, we differentiated recurrent disease from radiation effects in non-cancerous prostate. Dynamic contrast-enhanced (DCE-) MRI was necessary to make this distinction.
The prognostic value of quantitative MRI is investigated in the IQ-EMBRACE trial, a multi-center imaging study of patients receiving chemoradiotherapy for cervical cancer that we initiated in collaboration with Aarhus University.

MRI-guided radiotherapy

The department of Radiation Oncology has started MRI-guided treatments with the MR-linac. Studies to improve image quality and investigate the potential of quantitative imaging on the MR-linac are ongoing. The Umbrella-II trial has started, allowing us to investigate the feasibility of multiple techniques and software for MR-guided adaptive radiation therapy on the Elekta Unity MR-linac.
In the previous years we adapted the system for electronic portal imaging dosimetry so that it can be used on the MR-linac. The clinical validation of this system is currently ongoing.

Image-guided radiotherapy of rectal cancer

To improve the results of radiotherapy for rectal cancer, we investigated various image-guidance strategies. In the Remark study, the feasibility of gold fiducial markers for image guidance was investigated. Implantation strategies were studied and visualization of the fiducial markers on MRI was optimized.
Boost strategies using image-guided brachytherapy are currently investigated in the OPPER trial, in collaboration with the Leiden UMC. MR-guided strategies both for brachytherapy and external-beam irradiation are currently developed.

V

Michiel van der Heijden

Group leader Division Molecular Carcinogenesis

Michiel van der Heijden MD PhD Group leader
Kristan van der Vos PhD Post-doc
Jeroen van Dorp MD PhD student
Nick van Dijk MD PhD student
Sander Palit PhD student
Daniel Vis PhD Bioinformatician

Selected publications

Mariathasan S, Turley SJ, Nickles D, Castiglioni A, Yuen K, Wang Y, Kadel Iii EE, Koeppen H, Astarita JL, Cubas R, Jhunjhunwala S, Banchereau R, Yang Y, Guan Y, Chalouni C, Ziai J, Şenbabaoğlu Y, Santoro S, Sheinson D, Hung J, Giltnane JM, Pierce AA, Mesh K, Lianoglou S, Riegler J, Carano RAD, Eriksson P, Höglund M, Somarriba L, Halligan DL, van der Heijden MS, Loriot Y, Rosenberg JE, Fong L, Mellman I, Chen DS, Green M, Derleth C, Fine GD, Hegde PS, Bourgon R. Powles T. TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. Nature. 2018;554(7693):544-548

Seiler R, Gibb EA, Wang NQ, Oo HZ, Lam HM, van Kessel KE, Voskuilen CS, Winters B, Erho N, Takhar MM, Douglas J, Vakar-Lopez F, Crabb SJ, van Rhijn BWG, Fransen van de Putte EE, Zwarthoff EC, Thalmann GN, Davicioni E, Boormans JL, Dall'Era M, van der Heijden MS, Wright JL, Black PC. Divergent Biological Response to Neoadjuvant Chemotherapy in Muscle-invasive Bladder Cancer. Clin Cancer Res. 2018

Van Dijk N, Funt SA, Blank CU, Powles T, Rosenberg JE, van der Heijden MS. The Cancer Immunogram as a Framework for Personalized Immunotherapy in Urothelial Cancer. Eur Urol. 2018

Personalized treatment 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. Most patients will eventually die of their 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 to bladder cancer by exploring novel molecular targets, mechanisms of resistance and biomarkers that can guide systemic therapy. Our key focus is on the neoadjuvant setting, as we believe the highest gains in cure rates can be achieved here. Through the large number of bladder cancer patients, excellent multidisciplinary collaboration and broad availability of clinical trials with novel therapeutics at the NKI-AVL, discoveries can rapidly be translated into clinical trials.

Neoadjuvant treatment with combination Immunotherapy

In 2018, we opened the NABUCCO study. This study investigates the feasibility of pre-operative ipilimumab/nivolumab in locoregionally advanced bladder cancer. This study will not only provide important clinical data, but will also provide an unique biobank of pre- and on-treatment bladder cancer tissue. Using this biobank, we will explore the effects of combined inhibition of the PD1/PDL1 axis and CTLA4 on the tumor-immune microenvironment. Additionally, we aim to define which patients are most likely to benefit from pre-operative immunotherapy.

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.

Cancer survivorship

Lonneke van de Poll-Franse

Group leader Division Psychosocial Research and Epidemiology

Lonneke van de Poll-Franse PhD Group leader
Annelies Boekhout PhD Senior scientist
Marieke van Leeuwen PhD Post-doc
Lianne van Soolingen MD PhD student
Barbara Wollersheim MSc PhD student
Silvie Janssen Research assistant
Jacobien Kieffer MSc Statistical analyst

Selected publications

Arts LPJ, Oerlemans S, Tick L, Koster A, Roerdink HTJ, van de Poll-Franse LV. More frequent use of health care services among distressed compared with nondistressed survivors of lymphoma and chronic lymphocytic leukemia: Results from the population-based PROFILES registry. Cancer. 2018;124(14):3016-3024

De Rooij BH, Ezendam NPM, Vos MC, Pijnenborg JMA, Boll D, Kruitwagen RFPM, van de Poll-Franse LV. Patients' information coping styles influence the benefit of a survivorship care plan in the ROGY care trial: New insights for tailored delivery. Cancer. 2018

Van de Poll-Franse LV, Oerlemans S, Bredart A, Kyriakou C, Sztankay M, Pallua S, Daniëls L, Creutzberg CL, Cocks K, Malak S, Caocci G, Molica S, Chie W, Efficace F; EORTC Quality of Life Group. International development of four EORTC disease-specific quality of life questionnaires for patients with Hodgkin lymphoma, high- and low-grade non-Hodgkin lymphoma and chronic lymphocytic leukaemia. Qual Life Res. 2018;27(2):333-345

Our research objective is to understand the impact of cancer, treatment and supportive care strategies on physical and psychosocial functioning of cancer survivors.

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

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 25.000 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. We are currently collecting novel data that includes biological markers, biosensor data, online food diaries and body composition.

International development of quality of life questionnaires

We have developed four disease-specific EORTC QoL questionnaires for patients with (non) Hodgkin lymphoma (N-HL) or chronic lymphocytic leukaemia (CLL). These were tested in five European countries and resulted in questionnaires with 27 items for HL, 29 items for high grade NHL, 20 items for low grade NHL and 17 items for CLL. We are currently conducting an international validation study. Furthermore, in the past years we have been developing an EORTC cancer survivorship questionnaire that includes physical, emotional and practical functioning.

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. Among ovarian cancer patients, no overall differences were observed between the trial arms on satisfaction with information provision, satisfaction with care or health care utilization. Combining data from both endometrial and ovarian cancer survivors showed that SCPs may be beneficial for patients who desire information about their disease, whereas SCPs may be less beneficial for patients who avoid medical information, suggesting a need for tailored SCP delivery to improve survivorship care.

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 with (non) Hodgkin lymphoma 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. Patient recruitment has been completed in 2018, first results are expected in 2019.

In 2018 we furthermore started the data collection for the pragmatic cluster randomized GERSOC (GERiatric Screening in the treatment of elderly patients with Ovarian Carcinoma) trial and the individually randomized PROSPEC (PROstate cancer follow-up care in Secondary and Primary hEalth Care) trial.

Wim van Harten

Group leader Division Psychosocial Research and Epidemiology

Wim van Harten MD PhD Group leader
Valesca Retèl PhD Post-doc
Wim Groen PhD Senior post-doc
Anke Wind PhD Post-doc
Ann-Jean Beck MD PhD student
Willeke Naaktgeboren MD PhD student
Laura Kooij MSc PhD student
Nora Franzen MSc PhD student
Melanie Lindenberg MSc PhD student
Danalyn Bing MSc PhD student
Joost Verbeek MSc PhD student
Bruno Vieira MSc PhD student
Hester van de Wiel MSc PhD student
Charlotte IJsbrandy MSc PhD student

Selected publications

Lindenberg MA, Retèl VP, van den Berg JH, Geukes Foppen MH, Haanen JB, van Harten WH. Treatment With Tumor-infiltrating Lymphocytes in Advanced Melanoma: Evaluation of Early Clinical Implementation of an Advanced Therapy Medicinal Product. J Immunother. 2018;41(9):413-425

Groen WG, van Harten WH, Vallance JK. Systematic review and meta-analysis of distance-based physical activity interventions for cancer survivors (2013-2018): We still haven't found what we're looking for.
Cancer Treat Rev. 2018;69:188-203

Wind A, Gonçalves FR, Marosi E, da Pieve L, Groza M, Asioli M, Albini M, van Harten W. Benchmarking Cancer Centers: From Care Pathways to Integrated Practice Units. J Natl Compr Canc Netw. 2018;16(9):1075-1083

Early stage technology assessment, operations research 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 2010, a HTA study was conducted 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, approved by the BIG consortium and EORTC, by end of 2018.
In 2015 an early stage technology assessment of TIL-adoptive cell technology in advanced melanoma started in a Coverage with Evidence Development project, as well as in 2017 for gastric HIPEC and high dose chemotherapy for triple negative breast cancer. Valesca Retel 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 primary investigator in the TANGO project in the Personalized Medicine program of ZonMw (in which Wim van Harten is HTA coordinator). Ann-Jean Beck works on HTA of various interventions in Head & Neck survivorship care. Melanie Lindenberg is evaluating early stage translational technologies in oncology including image guided interventions. Danalyn Bing is active in the field of HTA in early stage breast cancer and active surveillance versus usual care in DCIS treatment. Nora Franzen is working on research and modelling of alternatives for the present system of patents and pricing in expensive cancer drugs. Joost Verbeek started a PhD project on the ongoing Coverage with Evidence Development projects.

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 in order to develop and pilot a European benchmarking system on Comprehensive Cancer Care. Pathway and center benchmarking studies were published in 2018, as final publications of the thesis of Anke Wind. Especially the paper on pathway benchmarking and relating this to Value Based Health Care draw attention as it was published in the NCCN journal. Meanwhile a follow up project on pathway benchmarking was started. Bruno Vieira is conducting a PhD project on improving radiotherapy Logistics by use of Operations Research methods until 2020.

Rehabilitation, Physical Activity and Cancer

Survivorship care and rehabilitation are important elements of a cancer centre's program.
A major Alpe d'Huzes/KWF project was started early 2011, focusing on patient empowerment, return to work, tele-monitoring and implementation of relevant findings and programs related to physical exercise and supported by innovative IT. This program, totalling up to 2,8 million euros, held its final symposium in April 2016, and the evaluation ran until mid-2018. As further development in this field Laura Kooij performs research into e-health interventions and survivorship care, such as IT-supported stepped care and video consultation.
Also a PhD student co-supervised by Wim van Harten works at IQ-Healthcare in Nijmegen on the structured implementation of ACARE projects' findings in ten Dutch hospitals.
Following up on the ACARE2 project, and financed by KWF, the PABLO trial involves 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 (Hester van de Wiel) focusing on aspects that influence effectiveness from both physical as well as psychological perspectives. Willeke Naaktgeboren performs a PhD project on cardiovascular status and late effects after physical activity interventions during chemotherapy in the HEART study.
A systematic review on the effects of distance based physical activity interventions was published in Cancer Treatment Reviews.

Cancer epidemiology

Flora van Leeuwen

Division head, group leader Division Psychosocial Research and Epidemiology

Matti Rookus

Project leader Division Psychosocial Research and Epidemiology

Flora van Leeuwen PhD Group leader
Matti Rookus PhD Project leader
Michael Schaapveld PhD Research associate
Berthe Aleman MD PhD Radiation oncologist
Sandra van den Belt-Dusebout PhD Post-doc
Nina Berentzen PhD Post-doc
Naomi Boekel PhD Post-doc
Miriam Haaksma PhD Post-doc
Hugoline de Haan PhD Post-doc
Annelies Nijdam PhD Post-doc
Anouk Pijpe PhD Post-doc
Yvonne Geurts PhD student
Harmke Groot MSc PhD student
Judy Jacobse MD PhD student
Inge Krul MSc PhD student
Suzanne Neppelenbroek PhD student
Lieske Schrijver MSc PhD student
Mandy Spaan MSc PhD student
Lara Terra MSc PhD student
Simone de Vries MSc PhD student
Thea Mooij MSc Statistical analyst
Gabey Ouwens Research assistant
Marieke Bras MSc Research assistant
Sandra Fase MSc Research assistant
Viviana Groutars Research assistant
Rianne Hoek Research assistant
Katinka John MSc Research assistant
Karline Pellikaan Research assistant

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

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 radiotherapy (RT), chemotherapy (CT) and immunotherapy for Hodgkin lymphoma (HL, n=8,500), non-Hodgkin lymphoma (n=2,800), testicular cancer (n=7,100) and breast cancer (n~30,000) over a period of up to 40 years after primary treatment.

We evaluated risk of solid cancers after treatment for testicular cancer among 5,848 one-year survivors treated before 50 years of age between 1976-2006. Non-seminoma patients experienced increased risk of cancers of the lung, stomach, pancreas, colon, bladder and thyroid, melanoma and soft tissue sarcoma, whereas seminoma patients experienced increased risk of cancers of the small intestine, pancreas, and urinary bladder. Remarkably, platinum-based CT 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 CT (P-value for linear trend <0.001). The risk of gastrointestinal solid cancers even increased with 53% for each additional cycle. Our study is the first to provide evidence for a dose-response relationship between the number of platinum-containing CT cycles and solid cancer risk in testicular cancer patients. This is also relevant for other cancer patients.

HL survivors have a strongly increased risk of breast cancer after chest RT and we investigated whether genetic susceptibility contributes to RT-induced breast cancer. We conducted an international case-case analysis including 327 breast cancer patients after chest RT for HL and 4,671 first primary breast cancer patients from BCAC. Nine SNPs showed statistically significant interaction with RT on BC risk. A polygenic risk score (PRS) composed of these SNPs (RT-interaction-PRS) and a previously published BC-PRS derived in the general population were evaluated in a case-control analysis comprising the 327 HL patients with breast cancer and 491 chest-irradiated HL patients without breast cancer. Patients in the highest tertile of the RT-interaction-PRS had a 1.6-fold higher BC risk than those in the lowest tertile. After external validation this RT-interaction PRS can be incorporated in risk prediction models for HL patients. Remarkably, we observed a 4-fold increased RT-induced risk in the highest compared with the lowest decile of the BC-PRS, similar to the effect size found in the general population. We intend to incorporate the BC-PRS in prediction models for HL patients.

Female survivors of HL treated with alkylating CT and/or pelvic RT have an increased risk of premature ovarian insufficiency (POI). As women with a *natural early* menopause have an increased risk of CVD, we examined whether treatment-induced POI adds to the already high risk of CVD in chest-irradiated HL survivors. After a median follow-up of 24 years, 32% of women treated before age 41 (n=918) had developed POI (median menopausal age, 34 years). POI was not associated with subsequent CVD risk (HR:0.85) compared with a menopausal age of ≥40 years. Also, a short duration of ovarian function after treatment (<5 years) did not increase CVD risk compared to a long duration (≥25 years). Similar results were found for coronary heart disease as separate outcome. Our results are reassuring for HL survivors who already have a high CVD risk.

Etiology of hormone-related cancers

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

Anja van der Wal Research assistant
Denise Jenner MSc Data manager
Rosemarie Wijnands MSc Data manager

Selected publications

Boekel NB, Jacobse JN, Schaapveld M, Hooning MJ, Gietema JA, Duane FK, Taylor CW, Darby SC, Hauptmann M, Seynaeve CM, Baaijens MHA, Sonke GS, Rutgers EJT, Russell NS, Aleman BMP, van Leeuwen FE. Cardiovascular disease incidence after internal mammary chain irradiation and anthracycline-based chemotherapy for breast cancer. Br J Cancer. 2018;119(4):408-418

Groot HJ, Lubberts S, de Wit R, Witjes JA, Kerst JM, de Jong IJ, Groenewegen G, van den Eertwegh AJM, Poortmans PM, Incrocci L, van den Bergh ACM, Jozwiak K, van den Belt-Dusebout AW, Horenblas S, Gietema JA, van Leeuwen FE, Schaapveld M. Risk of Solid Cancer After Treatment of Testicular Germ Cell Cancer in the Platinum Era. J Clin Oncol. 2018;36(24):2504-2513

Krul IM, Opstal-van Winden AWJ, Janus CPM, Daniels LA, Appelman Y, Maas A, de Vries S, Jozwiak K, Aleman BMP, van Leeuwen FE. Cardiovascular Disease Risk After Treatment-Induced Premature Ovarian Insufficiency in Female Survivors of Hodgkin Lymphoma. J Am Coll Cardiol. 2018;72(25):3374-3375

Opstal-van Winden AWJ, de Haan HG, Hauptmann M, Schmidt MK, Broeks A, Russell NS, Janus CPM, Krol ADG, van der Baan FH, De Bruin ML, Couch FJ, Pharoah P, Orr N, Easton DF, Aleman BMP, Strong LC, Bhatia S, Cooke R, Robison LL, Swerdlow AJ, van Leeuwen FE. Genetic susceptibility to radiation-induced breast cancer after Hodgkin Lymphoma. Blood. 2018

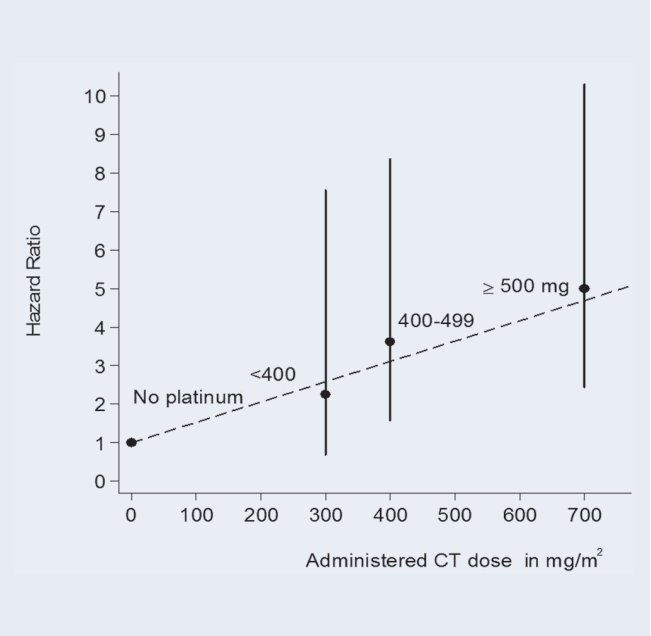
Schrijver L, Olsson H, Phillips K-A, Thea TM, Andrieu N, Easton DF, van Leeuwen FE, Hopper JL, Milne RL, Antoniou AC, Rookus MA. Oral Contraceptive Use and Breast Cancer Risk: Retrospective and Prospective Analyses From a BRCA1 and BRCA2 Mutation Carrier Cohort Study. JNCI Cancer Spectrum. 2018;2(2):pky023

Spaan M, van den Belt-Dusebout AW, van den Heuvel-Eibrink MM, Hauptmann M, Lambalk CB, Burger CW, van Leeuwen FE, on behalf of the OMEGA-steering group. Risk of cancer in children and young adults conceived by assisted reproductive technology. Human Reproduction 2019 (in press)

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 the International BRCA Carrier Cohort Study (6,030 BRCA1 and 3,809 BRCA2 mutation carriers) we examined the association between use of oral contraceptives and breast cancer risk in retrospective and first prospective analyses (269 incident cases of breast cancer). In BRCA1 mutation carriers, use of oral contraceptives was not associated with risk of breast cancer in prospective analyses, but in retrospective analyses, risks were increased by 26% (95%CI=6%-51%). For BRCA2 mutation carriers, power was still limited for prospective analyses, and retrospective analyses showed no association. We conclude that long-term increased risks of breast cancer are not likely for BRCA1 and BRCA2 mutation carriers, while a temporal increased risk during use cannot be excluded for BRCA1 mutation carriers.

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. Recent linkage with the Netherlands Cancer Registry will allow us to further study the potential effects of circadian disruption on breast cancer risk among a highly exposed population.

The aim of the nationwide OMEGA study is to assess risk of hormone-related cancers after ovarian stimulation for in-vitro fertilization (IVF). The cohort comprises 30,838 women treated with IVF between 1983 and 2001.and 10,013 women treated with subfertility treatments other than IVF. In 2018, we assessed cancer risk in the OMEGA children's cohort comprising all live born children of OMEGA participants. (n=47,690). Of these children, 24,269 were conceived by assisted reproductive technology (ART, i.e. (IVF or intracytoplasmic sperm injection (ICSI)) and 13,761 were naturally conceived. The children's cohort was linked to the Netherlands Cancer Registry, yielding 231 incident cancers after a median follow-up of 21 years. The overall risk for childhood cancer in ART-conceived children was not increased. From 18 years of age onwards, the hazard ratio of cancer in ART-conceived versus naturally-conceived individuals was 1.25 (95%CI=0.73-2.13). Cancer risk was somewhat increased, although not statistically significantly so, in children conceived after ICSI or from cryo-preserved embryos. As currently more children are born through these techniques, long-term cancer risk is now being investigated in an expanded cohort of 30,000 children born through ART.



Increasing risk of gastro-intestinal second malignancies by cumulative dose of cisplatin.

Chromatin Dynamics

Fred van Leeuwen

Group leader
Division Gene Regulation

Fred van Leeuwen PhD Group leader
Ila van Kruijsbergen PhD Post-doc
Tessy Korthout MSc PhD student
Eliza Mari Maliepaard MSc PhD student
Thom Molenaar MSc PhD student
Deepani Poramba Liyanage MSc PhD student
Tibor van Welsem Technical staff

Selected publications

Korthout T, Poramba-Liyanage DW, van Kruijsbergen I, Verzijlbergen KF, van Gemert FPA, van Welsem T, and Van Leeuwen F. Decoding the chromatin proteome of a single genomic locus by DNA sequencing. PLOS Biol 2018; 16: e2005542

Korthout T, Poramba-Liyanage DW, van Kruijsbergen I, Verzijlbergen KF, van Gemert FPA, van Welsem T, and Van Leeuwen F. Epi-ID: systematic and direct screening for chromatin regulators in yeast by Barcode-ChIP-Seq. Methods in Mol Biol. 2018 (in press)

Van Welsem T, Korthout T, Ekkebus R, Morais D, Molenaar TM, Van Harten K, Poramba-Liyanage DW, Sun SM, Lenstra TL, Srivas R, Ideker T, Holstege FCP, van Attikum H, El Oualid F, Ovaa H, Stulemeijer IJE, Vlaming H, and Van Leeuwen F. Dot1 promotes H2B ubiquitination by a methyltransferase-independent mechanism. Nucleic Acids Res. 2018;46(21):11251-11261

Switching genes on or off and keeping them in that state involves packaging of the genome by wrapping it around histone proteins. Histones carry different chemical modifications that affect the packaging of DNA by epigenetic mechanisms. The Van Leeuwen lab studies mechanisms and principles of epigenetic regulation using innovative proteomic, genetic, and (epi)genomics approaches. Our general strategy is to develop new tools and technologies, most recently two barcode-ChIP-sequencing approaches to discover epigenetic regulators and to decode the proteomes of genomic loci. These innovations enable us to explore new areas of chromatin biology and to dissect specific chromatin processes in high molecular detail, such as the regulation and function of histone methylation. We take advantage of yeast as a powerful model system and in parallel we are developing tools in mice and cultured human cells using CRISPR-Cas9 to translate our findings to mammals.

Function and regulation of histone methylation

Errors in the chemical modifications of histones can lead to changes in gene expression and cancer. We previously discovered the histone methyltransferase Dot1, which methylates lysine 79 of histone H3 (H3K79). This modification influences gene regulation and oncogenic transformation in mammals. A major goal of our research is to understand the regulation of H3K79 methylation and its function in gene control. Our previous work uncovered new insights into the activation of Dot1 by ubiquitination of histone H2B. We recently discovered that this trans-histone crosstalk works in two directions: Dot1 promotes the occurrence of H2B ubiquitin by a mechanism that is independent of its methyltransferase activity. Together with the group of Heinz Jacobs we are currently studying the regulation and function of DOT1L in mammals in epigenetic control of lymphocyte development and oncogenic transformation.

Decoding chromatin proteomes by DNA sequencing

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 barcoding and DNA sequencing. Using Epi-Decoder we identified hundreds of chromatin-interacting proteins at an actively transcribed reporter gene. We obtained quantitative information on protein interactions and observed broad rewiring of local chromatin proteomes during replication stress. Native genomic loci can be efficiently barcoded by CRISPR-Cas9-mediated genome editing. Thus, Epi-Decoder is an effective strategy to identify and quantify in an unbiased and systematic manner the proteome of an individual genomic locus by 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, the aim of our studies is to provide a deep molecular understanding of the dynamics and inheritance of protein-based epigenetic information in dividing cells and the impact of chromatin-based information on gene regulation in normal development and disease.

Maarten van Lohuizen

Division head, group leader Division Molecular Genetics

Maarten van Lohuizen PhD Group leader
Jitendra Badhai PhD Senior post-doc
Elisabetta Citterio PhD Senior post-doc
Gayathri Chandrasekaran PhD Post-doc
Gaurav Pandey PhD Post-doc
Jawahar Kopparam PhD Post-doc
Jasper van Genugten MSc PhD student
Santiago Gisler MSc PhD student
Nick Landman MSc PhD student
Danielle Hulsman Technical staff

Publication

Serresi M, Siteur B, Hulsman D, Company C, Schmitt MJ, Lieftink C, Morris B, Cesaroni M, Proost N, Beijersbergen RL, van Lohuizen M, Gargiulo G. Ezh2 inhibition in Kras-driven lung cancer amplifies inflammation and associated vulnerabilities. J Exp Med. 2018;215(12):3115-3135

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

We study transcriptional repression by Polycomb-group (PcG) protein complexes, and the effects of deregulation of PcG genes on development, cell cycle control, cancer and stem cell maintenance. For this a range of conditional polycomb transgenic and knockout mouse models are used in combination with specific cancer-predisposing mutations mimicking closely cognate human cancers. Recent focus is on using CISPR screens in selected polycomb-dependent tumor models to uncover new synthetic lethal interactions and vulnerabilities.

Context-dependent roles of PRC2 in tumorigenesis

We recently demonstrated an oncogenic role for *Ezh2* (histone methyltransferase and catalytic subunit of Polycomb repressive complex 2 (PRC2) in *Kras* driven non-small cell lung cancer. However, prolonged inactivation of PRC2 in aggressive *Kras;P53* mutant NSCLC uncovered a profound tumor suppressive function for PRC2 loss resulting in tumor cell identity change, driven by inflammatory responses and EMT. This resulted in new vulnerabilities that can be exploited using combined inhibition of PRC2 and inflammatory responses. Ezh2 is overexpressed in glioblastoma multiforme (GBM) suggesting a possible oncogenic role. In a mouse model for GBM we demonstrated using inducible Ezh2 shRNAs and specific Ezh2 inhibitors that short-term intermitted inhibition indeed slowed tumor growth and prolonged survival. However, prolonged Ezh2 inhibition caused a robust switch in cell fate, resulting in enhanced proliferation and invasion, enhanced DNA repair and activation of a stem cell pluripotency network, resulting in therapy-resistant aggressive GBM. This illustrates that dosing of Ezh2 inhibition is critical, and Ezh2 inhibitors need to be used with caution. We are using these GBM models with CRISPR screens to find more effective combination therapies.

Modeling and investigating BAP1-deficient malignant mesothelioma

Besides PRC2, also a variety of PRC1 complexes contribute to dynamic polycomb repression. These PRC1 complexes differ in subunit constitution but all harbor a critical E3 ubiquitin ligase monoubiquitylates H2A at K119. This mark can be removed by the de-ubiquitylase BAP1. Interestingly, BAP1 is a prominent tumor suppressor that is frequently mutated in malignant mesothelioma (MM), uveal melanoma and clear cell renal cancers. Together with the Berns lab we have generated a conditional mouse model that closely mimics BAP1-deficient human MM. Interestingly, BAP1 deficient MM shows increased polycomb repression and recruitment and dependency on PRC2 and Ezh2. We are using this model and tumor cell lines to screen for the underlying cancer relevant polycomb targets and pathways. This model is also used to screen for new vulnerabilities and targeted combination therapies.

Genome wide Chromatin profiling using a 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). The power of TRIP lies in combining different (inducible) transcriptional reporters in transposons with random barcoding and high throughput sequencing to study position effects and influences of local chromatin and epigenetic states on reporter expression. As an example, we recently used TRIP to test the genome-wide influence of epigenomic context on CRISPR-Cas9 activity.

Jacco van Rheenen

Group leader
Division Molecular Pathology

Intravital Microscopy of cancer plasticity

Our laboratory studies the identity, behavior, and fate of cells that drive tumor initiation, progression, metastasis and the development of therapy resistance. These population 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 the primary tumor and at distant organs for several weeks, we combine genetic mouse models for breast and colorectal cancer with fluorescent mouse models in which identity, behavior or lineage is labeled by fluorescent colors.

Tumor initiation revealed at the single cell level

Adult stem cells (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. Using intravital microscopy, we have identified the behavior of the adult stem cells that drive the development and homeostasis of intestinal and breast tissues. By developing new fluorescent mouse models, intravital microscopy, mathematical modelling, and single cell sequencing we are currently investigating how the dynamic behavior and fate of these SCs can be manipulated to reduce the initiation and progression of colon and breast tumors. For example, we are investigating whether we can manipulate the competition between mutant and wild-type stem cells by diet (e.g. calorie restriction) thereby enhancing the elimination of mutant (APC negative) stem cells from healthy tissues.

Metastasis and minimal residual disease revealed at the single cell level

Only a minority of cells within a tumor acquire traits and are surrounded by microenvironments that enable them to resist therapy, gain long-term clonogenic capacity, and/or to disseminate and form distant metastases. We have established genetic colorectal and breast cancer mouse models in which cells that possess or acquire these states are fluorescently marked. We are currently filming these cells during the metastatic cascade and during and after therapy. Moreover, we try to identify the tumor microenvironment that induces the deleterious cellular states that cancer cells can acquire, and how these states and microenvironment be manipulated to inhibit metastases and the recurrence of therapy resistant tumors.

Cellular mechanisms that drive therapy resistance

The cellular composition of tumors is highly heterogeneous, and can have a large influence on how patients respond to therapy. Through single-cell sequencing we identified gene expression profiles for all the cellular components of a set of heterogeneous breast tumors. Moreover, we developed Tumor Cell Deconvolution (TCD), a computational algorithm that utilizes these reference profiles to reveal the cellular composition of tumors for which only bulk RNA sequencing data is available. By applying TCD on RNA seq data from clinical trials, we are currently correlating the cellular composition of individual tumors to their sensitivity to therapeutics, in order to identify new biomarkers for personalized medicine.

Jacco van Rheenen PhD Group leader
Evelyne Beerling PhD Academic staff
Amalie Dick PhD Academic staff
Saskia Ellenbroek PhD Senior post-doc
Saskia Suijkerbuijk PhD Senior post-doc
Kerstin Hahn PhD Post-doc
Lennart Kester PhD Post-doc
Jessica Morgner PhD Post-doc
Claire Vennin PhD Post-doc
Miguel Vizoso PhD Post-doc
Laura Bornes MSc PhD student
Lotte Bruens MSc PhD student
Andrea Da Cruz Margarido MSc PhD student
Arianna Fumagalli MSc PhD student
Jeroen Lohuis MSc PhD student
Daniel Postrach MSc PhD student
Colinda Scheele MSc PhD student
Danielle Seinstra MSc PhD student
Sander Steenbeek MSc PhD student
Rebecca Uceda Castro MSc PhD student
Tim Schelfhorst BSc Technical staff

Selected publications

Fumagalli A, Suijkerbuijk SJE, Begthel H, Beerling E, Oost KC, Snippert HJ, van Rheenen J, Drost J. A surgical orthotopic organoid transplantation approach in mice to visualize and study colorectal cancer progression. Nat Protoc. 2018;13(2):235-247

Steenbeek SC, Pham TV, de Ligt J, Zomer A, Knol JC, Piersma SR, Schelfhorst T, Huisjes R, Schiffelers RM, Cuppen E, Jimenez CR, van Rheenen J. Cancer cells copy migratory behavior and exchange signaling networks via extracellular vesicles. EMBO J. 2018;37(15)

Oost KC, et al. Specific labeling of stem cell activity in human colorectal organoids using an ASCL2-responsive minigene. Cell Rep. 2018; 22(6):1600-1614

V

Bas van Steensel

Division head, group leader Division Gene Regulation

Bas van Steensel PhD Group leader
Joris van Arensbergen PhD Post-doc
Federico Comoglio PhD Post-doc
Stefano Manzo PhD Post-doc
Ezequiel Miron Sardiello PhD Post-doc
Eva Brinkman MSc PhD student
Laura Brückner MSc PhD student
Christ Leemans MSc PhD student
Miguel Martinez Ara MSc PhD student
Ruben Schep MSc PhD student
Tom van Schaik MSc PhD student
Xabier Vergara Ucin MSc PhD student
Ludo Pagie PhD Bioinformatician
Marcel de Haas Technical staff
Daniel Peric Hupkes PhD Technical staff
Marloes van der Zwalm MSc Technical staff

Selected publications

Brinkman EK, Kousholt AN, Harmsen T, Leemans C, Chen T, Jonkers J, van Steensel B. Easy quantification of template-directed CRISPR/Cas9 editing. Nucleic Acids Res. 2018;46:e58

Brinkman EK, Chen T, de Haas M, Holland HA, Akhtar W, van Steensel B. Kinetics and fidelity of the repair of Cas9-induced double-strand DNA breaks. Mol Cell 2018;70:801-813

Van Steensel B. Scientific honesty and publicly shared lab notebooks. EMBO Rep. 2018;19:e46866

Chromatin Genomics

Gene expression is controlled by promoters, enhancers and 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 study the architecture of chromosomes inside the nucleus.

Genomics tools to study gene regulation

We previously developed SuRE, a genome-wide method to study how regulatory elements are functioning when taken out of their natural chromatin context. We recently applied SuRE to study the impact of human genetic variation on gene regulation. Among ~6 million single-nucleotide variants we identified ~30,000 that alter the activity of enhancers and promoters. These data can help to overcome the limited mapping resolution of large genome-wide association studies, to pinpoint genetic variants responsible for various human traits and predisposition to disorders such as cancer. Furthermore, we are developing new approaches to study the communication between enhancers and promoters.

Spatial organization of the genome and gene regulation

We previously found that the genome of mammalian cells is associated with the nuclear lamina through ~1,300 large Lamina-Associated Domains (LADs). By gene expression analysis and systematic genome transplantation approaches we identified hundreds of genes that are repressed inside LADs. Another set of genes is much less sensitive to the LAD context. We found that these differences are in part encoded in the promoters, and in part due to local variation in the repressive potential of LADs. Conversely, we found that forced activation of genes inside LADs can lead to local detachment of these genes from the lamina. Further studies of the underlying mechanisms are ongoing. As part of the NIH 4D Nucleome consortium, we have generated 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. This extends our understanding of the dynamic spatial architecture of chromosomes in relation to gene regulation.

Facilitating and understanding genome editing

We previously developed TIDE, a cheap and simple assay to monitor the efficacy of genome editing by CRISPR/Cas9 (Brinkman et al, Nucl Acids Res 2014). This technology is now widely used. We recently extended this method with TIDER, a variant of the technology that can quantify "designer" CRISRPR/Cas9 editing events such as oligonucleotide-templated nucleotide substitutions. In addition, we have precisely measured the repair events that follow the induction of a single double-strand break by CRISPR/Cas9. Mathematical modeling of these data indicates that repair of such breaks takes several hours and is mostly mutagenic. This offers a better understanding of the widely used CRISPR/Cas9 technology, and provides insights into DNA repair. We are now extending this approach to hundreds of genomic locations in parallel. This should provide fundamental insights in the impact of chromatin context on the process of DSB repair.

Olaf van Tellingen

Group leader
Division
Pharmacology

Olaf van Tellingen PhD Group leader
Mark de Gooijer MSc PhD student
Paul Slangen MSc PhD student
Artur Burylo Technical staff
Ceren Çitirikkaya Technical staff
Hilal Colakoglu Technical staff

Selected publications

De Gooijer MC, de Vries NA, Buckle T, Buil LCM, Beijnen JH, Boogerd W, van Tellingen O. Improved Brain Penetration and Antitumor Efficacy of Temozolomide by Inhibition of ABCB1 and ABCG2. Neoplasia. 2018;20(7):710-20

De Gooijer MC, Guillen Navarro M, Bernards R, Wurdinger T, van Tellingen O. An Experimenter's Guide to Glioblastoma Invasion Pathways. Trends Mol Med. 2018;24(9):763-80

De Gooijer MC, Zhang P, Buil LCM, Citirikkaya CH, Thota N, Beijnen JH, van Tellingen O. Buparlisib is a brain penetrable pan-PI3K inhibitor. Sci Rep. 2018;8(1):10784

Glioblastoma and the quest for better therapies

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.

Getting drugs through the blood-brain barrier into the brain tumor

This year, we have brought a substantial number of our preclinical studies into publications. A major part of our work is dedicated to characterizing the impact of the blood-brain barrier (BBB) in brain tumors on treatment outcome. It is obvious that adequate drug delivery to the tumor is a requirement for any therapy response. The BBB is a major impediment for drug delivery to the healthy brain, but since the integrity of the BBB may be compromised by the tumor, it was unclear how much protection the BBB can offer to the tumor. We have conducted a series of experiments using several brain tumor models in which we characterized the integrity of the BBB by contrast-enhanced MRI. Very invasive tumors that lack contrast-enhancement (*i.e.* non-leaky BBB) do not accumulate more drug than normal healthy brain and failed to respond to therapy. Tumors with contrast-enhancement, that were grafted in recipient mice lacking the drug efflux transporters Pgp and BCRP, responded better to a substrate drug than when the tumor was grafted in wildtype mice that do express P-gp and BCRP at the BBB. This correlated with differences in drug uptake. Thus, we show that even in leaky tumors, the tumor blood vessels still maintain barrier properties by expression of drug efflux proteins that reduce drug distribution and efficacy. Importantly, this also applies to the drug temozolomide, which is a cornerstone in the treatment of GBM. We show that inhibition of these transport proteins increases the tumor distribution of temozolomide by 50%, without increasing systemic exposure. Moreover, this was also seen with vemurafenib in $BRAF^{v600e}$ melanoma brain metastases (MBM). Brain metastases in general have more leaky blood vessels, but MBM's in wildtype mice responded much less to vemurafenib than MBM's in P-gp/BCRP deficient mice. Intriguingly, although MBMs were responsive in the latter, the duration of the response was short and regrowth of tumor growth occurred while the animals were still receiving daily treatment with vemurafenib. This finding is in line with the overall shorter response duration of MBMs in patients relative to extracranial melanoma lesions. Since canonical pathways were still inhibited, this acquired resistance may be related to the brain microenvironment.

Improving drug delivery to brain tumors by inhibition of both P-gp and BCRP is an important topic of our research. Elacridar is a dual P-gp and BCRP inhibitor that works efficiently in mice, because relatively high plasma concentrations can easily be achieved in this species. Unfortunately, the oral bioavailability of elacridar is much lower in humans than in mice, due to poor drug formulation and significant first-pass metabolism. We are working to find solutions for these pharmacokinetic issues, in order to repurpose elacridar for improving drug delivery to the brain. Importantly, the availability of such an inhibitor may not only benefit brain cancer patients, but also patients suffering from other CNS diseases.

Marcel Verheij

Group leader
Division Cell Biology

Marcel Verheij MD PhD Group leader
Conchita Vens PhD Associated research staff member, Radiobiologist
Paul Essers PhD Post-doc
Rosemarie de Haan MD Resident, PhD student
Martijn van der Heijden MD PhD student
David Vossen MD PhD student
Shuraila Zerp MSc Technical staff
Ben Floot BSc Technical staff
Manon Verwijs Technical staff

Selected publications

De Haan R, Pluim D, van Triest B, van den Heuvel M, Peulen H, van Berlo D, George J, Verheij M, Schellens JHM, Vens C. Improved pharmacodynamic (PD) assessment of low dose PARP inhibitor PD activity for radiotherapy and chemotherapy combination trials. Radiother Oncol. 2018;126:443-9

Verhagen CVM, Vossen DM, Borgmann K, Hageman F, Grénman R, Verwijs-Janssen M, Mout L, Kluin RJC, Nieuwland M, Severson TM, Velds A, Kerkhoven R, O'Connor MJ, van der Heijden M, van Velthuysen ML, Verheij M, Wreesmann VB, Wessels LFA, van den Brekel MWM, Vens C. Fanconi anemia and homologous recombination gene variants are associated with functional DNA repair defects in vitro and poor outcome in patients with advanced head and neck squamous cell carcinoma. Oncotarget. 2018;9:18198-213

Vossen DM, Verhagen CVM, Grénman R, Kluin RJC, Verheij M, van den Brekel MWM, Wessels LFA, Vens C. Role of variant allele fraction and rare SNP filtering to improve cellular DNA repair endpoint association. PLoS One. 2018;13:e0206632

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 manner. 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.

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 M van den Heuvel) and HNSCC (with M 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. 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.

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 Department of Head and Neck Surgery and Oncology. In preliminary studies these showed promise, identifying a subgroup of patients with different outcome parameters that warrant validation in an independent cohort.

Emile Voest

Group leader Division Molecular Oncology & Immunology

Emile Voest MD PHD Group leader
Chelsea McLean PhD Post-doc
Rhode Bijlsma MD PhD student
Chiara Cattaneo PhD student
Myriam Chalabi MD PhD student
Krijn Dijkstra MD PhD student
Joris van der Haar MD PhD student
Louisa Hoes MD PhD student
Salo Ooft PhD student
Luuk Schipper MD PhD student
Danielle Seinstra MD PhD student
Daphne van der Velden MD PhD student
Fleur Weeber MD PhD student
Roel Wouters MD PhD student
Sovann Kaing Technical staff

Emile Voest is medical director of the Netherlands Cancer Institute, medical oncologist and translational scientist.

Selected publications

Dijkstra K, Cattaneo C, Weeber F, Chalabi M, van de Haar J, Fanchi L, Slagter M, van der Velden D, Kaing S, Kelderman S, van Rooij N, van Leerdam M, Depla A, Smit E, Hartemink K, Groot R, Wolkers M, Sachs N, Snaebjornsson P, Monkhorst K, Haanen J, Clevers H, Schumacher T, Voest E. Facilitating individualized T cell therapy by co-culture of peripheral blood lymphocytes and tumor organoids. Cell 2018;174(6):1586-1598

Van der Velden DL, [...], Voest EE. Phase I study of combined indomethacin and platinum-based chemotherapy to reduce platinum-induced fatty acids. Cancer Chemother Pharmacol. 2018;81(5):911-921

Van der Velden DL, [...], Voest EE. Detection of endogenously circulating Mesenchymal Stem Cells in human cancer patients. Int J Cancer 2018;143(10):2516-2524

Personalized Medicine by employing tumor organoids and genomics

Genomics, immunotherapy and (tumor)organoids

Genomics-guided personalized medicine

We continued the Drug Rediscovery Protocol, in short the DRUP study. In this multi-pharma (12 companies to date), multi-drug (25 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. At the closure of 2018, we have received and reviewed >830 patient submissions of which 344 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 ~35%. This is surprisingly high and reflects that patient selection is key in such a personalized medicine approach.

A true highlight of the DRUP approach is the agreement with the Dutch Healthcare Institute and national health care insurers to reimburse on a pay for performance basis successful cohorts of DRUP, starting with MSI tumors treated with nivolumab.

Immunotherapy

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.

In 2018 a very exciting translational study to generate better understanding of which tumors are recognized by T cells was completed and published in Cell. In this study we used autologous 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 and paves the way to better understand resistance to the immune system.

Organoids as a tool to personalize medicine

We have initiated several clinical trials to investigate the value of 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. We have now shown that tumor organoids can predict non responsiveness to irinotecan-based chemotherapy but not to oxaliplatin-based treatment.
Unfortunately, studies with breast cancer organoids have been terminated due to very slow growth rate and success rate to create organoids of biopsies (44%).

In summary, my group is strongly committed to develop a better understanding of individual tumors and their responsiveness to immunotherapy and chemotherapy.

Jelle Wesseling

Group leader
Division Molecular Pathology

Jelle Wesseling MD PhD Group leader
Esther Lips PhD Associate staff scientist
Proteeti Bhattacharjee PhD Project manager
Sena Alaeikhanehshir MD PhD student
Mathilde Almekinders MD PhD student
Carolien van der Borden MD PhD student
Emilie Groen MD PhD student
Marte Liefaard MD PhD student
Maartje van Seijen MD PhD student
Lindy Visser PhD student
Li-Ping Fu MSc Research assistant, data manager
Petra Kristel Technical staff
Lennart Mulder Technical staff
Saskia Stoffels Technical staff

Selected publications

Elshof LE, Schmidt MK, Rutgers EJT, van Leeuwen FE, Wesseling J, Schaapveld M. Cause-specific Mortality in a Population-based Cohort of 9799 Women Treated for Ductal Carcinoma In Situ. Ann Surg 2018;267:952–958

Van Seijen M, Mooyaart AL, Mulder L, Hoogstraat M, Drukker CA, Loo CE, Pouw B, Sonke GS, Wesseling J, Lips EH. Enrichment of high-grade tumors in breast cancer gene expression studies. Breast Cancer Res Treat 2018;168:327–335

Visser LL, Elshof LE, Schaapveld M, van de Vijver K, Groen EJ, Almekinders MM, Bierman C, van Leeuwen FE, Rutgers EJ, Schmidt MK, Lips EH, Wesseling J. Clinicopathological Risk Factors for an Invasive Breast Cancer Recurrence after Ductal Carcinoma In Situ-A Nested Case-Control Study. Clin Cancer Res 2018;24:3593–3601

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)

Ductal carcinoma in situ (DCIS) now represents 20-25% of all breast neoplasia due to large-scale detection by population-based breast cancer screening programs. Uncertainty as to which DCIS lesions will progress to invasive drives massive overtreatment of this often harmless disease. Distinguishing DCIS that may progress to lethal disease from the majority of harmless DCIS is therefore an urgent need to save thousands of women with low risk DCIS the burden of radical treatment without any survival benefit. Therefore, we started the PRECISION (PREvent ductal Carcinoma In Situ Overtreatment Now) initiative in 2015, to distinguish harmless DCIS from hazardous DCIS. In 2017 the PRECISION team received the Cancer Research UK Grand Challenge Award, co-funded by the Dutch Cancer Society.

We aim to reduce the burden of overtreatment of DCIS (surgery, radiation therapy, hormonal therapies) through the development of novel tests that promote informed and shared decision-making between patients and clinicians, without compromising the excellent outcomes for DCIS management presently achieved. We collected a nation-wide population-based cohort of 10,000 women treated for primary DCIS between 1989 and 2004 in the Netherlands. Within this cohort 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. A main finding was that women with HER positive and COX 2 overexpression had a fourfold increased risk of developing a subsequent invasive breast cancer. A second intriguing finding is that, when we compared matched DCIS and invasive recurrences, 40% of the paired lesions has a different copy number profile, indicating a second primary tumor, or outgrowth of a minor subclone. We are now continuing our efforts to unravel DCIS progression. In addition to our retrospective research, a prospective active surveillance trial (the LORD study) is up and running in the Netherlands and other European countries.

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

(collaboration with Lodewyk Wessels and Gabe Sonke)

We continued our work to identify predictive biomarkers for neoadjuvant chemotherapy treatment in breast cancer. An extensive molecular characterization of matched pre- and post-treatment samples of 22 luminal and triple negative patients showed a multitude of differences between pre- and post-chemotherapy samples, revealing a wide range of potential, distinct mechanisms of resistance. Among these, proliferation- and stroma-related genes play a prominent role. The large degree of heterogeneity in possible resistance mechanisms makes effectively targeting chemotherapy resistant cells challenging. New projects are ongoing to unravel treatment resistance mechanisms in HER2 positive breast cancer.

Computational cancer biology

Lodewyk Wessels

Division head, group leader Division Molecular Carcinogenesis

Lodewyk Wessels PhD Group leader
Kathy Jastrzebski PhD Associate scientific staff member
Jinhyuk Bhin PhD Post-doc
Tycho Bismeijer PhD Post-doc
Evert Bosdriesz PhD Post-doc
Gergana Bounova PhD Post-doc
Sander Canisius PhD Post-doc
Marlous Hoogstraat PhD Post-doc
Tesa Severson PhD Post-doc
Bram Thijssen PhD Post-doc
Daniel Vis PhD Post-doc
Nanne Aben MSc PhD Student
Joris van de Haar MSc PhD student
Soufiane Mourragui MSc PhD student
Maarten Slagter MSc PhD student
Marie Corradi MSc Bioinformatician
Kat Moore PhD Bioinformatician
Silvana Roos MSc Technical staff

Selected publications

Bismeijer T, Canisius S, Wessels LFA. Molecular characterization of breast and lung tumors by integration of multiple data types with functional sparse-factor analysis. PLoS Comput Biol. 2018;14(10):e1006520

Bosdriesz E, Prahallad A, Klinger B, Sieber A, Bosma A, Bernards R, Blüthgen N, Wessels LFA. Comparative Network Reconstruction using mixed integer programming. Bioinformatics. 2018;34(17):i997-i1004

Jastrzebski K, Thijssen B, Kluin RJC, de Lint K, Majewski IJ, Beijersbergen RL, Wessels LFA. Integrative Modeling Identifies Key Determinants of Inhibitor Sensitivity in Breast Cancer Cell Lines. Cancer Res. 2018;78(15):4396-4410

We aim to quantify and understand treatment response in model systems and human patients. To this end we 1) develop data-driven approaches to analyse large-scale datasets to find determinants of drug sensitivity and synergies; 2) we construct semi-mechanistic models based on knowledge and measurements to understand drug response and 3) we perform multiplexed, single cell perturbation and profiling assays to map drug response at the single cell level (figure 1). Below we present a number of highlights from the past year.

Identifying epistasis in cancer genomes: a delicate affair

Recent studies of the tumor genome seek to identify cancer pathways as groups of genes in which mutations are epistatic with one another or, specifically, 'mutually exclusive'. However, many mutations appear to be mutually exclusive not due to pathway structure, but to the fact that prominent cancer genes are more frequently mutated in tumors with low overall mutation load. Consequently, these cancer genes are less likely to be co-mutated with others, leading to many misleading findings in current epistatic interaction maps. Researchers should view these maps with caution until we better understand the multiple cause-and-effect relationships among factors such as positive selection for mutations, disease subtypes, and gross tumor characteristics including mutational signatures and load.

GR50: Is it a useful approach to correct for growth rate in drug screens?

High-throughput, large-scale compound screens use viability-based measures, such as the IC50, as an endpoint. It has recently been suggested that growth rate-based measures, such as the GR50, would be more suitable. However, using three independent high-throughput screens, we find that IC50 and GR50 estimates are highly correlated. The biggest differences were found for slow-growing cell lines, where we show that this can be attributed to amplification of noise in the growth rate correction. Consequently, reproducibility was lower for GR50s than for IC50s, both within and between screens. We performed screens to test other suggested benefits of the GR50, such as cytotoxicity prediction or invariance to measurement type and seeding density. In all cases, we do not find the GR50 to be better than the IC50. We therefore recommend using the IC50 as endpoint.

Pan-cancer drug combination screen in 765 cell lines and 56 drugs

Monotherapies are often not effective by themselves, but efficacy can be greatly improved by the addition of a second drug. This phenomenon, where a two-drug combination is more effective than any single drug, is referred to as synergy. Many synergistic drug combinations have previously been reported, but have often only been tested in small subsets of cell lines. Hence, it is not clear whether these are robust, generalize to other tumor types and very few biomarkers for drug synergy have been identified. To address these problems, we have performed a large-scale drug combination screen of 56 drug combinations and 765 tumor cell lines. We find that synergistic combinations are not cancer type specific. Specifically, we find five combinations that result in synergy, including the combination of Olaparib with Temozolomide, a DNA damaging agent (DDA), and several combinations of AZD7762 (CHEK1/2) with a DDA.

Lotje Zuur

Group leader
Division Tumor
Biology & Immunology

Lotje Zuur MD PhD Group leader
Xiaohang Qiao PhD Post-doc
Charlotte Duinkerken PhD student
Jos Elbers PhD student
Anne van der Leun PhD student
Joris Vos PhD student

Selected publications

Cioni B, Jordanova ES, Hooijberg E, van der Linden R, de Menezes RX, Tan K, Willems S, Elbers JBW, Broeks A, Bergman AM, Zuur CL, de Boer JP. HLA class II expression on tumor cells and low numbers of tumor-associated macrophages predict clinical outcome in oropharyngeal cancer. Head Neck. 2019;41:463-478

Dohmen AJC, Sanders J, Canisius S, Jordanova ES, Aalbersberg EA, van den Brekel MWM, Neefjes J, Zuur CL. Sponge-supported cultures of primary head and neck tumors for an optimized preclinical model. Oncotarget. 2018;9(38):25034-25047

Elbers JBW, Al-Mamgani A, van den Brekel MWM, Jóźwiak K, de Boer JP, Lohuis PJFM, Willems SM, Verheij M, Zuur CL. Salvage Surgery for Recurrence after Radiotherapy for Squamous Cell Carcinoma of the Head and Neck. Otolaryngol Head Neck Surg. 2018

Improving treatment responses in Head and Neck cancer

Novel treatments to improve clinical outcome in head and neck cancer

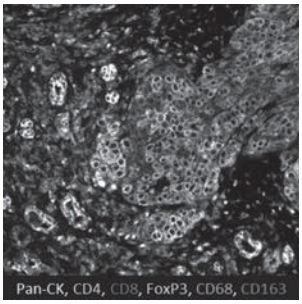
Head and neck cancer can be categorized by two distinct aetiologies: tobacco and/or alcohol use in combination with genetic predisposition, or infection and activity of viral oncogenes. Head and neck cancers are characterized by a microenvironment invaded by various immune cells (see figure) that each may play a role in treatment response and resistance. Despite intensive treatment regimens of surgery w/wo (chemo-)radiotherapy (RT), prognosis in our patients remains relatively poor.

To improve clinical outcome in our patients, my group 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 immunotherapy neoadjuvant to standard of care (extensive surgery) in patients with advanced disease. Phase 1 was completed in 2018, Phase 2 is now open for accrual.

Also, in 2018, we identified a promising novel lead compound that showed tumor selective radiosensitizing activity in vitro, while having no effect on cell viability in the absence of irradiation. The target was found to be ATM, part of the DNA repair pathway. We are currently testing this compound in vitro and in mice. These studies are performed in collaboration with the Division of Chemical Immunology of Prof Neefjes and Prof Ovaa of the LUMC in Leiden, The Netherlands, and should define better options for radiotherapy in our patients.

In 2018 we have also completed a phase 1 trial providing trans-tympanic administration of an oto-protective drug to rescue patients from irreversible hearing loss due to high-dose cisplatin anti-cancer treatment. The idea is that the rescue drug will diffuse from the middle ear to the inner ear via the round window. In this phase 1 trial we could safely administer the drug in all patients. Moreover, to our great enthusiasm, our protocol and mode of administration of the drug indeed resulted in successful oto-protection in single patients.

In 2018 Amy Dohmen, MD PhD successfully defended her thesis *Head and neck cancer treatment, a basic step forward*.



Tumor microenvironment of oropharyngeal cancer. Various coloured cells represent the various immune cells that surround and invade the squamous cell carcinoma. (Courtesy Bianca Cioni, Jan Paul de Boer, André Bergman, Erik Hooijberg)

Wilbert Zwart

Group leader
Division
Oncogenomics

Wilbert Zwart PhD Group leader
Yongsoo Kim PhD Post-doc
Stefan Prokovic PhD Post-doc
Abhishek Singh PhD Post-doc
Koen Flach MSc PhD student
Stacey Joosten MSc PhD student
Jeroen Kneppers MSc PhD student
Simon Linder MSc PhD student
Rebecca Louhanepessy MSc PhD student
Isabel Mayayo Peralta MSc PhD student
Laurel Schunselaar MSc PhD student
Suzan Stelloo MSc PhD student
Anniek Zaalberg MSc PhD student
Yanyun Zhu MSc PhD student
Karianne Schuurman BSc Technical staff

Selected publications

Severson TM, Kim Y, Joosten SEP, Schuurman K, van der Groep P, Moelans CB, Ter Hoeve ND, Manson QF, Martens JW, van Deurzen CHM, Barbe E, Hedenfalk I, Bult P, Smit VTHBM, Linn SC, van Diest PJ, Wessels L, Zwart W. Characterizing steroid hormone receptor chromatin binding landscapes in male and female breast cancer. Nat Commun. 2018;9(1):482

Stelloo S, Nevedomskaya E, Kim Y, Schuurman K, Valle-Encinas E, Lobo J, Krijgsman O, Peeper DS, Chang SL, Feng FY, Wessels LFA, Henrique R, Jerónimo C, Bergman AM, Zwart W. Integrative epigenetic taxonomy of primary prostate cancer. Nat Commun. 2018;9(1):4900

Singh AA, Schuurman K, Nevedomskaya E, Stelloo S, Linder S, Droog M, Kim Y, Sanders J, van der Poel H, Bergman AM, Wessels LFA, Zwart W. Optimized ChIP-seq method facilitates transcription factor profiling in human tumors. Life Sci Alliance, 2018 (in press)

Hormones in cancer

Hormonal therapies represent 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 as well as in the treatment of metastatic disease. Still, resistance to hormonal therapeutics is commonly observed, and many patients relapse despite treatment. It is therefore absolutely crucial to better understand hormonal signalling and therapy resistance in these two most-frequently diagnosed cancers.

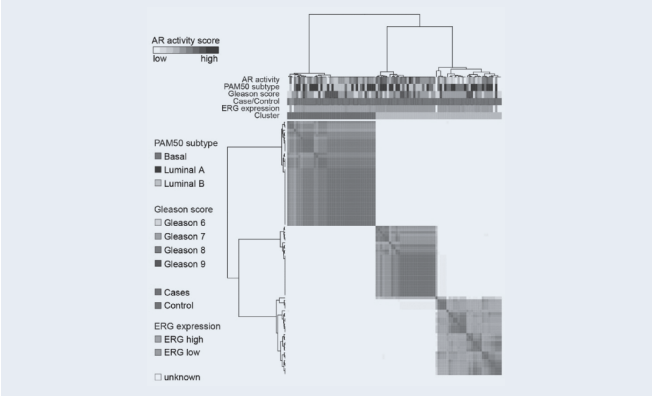
We study hormone receptor action in multiple tumor types, including breast and prostate cancer. The ultimate goal of our research is to personalize clinical decision-making, optimize treatment selection and minimize over-treatment. By expanding our knowledge on steroid hormone receptor function in cancer and elucidating mechanisms of treatment resistance, we aim to achieve tailored endocrine treatment selection, selecting the most-suitable therapy for the individual patient.

Hormonal crosstalk in male and female 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. In addition, most breast cancers also express Androgen Receptor (AR), Progesterone Receptor and Glucocorticoid Receptor. In both male and female breast cancers, we profiled the chromatin interaction landscapes of all these hormone receptors (Severson et al., 2018). A remarkable high level of overlapping chromatin interaction sites was found for all hormone receptors, in which practically all AR sites were localized at DNA regions co-occupied by ERα. These data suggest extensive genomic crosstalk between hormone receptors in clinical specimens. Furthermore, between both sexes practically all hormone receptor/DNA binding sites were shared. However, those selective enhancer regions with prognostic potential were sex-specific, revealing a prognostic gene signature that was specifically geared for outcome prediction in male breast cancer patients.

Epigenetics-based prostate cancer patient stratification

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. In prostate cancer, no clear pathological subtypes are known. We profiled epigenetic marks (H3K4me3, H3K27ac, H3K27me3) and AR chromatin interactions in 100 primary prostate cancers, which was integrated with transcriptomics data, DNA copynumber analyses and somatic mutations. Through integrative genomic analyses, we successfully identified a novel prostate cancer subtype (Stelloo et al., 2018). These tumors are hallmarked by low mutational burden and little DNA copy number variations. Surprisingly, tumors in this novel subtype also exposed low AR activity even though the receptor was readily expressed, suggesting that hormonal blockade may not be effective in these patients. Pathway analyses revealed other signalling cascades as potential drivers of the disease, including FGF and WNT signalling.



Epigenetics-based classification of primary prostate cancers reveals three distinct tumor subtypes. Heatmap displays the consensus matrix of integrative analysis (MIV-NMF) on the basis of RNA-seq, AR, H3K27ac, H3K4me3, and H3K27me3 ChIP-seq for $k = 3$ (three clusters). Rows and columns are samples, and the more frequently samples occur in the same cluster, the darker

Marcel Stokkel

Head Division Diagnostic Oncology

DEPARTMENT OF CLINICAL CHEMISTRY

Daan van den Broek PhD Academic staff, head
Huub van Rossum Academic staff
Tiny Korse PhD Scientific Staff
Daan Vessies MSc PhD student
Lennart van Winden MSc PhD student

DEPARTMENT OF MEDICAL PHYSICS AND TECHNOLOGY

Michiel Sinaasappel PhD Academic staff, head
Leon ter Beek PhD Academic staff
Esther Martens PhD Academic staff
Sara Muller PhD Academic staff
Erik-Jan Rijkhorst PhD Academic staff
Wilfred de Beukelaar Technical staff
Simon Bullock Technical staff
Jessica Kamp Technical staff
Hanny Keep Technical staff
Sanny Kraan Technical staff
Hans Palmboom Technical staff
Suzanne Nanninga Technical staff
Ton Vlasveld Technical staff

THE NETHERLANDS CANCER INSTITUTE FAMILY CANCER CLINIC

Lizet van der Kolk MD PhD Academic staff, head
Muriel Adank MD PhD Academic staff
Fonnet Bleeker MD PhD Academic staff
Eveline Bleiker PhD Academic staff
Daniela Hahn Academic staff
Frans Hogervorst PhD Academic staff
Fred Menko MD PhD Academic staff
Petra Nederlof PhD Academic staff
Efraim Rosenberg PhD Academic staff
Marielle Ruijs MD PhD Academic staff
Maartje Vogel PhD Academic staff
Marijke Hagmeijer Genetic associate
Anja van Rens Genetic associate
Sophie van der Velden Genetic associate
Daoud Ait Moha Research assistant
Kiki Jeanson Research assistant
Ivon Tielen Quality manager
Mohamed Achahchah Technical staff
Abderrahim Ajouaou Technical staff
Majella Boutmy-de Lange Technical staff
Rashmie Debipersad Technical staff
Daphne Dieduksman Technical staff
Mobien Kasiem Technical staff
Rob Plug Technical staff
Roelof Pruntel Technical staff
Esther Scheerman Technical staff
Ruben Moritz BSc Bioinformatician
Rubayte Rahman MSc Bioinformatician

DEPARTMENT OF NUCLEAR MEDICINE

Marcel Stokkel MD PhD Academic staff, head
Else Aalbersberg MSc Academic staff
Christel Brouwer MD Academic staff
Maarten Donswijk MD Academic staff
Martine Geluk-Jonker MSc Pharmacist
Bernies van der Hiel MD Academic staff
Karen van Os MD Academic staff
Emilia Owers MD Academic staff
Erik Vegt MD PhD Academic staff
Michelle Versleijen MD PhD Academic staff
Wouter Vogel MD PhD Academic staff
Linda de Wit-van der Veen MSC PhD Academic staff
Jeroen Hendrikx MSc Clinical pharmacist
Daan Hellingman MSc PhD student
Daphne Huizing MSc PhD student
Judith Oldeheuvel MSc PhD student
Hajar el Aissati Technical staff
Saskia Baank Technical staff
Ilse van Beelen-Post Technical staff
Natascha Bruin Technical staff
Cas Chrispijn Technical staff
Marien Dekker Technical staff
Aafke Ebbens Technical staff
Christel Feenstra Technical staff
Simone Gouw Technical staff
Mariëtte Kieft Technical staff
Ted Kuijer Technical staff
Marintha Louwe Technical staff
Chelvi Mylvaganan Technical staff
Kirsten Manuel-Peen Technical staff
Danielle Ekelschot-Pijlsma Technical staff
Lyandra Kronenburg-Rooze Technical staff
Esther Streefkerk Technical staff
Colinda Vroonland Technical staff
Jeroen Effing Technical staff
Jelmer van der Veen Technical staff

DEPARTMENT OF PATHOLOGY

Gerrit Meijer MD PhD Academic staff, head
Mathilde Almekinders MD Academic staff
Elise Bekers MD PhD Academic staff
Jose van den Berg MD MD PhD Academic staff
Jonathan Bijron MD PhD Academic staff
Mirjam Boelens PhD Academic staff
Mijke Bol MD Academic staff
Linda Bosch PhD Academic staff
Hester van Boven MD PhD Academic staff
Annegien Broeks PhD Academic staff
Beatriz Carvalho PhD Academic staff
Janneke van Denderen PhD Academic staff
Remond Fijneman PhD Academic staff
Emilie Groen MD Academic staff

Division of Diagnostic Oncology

In 2018, a scientific site visit of the division of Diagnostic Oncology was performed in order to assess current scientific status and, moreover, to address scientific opportunities. In addition to the good and excellent scores of the departments visited, the most important outcome was the recommendation to increase the collaboration within the division focusing on one main topic. Although focus of research is already established within the research themes of the NKI, a general theme for the division should be implemented in future plans in order to improve its position, to increase scientific output and to be able to valorize the input. "The development of early markers of disease and response" has been identified as main topic harboring input of all departments within this division, but also the close collaboration with other divisions and pre-clinical research groups. In 2019, more detailed plans will be developed in which innovation and improvement of outcome measures in patient care are ultimate goals. The division, again, was very successful this year with a large number of papers published, graduations, grant applications awarded and, finally, the appointment of Jelle Wesseling as professor at Leiden University Medical Center.

DEPARTMENT OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

Daan van den Broek

Liquid Biopsies and improved "in vitro diagnostics"

The department focuses on translational research and implementation of innovative diagnostics into clinical practise. Such an innovative approach to cancer diagnostics are liquid biopsies. Our department is running multiple ctDNA studies as well as local and national biobank initiatives for different tumor-types and different fluids. One of the great knowledge gaps in commercially available methods for the detection of ctDNA is standardisation and a direct comparison of the performance of different methods. To address this we ran a study comparing four major commercial platforms with respect to sensitivity, detection rate and total cost of analysis. In addition to PCR-based methods, sequencing of ctDNA can broaden the diagnostic information provided by ctDNA analysis. We evaluated and validated the Roche AVENIO plasma sequencing pipeline and validated this approach for clinical use. Together with the department of Pathology funding was obtainedfor the COIN project. The Coin consortium brings together all research groups and laboratories in the Netherlands working on ctDNA to build a biomarker implementation framework. This will enable a coordinated evidence-based introduction of ctDNA in the Netherlands. In addition the project involves the initiation of a biomarker driven intervention study in colorectal cancer (MEDOCC-Create).

Apart from our molecular work we have developed a new, liquid chromatography mass spectrometry based method for the analysis of the steroid hormones. For testosterone this method has a 20 time lower limit of detection and allowed quantitation of testosterone in a large number of samples that could otherwise not be determined. Especially for advanced prostate cancer this might be relevant since androgen deprivation therapy is the cornerstone of treatment. Also a similar method for estrogens has been developed.

Clinical and diagnostic validation of biomarkers

For monitoring of cancer, tumor biomarkers are often used. Unfortunately for many of these markers used in daily practice objective insights is lacking in what consecutively obtained results clinically mean. A platform called Re-marker was developed that included a newly designed graphical presentation, called BReC plot, to diagnostically validate and better support treatment decisions.

Validation of the NETest®, a blood neuroendocrine tumour gene signature in a Dutch cohort

The lack of effective strategies to identify gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) is one of the reasons why diagnosis is delayed for up to 7 years. We investigated the discriminative value of the NETest® as well as the association between tumor characteristics, compared to CgA. The NETest® measures gene expression of 51 circulating NET marker genes simultaneously by q-PCR21. The superior sensitivity of the NETest® over CgA in this study supports the clinical potential of the NETest® as follow-up marker and indicator for residual disease after surgery.

DEPARTMENT OF MEDICAL PHYSICS AND TECHNOLOGY

Michiel Sinaasappel

This department actively participates in several hospital-wide research lines. We introduce new techniques, facilitate their implementation, and advise on regulatory issues. A mechanical workshop is part of our department, where we build, adapt, and design devices used in several clinical and pre-clinical research projects.

The department has the following expertise and skills. MR physics: develop, implement, and evaluate new MRI sequences for biomarkers and image-guided therapy applications. Medical imaging: develop segmentation, registration, and visualization algorithms for image-guided therapy applications. PACS interface to facilitate large-scale imaging studies (in collaboration with the Radiomics group). Pharmacokinetic modeling and radiation dose calculations. Optical and physiological measurement techniques: development, implementation, and evaluation.

In 2018 the department achieved the following highlights. In collaboration with Wouter Vogel (Nuclear Medicine), we evaluated the robustness of ASL MR for quantitative perfusion monitoring of potentially inhibited salivary gland function. A reduced salivary gland perfusion may lead to reduced uptake and toxicity from systemically administered pharmaceuticals, thereby potentially minimizing xerostomia.

Frans Hogervorst PhD Academic staff
Erik Hooijberg PhD Academic staff
Hugo Horlings MD PhD Academic staff
Jeroen de Jong MD PhD Academic staff
Kim Monkhorst MD PhD Academic staff
Petra Nederlof PhD Academic staff
Liudmilla Peppelenbosch-Kodach MD PhD Academic staff
Efraim Rosenberg PhD Academic staff
Joyce Sanders MD Academic staff
Laura Smit MD PhD Academic staff
Petur Snaebjornsson MD Academic staff
Maartje Vogel PhD Academic staff
Jacqueline van der Wal MD PhD Academic staff
Jelle Wesseling MD PhD Academic staff
Bart van de Wiel MD Academic staff
Sanneke Heijker MD Temporary staff
Petra Ghuijs MD Temporary staff
Sanne Martens-de Kemp PhD Post-doc
Meike de Wit PhD Post-doc
Karlijn Hummelink MD PhD student
Gosia Komor MSc PhD student
Meta van Lanschot MD PhD student
Iris van 't Erve PhD student
Abderrahim Ajouaou Technical staff
Mariska Bierkens PhD Technical staff
Carolien Bierman Technical staff
Anne Bolijn Technical staff
Pien Delis-van Diemen Technical staff
Kelly van Deventer Technical staff
Alex Henneman PhD Technical staff
Annemieke Hiemstra MSc Technical staff
Brenda Hijmans PhD Technical staff
Margriet Lemmens Technical staff
Joyce Lübeck Technical staff
Donné Majoor Technical staff
Pauline van Mulligen MA Technical staff
Roelof Pruntel Technical staff
Rubayte Rahman Technical staff
Christian Rausch PhD Technical staff
Jan-Nico Ridderbos Technical staff
Charlotte van Rooijen Technical staff
Brian Severins Technical staff
Marianne Tijssen Technical staff
Menno de Vries MSc Technical staff
Rianne van der Wiel Technical staff

DEPARTMENT OF RADIOLOGY

Regina Beets-Tan MD PhD Academic staff, head
Tarik Baetens MD Academic staff
Annemarieke Bartels-Rutten MD PhD Academic staff
Annemarie Bruining MD Academic staff
Fernando Gomez-Muñoz MD Academic staff
Birthe Heeres MD Academic staff
Stijn Heijmink MD PhD Academic staff
Farshad Imani MD Academic staff
Bas Jasperse MD PhD Academic staff
Petra de Koekkoek-Doll MD Academic staff
Lisa Klompenhouwer MD PhD Academic staff
Max Lahaye MD PhD Academic staff
Doenja Lambregts MD PhD Academic staff
Charlotte Lange MD Academic staff
Ferry Lalezari MD Academic staff
Claudette Loo MD PhD Academic staff
Monique Maas MD PhD Academic staff
Philip Pevenage MD Academic staff
Samuel Rice MD Academic staff
Iris van 't Sant-Jansen MD Academic staff
Laurens Topff MD Academic staff
Japke van Urk MD Academic staff
Jan Vanrusselt MD Academic staff
Gonneke Winter-Warnars MD PhD Academic staff
Ingrid de Zwart MD PhD Academic staff
Hugo Aerts MSc PhD Post-doc
Irene van Kalleveen MSc PhD Post-doc
Robert-Jan Schipper MD PhD Post-doc
Ivo Schoots MD PhD Post-doc
Thi Dan Linh Nguyen-Kim MD PhD Post-doc
Brigit Aarts MD PhD student
Paula Bos MSc PhD student
Rianne Beckers MD PhD student
Rebecca Dijkhoff MD PhD student
Zuhir Elkarghali MD MSc PhD student
Maurits Engbersen MSc PhD student
Miriam van Heeswijk MD PhD student
Joost van Griethuysen MD PhD student
Kay van der Hoogt MD PhD student
Britt Hupkens MD PhD student
Jasenko Krdzalic MD PhD student
Ieva Kurilova MD PhD student
Lisa Min MD PhD student
Elias Nerad MD PhD student
Niels Schurink MSc PhD student
Stefano Trebeschi MSc PhD student
Marjanneh Taghavirazavizadeh MSc PhD student
Sophie Vollenbrock MD PhD student
Martine Bes Technical staff
Iris Beverwijk Technical staff
Arjan te Boekhorst Technical staff
Miriam Coenraads-Wiersma Technical staff
Dirk Doorenspleet Technical staff
Marjon van Engelen Technical staff
Ingeborg Franx Technical staff
Warda Gilani Technical staff
Cees de Graaf Technical staff
Patricia van der Groen Technical staff
Saskia Harren Technical staff
Saskia Havermans Technical staff
Zilca van Heijninge-van Diepen Technical staff
Annelies van Heusden Technical staff
Rien Hoogeboom Technical staff
Vanessa van Hout Technical staff
Huib Huurdeman Technical staff
Leonie Keizer Technical staff
Marjon de Koning Technical staff
Carolien Kos Technical staff
Fenna van der Krieke Technical staff
Chantal Kriesels Technical staff
Reinier Latenstein Technical staff
Megan van der Lubbe Technical staff
Lyanne Molenaar Research Technical staff
Marjan Nazaryfard Technical staff
Theo van Ooij Technical staff
Anita Paape Technical staff
Brenda Plakké Technical staff
Annemieke Poelmann Technical staff
Astrid Pontvuijst Technical staff
Joyce van Schaik-Ellenbroek Technical staff
Harmen Schraa Technical staff
José Sernee Technical staff
Edgar Smit Technical staff
Bob Spil Technical staff

Rick Straathof Technical staff
Irene Terpstra Technical staff
Yvonne Vasbinder-Palthé Technical staff
Ingrid Veldema Technical staff
Mauro Villanueva Technical staff
Marianne Visser Technical staff
Etha Voorham Technical staff
Maaike van der Voort-van Oostwaard Technical staff
Susanne van der Weijden Technical staff

Publications

SELECTED PUBLICATIONS DEPARTMENT OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

Holdenrieder S, Molina R, Qiu L, Zhi X, Rutz S, Engel C, Kasper-Sauer P, Dayyani F, Korse CM. Technical and clinical performance of a new assay to detect squamous cell carcinoma antigen levels for the differential diagnosis of cervical, lung and head and neck cancer. Tumor Biol. 2018;40(4)

Moritz R, Muller M, Korse CM, van den Broek D, Baas P, van den Noort V, Ten Hoeve JJ, van den Heuvel MM, van Rossum HH. Diagnostic validation and interpretation of longitudinal circulating biomarkers using a biomarker response characteristic plot. Clin Chem Acta 2018;487:6-14

Van Treijen MJC, Korse CM, van Leeuwaarde RS, Saveur LJ, Vriens MR, Verbeek WHM, Tesselaar MET, Valk GD. Blood transcript profiling for the detection of neuroendocrine tumors: results of a large independent validation study. Front Endocrinol (Lausanne) 2018;9:740

SELECTED PUBLICATIONS DEPARTMENT OF MEDICAL PHYSICS AND TECHNOLOGY

Borggreve AS, Mook S, Verheij M, Mul VEM, Bergman JJ, Bartels-Rutten A, ter Beek LC, Beets-Tan RGH, Bennink RJ, van Berge Henegouwen MI, Brosens LAA, Defize IL, Van Dieren JM, Dijkstra H, van Hillegersberg R, Hulshof MC, van Laarhoven HWM, Lam MGEH, van Lier ALHMW, Muijs CT, Nagengast WB, Nederveen AJ, Noordzij W, Plukker JTM, van Rossum PSN, Ruurda JP, van Sandick JW, Weusten BLAM, Voncken FEM, Yakar D, Meijer GJ. Preoperative image-guided identification of response to neoadjuvant chemoradiotherapy in esophageal cancer (PRIDE): a multicenter observational study. BMC Cancer. 2018;18(1):1006

Van Griethuysen JJM, Bus EM, Hauptmann M, Lahaye MJ, Maas M, ter Beek LC, Beets GL, Bakers FCH, Beets-Tan RGH, Lambregts DMJ. Gas-induced susceptibility artefacts on diffusion-weighted MRI of the rectum at 1.5 T - Effect of applying a micro-enema to improve image quality. Eur J Radiol. 2018;99:131-137

Vollenbrock SE, Voncken FEM, Van Dieren JM, Lambregts DMJ, Maas M, Meijer GJ, Goense L, Mook S, Hartemink KJ, Snaebjornsson P, ter Beek LC, Verheij M, Aleman BMP, Beets-Tan RGH, Bartels-Rutten A. Diagnostic performance of MRI for the assessment of response to neoadjuvant chemoradiotherapy in oesophageal cancer. BJS 2018 (accepted)

SELECTED PUBLICATIONS THE NETHERLANDS CANCER INSTITUTE FAMILY CANCER CLINIC

Mavaddat N, Michailidou K, Dennis J, [...] García-Closas M, Simard J, Easton DF. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. Am J Hum Genet. 2018

Menko, FH, Stege JA ter, Kolk L van der, Jeanson K, Schats W, Ait Moha D, Bleiker EMA. The uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome: a systematic review of the literature and implications for clinical practice Fam Cancer. 2019;18(1):127-135

Tudini E, Moghadasi S, Parsons MT, van der Kolk L, van den Ouweland AMW, Niederacher D, Feliubadaló L, Wappenschmidt B, Spurdle AB, Lazaro C. Substantial evidence for the clinical significance of missense variant BRCA1 c.5309G>T p.(Gly1770Val). Breast Cancer Res Treat. 2018;172(2):497-503

SELECTED PUBLICATIONS DEPARTMENT OF NUCLEAR MEDICINE

Aalbersberg EA, de Wit-van der Veen BJ, Versleijen MWJ, Saveur LJ, Valk GD, Tesselaar MET, Stokkel MPM. Influence of lanreotide on uptake of 68Ga-DOTATATE in patients with neuroendocrine tumours: a prospective intra-patient evaluation. Eur J Nucl Med Mol Imaging. 2018

In collaboration with the research group of Ludi Smeele (Head & Neck Oncology and Surgery) we evaluated an innovative fast T2-mapping MRI technique to visualize activated muscles based on an increased T2 relaxation time. Muscle activation was induced by a dedicated swallow exercise aid developed for muscle strengthening exercises to restore swallowing function after head and neck cancer treatment.

In collaboration with the research group of Theo Ruers we developed an automatic segmentation method for extracting liver, hepatic vasculature, and biliary tree anatomy from multi-phase contrast-enhanced MRI. Our method was evaluated using data of 15 patients showing good correlation with expert manual segmentations. Resulting 3D models of patient-specific liver anatomy facilitate computer-aided planning of surgeries and interventions.

Pharmaceutical research into oral chemotherapy in tablet form enables future patients to take their medication at home, potentially replacing IV administration at the hospital. Since it is expensive medication, it is important to first test this new method on a small-scale. Our mechanical workshop manufactured a high quality mini-extruder for this small-scale lab testing.

THE NETHERLANDS CANCER INSTITUTE FAMILY CANCER CLINIC

Lizet van der Kolk

For many of the 1450 patients (families) visiting the Family Cancer Clinic the indication for referral is a possible genetic predisposition for breast and/or ovarian cancer. Other indications include suspected Lynch syndrome, colorectal polyposis syndromes, Li-Fraumeni syndrome and a possible genetic predisposition for stomach cancer, renal cancer, melanofma and pancreatic cancer. Increasingly, results of DNA-analysis have implications for the treatment of cancer. This development results in more referrals and, sometimes, a different way of genetic counselling.

The DNA-diagnostic laboratory of the Family Cancer Clinic

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. Several clinical trials require rapid testing of tumor DNA for a BRCA1 specific or a BRCAness profile. For this we 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 (in collaboration with P. Nederlof, head Molecular Diagnostics). In 2018 the following genes were added to our NGS tests: TP53, MLH1, MSH2, MSH6 and PMS2. Furthermore, we have implemented the automated isolation of DNA from blood using a Qiagen Symphony robot. In parallel, we introduced barcoding of our DNA samples to improve sample registration and tracking during the molecular diagnostic tests.

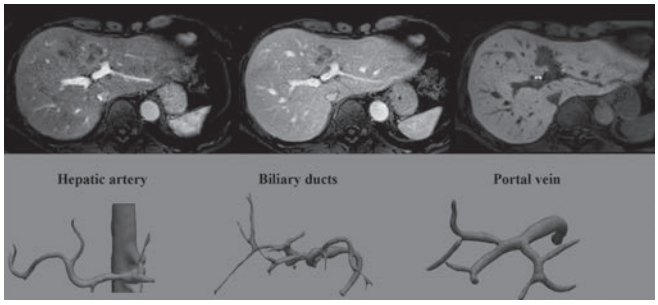
Research projects

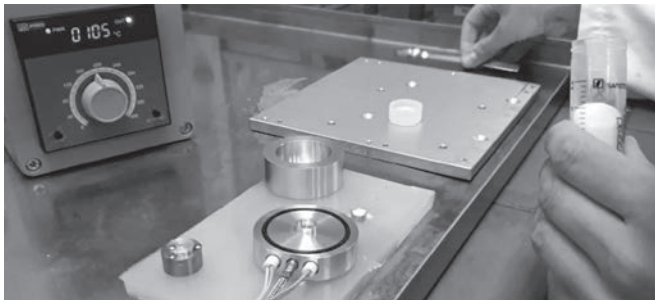
We contribute to national (HEBON) and international (BCAC, CIMBA) efforts to understand the etiology, risk and outcome of breast cancer. We are involved in international efforts to establish polygenic risk scores for breast cancer. In 2017 an unique prospective breast cancer study was granted by Pink Ribbon/KWF (In close cooperation with M.J. Hooning and A. Hollestelle, ErasmusMC, M.K. Schmidt, and M.A. Adank, NKI) to assess all aspects of breast cancer in women from families with a CHEK2 c.1100delC mutation.

TP53-mutation carriers from Li-Fraumeni syndrome families nation-wide 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)). The first data were shared with patients and their doctors on December 13 2018 in a symposium: Li-Fraumeni syndrome in the Netherlands.

In close colabortaion with E. Bleiker (PSOE) and the Family Cancer Clinic (F. Menko, L. van der Kolk) new methods for informing family members are developed and evaluated aimed at improving the communication of cancer risk and better use of preventive measures.

Furthermore, we participate in ongoing collaborations (inter) nationally to elucidate the clinical role of DNA variants found by the DNA diagnostic laboratory (INVUSE, BRCA1/2 VUS, ENIGMA). Our department is also interested in the ethical, legal and social aspects of unsolicited genomic findings, particularly in the context of clinical genetic testing and counseling, Lizet van der Kolk is a member of the core team of the ELSI Servicedesk.





DEPARTMENT OF NUCLEAR MEDICINE

Marcel Stokkel

Personalized Medicine

Over the past years, several new radiopharmaceuticals have become available for imaging and treating different tumor types. Examples of this are Ga68-DOTATATE, Ga68-PSMA, Zr89 labelled antibodies and Lu177-DOTATATE. Although many aspects are already well known, basic principles, such as influence of medication and treatment, are quite often unclear. This year, therefore, the department has shifted focus its of research on these aspects, with emphasis on neuro-endocrine tumors, melanoma and prostate cancer. In collaboration with several academic hospitals, such as UMC Utrecht, VUMC and Erasmus UMC, new studies have been initiated this year of which the intra-arterial administration of Lu177-DOTATATE is the most challenging one aiming to improve radiation dose in liver metastases of neuro-endocrine tumors. Finally, image analysis and quantification of uptake of tracers in tumors, so called Radiomics, has been studied in all afore mentioned tumor types in order to improve the diagnostic and prognostic value of imaging.

Image guided surgery

Since the introduction of Ga68-PSMA a new field of research has become available in which diagnostic aspects can be combined with surgical intervention. Using Cerenkov Light as one of the side-effects of positron emission, it might become possible

Hellingman D, Wan OY, de Wit-van der Veen BJ, van der Ploeg IM, Elkhuizen PHM, Rutgers EJT, Stokkel MPM. Predictive risk factors for sentinel lymph node nonvisualization on planar lymphoscintigraphy using an intratumoral injection in patients with primary breast cancer. Nucl Med Commun. 2018

Konert T, van de Kamer JB, Sonke JJ, Vogel WV. The developing role of FDG PET imaging for prognostication and radiotherapy target volume delineation in non-small cell lung cancer. J Thorac Dis. 2018

SELECTED PUBLICATIONS DEPARTMENT OF PATHOLOGY

Komor MA, Bosch LJ, Bounova G, Bolijn AS, Delis-van Diemen PM, Rausch C, Hoogstrate Y, Stubbs AP, de Jong M, Jenster G, van Grieken NC, Carvalho B, Wessels LF, Jimenez CR, Fijneman RJ, Meijer GA. Consensus molecular subtype classification of colorectal adenomas. J Pathol. 2018;246:266-76

Dijkstra KK, Cattaneo CM, Weeber F, Chalabi M, van de Haar J, Fanchi LF, Slagter M, van der Velden DL, Kaing S, Kelderman S, van Rooij N, van Leerdam ME, Depla A, Smit EF, Hartemink KJ, de Groot R, Wolkers MC, Sachs N, Snaebjornsson P, Monkhorst K, Haanen J, Clevers H, Schumacher TN, Voest EE. Generation of Tumor-Reactive T Cells by Co-culture of Peripheral Blood Lymphocytes and Tumor Organoids. Cell. 2018;174:1586-98.e12

Visser LL, Elshof LE, Schaapveld M, van de Vijver K, Groen EJ, Almekinders MM, Bierman C, van Leeuwen FE, Rutgers EJ, Schmidt MK, Lips EH, Wesseling J. Clinicopathological Risk Factors for an Invasive Breast Cancer Recurrence after Ductal Carcinoma In Situ-A Nested Case-Control Study. Clin Cancer Res. 2018;24:3593-601

SELECTED PUBLICATIONS DEPARTMENT OF RADIOLOGY

Van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, Habr-Gama A, Perez RO, Renehan AG, van de Velde CJH obo IWWD Consortium. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicenter registry study. The Lancet. 2018;3;391(10139):2537-2545

Van 't Sant I van Eden WJ, Engbersen MP, Kok MFM, Woensdregt K, Lambregts DWJ, Shanmuganathan S, Beets-Tan RGH, Aalbers AGJ, Lahaye MJ. Diffusion-weighted MRI assessment of the peritoneal cancer index before cytoreductive surgery. Br J Surg. 2018

Trebeschi S, van Griethuysen JJM, 2. Lambregts DMJ, Lahaye MJ, Parmar C, Bakers FCH, Peters NHGM, Beets-Tan RGH, Aerts HJWL. Deep Learning for Fully-Automated Localization and Segmentation of Rectal Cancer on Multiparametric MR. Sci Rep. 2018;8(1):2589

to assess margins of resection during surgery. The focus of research (funded by KWF) shifted over the past months from pre-clinical experiments towards clinical translation. In 2019, the first prostate cancer patients will be included in this study. In addition, Tc99m-PSMA will be introduced for lymph node detection and resection in prostate cancer. Both techniques aim to improve recurrence rates and avoidance of additional treatment.

Molecular imaging guided radiotherapy

Molecular imaging has become important in guiding external beam radiotherapy for various cancer types. The typical example is metabolic imaging using FDG PET/CT, applied for tumor characterization, treatment selection, target definition and follow-up.

However, this technique is still hampered by several issues. Visual interpretation of FDG PET/CT has a risk on observer variation, and many are looking at automatic lesion detection and contouring using radiomics-based feature detection. We have demonstrated that there are currently no robust, independent radiomics features for FDG PET that add information to current clinical parameters for detection of NSCLC. Concluding that FDG PET/CT-based radiotherapy of NSCLC remains an operator-dependent treatment, we focused at developing a world-wide training and implementation program in low- and middle-income countries in a joint effort with IAEA, with first results indicating that this results in a significant survival benefit for patients with stage III NSCLC in these countries.

We are now developing more modern implementations of molecular imaging to guide radiotherapy. One project has demonstrated that lymph drainage mapping with SPECT/CT can identify patients with head-neck tumours who can safely omit elective irradiation of the contralateral neck to spare toxicity. A second research line is focusing on molecular imaging for evaluation of normal tissues to develop more accurate and biologically relevant dose-effect relations. PSMA PET/CT is applied to specifically quantify the loss of vital secretory cells in salivary glands during and after radiotherapy, in a voxel-based approach. These evaluations will allow us to develop an entirely new class of dose constraints and planning objectives, aiming at maintained tumor control but with lower toxicity and better quality of life.

DEPARTMENT OF PATHOLOGY

Gerrit Meijer

Pathology is all about diagnosing the nature of disease processes, to guide clinical decision-making and optimize personalized and precision treatment of cancer patients. 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 progress of the research by the Translational Gastrointestinal Oncology group (PI's Beatriz Carvalho, Remond Fijneman and Gerrit Meijer), the lung group (PI Kim Monkhorst), the translational mamma research (PI Jelle Wesseling), and the computational pathology research (PI Hugo Horlings) can be found in the first part of this report.

The progress of the Laboratory of Familiar Tumors (head Frans Hogervorst) is summarized in the chapter of the Department of Clinical Genetics. In addition to the major lines of research the department is further developing its role as a key player in translational research through the Pathology Translational Research Core (PTRC). The PTRC provides research services for basic, translational and clinical researchers to accelerate laboratory discoveries into patient care. The PTRC offers state of the art expertise from pathologists, molecular biologists, biomedical scientists and bioinformaticians. The PTRC offers also data services related to pathology. Important asset to this is the Core Facility Molecular Pathology (CFMPB, head Annegien Broeks) which is key to tissue biobanking as well as laboratory support for translational studies. The PTRC supports the logistics of the pathology part of clinical studies, sample handling and shipping of tissues. In the context of the PTRC and in close collaboration with CFMPB, multi spectral imaging, employing Vectra-3 hardware and HALO image analysis software, is further developed (coordinated by Erik Hooijberg). Data analysis is supported as well. This has led to two publications in 2018 and support for additional grant applications. Moreover, NanoString technology has been introduced, coordinated by Linda Bosch. Researchers from in- and outside the NKI have successfully analyzed their samples using this robust technology and the first results have now been submitted for publication. The NKI has been selected as one of the three 'Center of Excellence' of NanoString, in which we have early access to the Digital Spatial Profiling (DSP) system. In close collaboration with Daan van den Broek (department of Clinical Chemistry), Remond Fijneman and Kim Monkhorst make use of clinical trials to perform translational research studies of cell-free circulating tumor DNA as prognostic and predictive biomarkers for colorectal cancer and lung cancer, respectively. Most staff members are actively involved in multidisciplinary research activities in the field of thoracic oncology, urology, gastrointestinal oncology, melanoma, ovarian cancer, head and neck cancer and immunotherapy. In 2018, the department was involved in 161 clinical studies, 312 translational studies and Jelle Wesseling became professor in Leiden. The scientific output includes 94 publications. Three projects were granted by ZonMW and KWF, with a total budget of € 3.3 M.

DEPARTMENT OF RADIOLOGY

Regina Beets-Tan

Imaging Research at the department of Radiology is multidisciplinary clinical, translational and fundamental research. It focuses on functional MRI for organ preservation, image guided intervention, artificial intelligence, imaging for immunotherapy and fundamental radiogenomics research. The research team consists of 18 PhD students, 5 postdocs and 13 radiologists' post-docs. **Rectal cancer imaging research focuses on Watch and Wait** investigating the role of MRI for better selection of complete responders after preoperative chemoradiotherapy. In 2018 the data of an international registry was published in the Lancet reporting safety and good outcome in 1000 patients. **Mulltiparametric imaging research** aims to build a model to improve prediction of response for various cancer treatments including a radiomics analysis of multicenter rectal cancer MRIs. **MRI of peritoneal carcinomatosis research** determines the impact of DWI-MRI for the detection of peritoneal carcinomatosis in colorectal cancer (CRC) and ovarian cancer. The first results in CRC were published in 2018. **Organ preservation** is also the focus of research **in oesophageal and breast cancer.** It validates functional MRI to identify patients with complete response after neoadjuvant treatment. The overall aim is to seek accurate tools to select patients for a non-operative treatment. The first results in oesophagael cancer were published in 2018. **In prostate cancer research** an MR prediction model for functional outcome after surgery is being externally validated with a patient cohort in Australia. **Ultrasound image fusion projects** fusing real time US with CT, MR or PET-CT aim to improve the characterization of cervical nodes in Head and Neck cancer and imaging guidance in treatment of vanishing liver metastases. Interventional radiology research runs a project investigating the safety and efficacy of **intra-hepatic Mitomycine-C in breast cancer also in combination with Y90 radioembolization**. **Kidney ablation projects** consist of an analysis of data in the NKI and a prospective registration of ablation combined with embolization for kidney tumors > 3 cm. **A cryoablation study to boost the efficacy of immunotherapy** in metastasized renal cell cancer is in preparation. **Y90 radioembolization study** in CRC patients with limited metastatic disease analyses biomarkers associated with local control and survival following treatment. **Radioimmunotherapy study for prostate cancer** is in collaboration with the nuclear medicine and urology department to investigate the feasibility of direct treatment of prostate cancer. **Artificial intelligence (AI)** is the focus of clinical, translational and fundamental research. AI models in rectal and head and neck cancer for response prediction and in breast DCIS for risk profiling are running. **AI Immunotherapy research** apply AI models for the prediction of response and for biological profiling. An AI model was developed wherein features were identified and the model was trained and tested on melanoma, NSCLC and urothelial cancer. External validation cohorts are being set up in- and outside the Netherlands. Similarly, radiomic features were identified that can discern clinically relevant genetic mutations in advanced CRC. Further expansion in radiogenomics analysis is underway. AI-powered analysis was executed to assess brain metastasis response to immunotherapy in melanoma. Studies on deep learning-derived volumetrics of brain metastatic edema, necrosis, and viable tumour parts have shown both prognostic and predictive values in immunotherapy. Patient expansion is currently underway to bolster the development of more clinically-robust AI models.

Jacqueline Stouthard

Head Division Medical Oncology
from July 1st, 2018

John Haanen

Head Division Medical Oncology
until July 1st, 2018

John Haanen MD PhD Head until June 2018
Jacqueline Stouthard MD PhD Head from July 2018
Paul Baas MD PhD Academic staff
André Bergman MD PhD Academic staff
Jos Beijnen PhD Academic staff
Christian Blank MD PhD Academic staff
Jan Paul de Boer MD PhD Academic staff
Henk Boot MD PhD Academic staff
Dieta Brandsma MD PhD Academic staff
Tineke Buffart MD PhD Academic staff
Wieneke Buikhuisen MD PhD Academic staff
Sjaak Burgers MD PhD Academic staff
Annemieke Cats MD PhD Academic staff
Myriam Chalabi Academic staff
Annette Compter MD PhD Academic staff
Vincent Dezentjé MD PhD Academic staff
Jolanda van Dieren MD PhD Academic staff
Marloes van Dongen MD PhD Academic staff
Jeantine de Feijter MD PhD Academic staff
Roel van Gijn PhD Academic staff
Winette van der Graaf MD PhD Academic staff
Cecile Grootscholten MD PhD Academic staff
Michiel van der Heijden MD PhD Academic staff
Alwin Huitema PhD Academic staff
Wanda de Kanter MD PhD Academic staff
Martijn Kerst MD PhD Academic staff
Marleen Kok MD PhD Academic staff
Joop de Langen MD PhD Academic staff
Monique van Leerdam MD PhD Academic staff
Sabine Linn MD PhD Academic staff
Lemonitsa Mammatas MD Academic staff
Serena Marchetti MD PhD Academic staff
Aafke Meerveld MD PhD Academic staff
Bastiaan Nuijen PhD Academic staff
Frans Opdam MD PhD Academic staff
Jan Schellens MD PhD Academic staff
Mart Schiefer MD Academic staff
Egbert Smit MD Phd Academic staff
Carolien Smorenburg MD PhD Academic staff
Gabe Sonke MD PhD Academic staff
Neeltje Steeghs MD PhD Academic staff
Willemijn Theelen MD PhD Academic staff
Hans van Thienen MD PHD Academic staff
Margot Tesselaar MD PhD Academic staff
Wieke Verbeek MD PhD Academic staff
Emile Voest MD PhD Clinical director
Reinier Wener MD Academic staff
Thomas de Wijkerslooth MD PhD Academic staff
Sofie Wilgenhof MD PhD Academic staff
Roos Achterbergh Temporary staff
Stefanie Altenburg-van der Velden Temporary staff
Leonora de Boo Temporary staff
Maria Disselhorst Temporary staff
Marjolein de Groot Temporary staff
Amy de Haar-Holleman Temporary staff
Eva Lamboo Temporary staff
Femke van der Meer Temporary staff
Annemiek van Ommen-Nijhof Temporary staff
Tanja Oostergo Temporary staff
Denise Sampiomon Temporary staff
Esther Reijm Temporary staff
Martin Rijlaarsdam Temporary staff
Firazia Rodjan Temporary staff
Maaike Schuur Temporary staff
Marieke Vollebergh Temporary staff
Stephanie van der Woude Temporary staff
Sushil Badrising PhD student
Bianca Cioni PhD student
Gwen Dackus PhD student
Nick van Dijk PhD student
Dianne de Gooijer PhD student
Bart Jacobs PhD student
Vincent de Jong PhD student
Chris Klaver PhD student
Simone Koole PhD student
Merel Lebbink PhD student
Marte Liefaard PhD student
Sonja Levy PhD student

Division of Medical Oncology

BREAST AND OVARIAN CANCER

Vincent Dezentjé, Marloes van Dongen, Marleen Kok, Sabine Linn, Lemonitsa Mammatas, Carolien Smorenburg, Gabe Sonke, Jacqueline Stouthard, Leonora de Boo, Marieke Bruggeman, Gwen Dackus, Marjolein Delfos, Marjo Holtkamp, Vincent de Jong, Inge Kemper, Chris Klaver, Simone Koole, Dinja Kruger, Marte Liefaard, Ingrid Mandjes, Lennart Mulder, Annemiek van Ommen, Suzanne Onderwater, Annelot van Rossum, Margaret Schot, Mariette Schrier, Tessa Steenbruggen, Sonja Vliek, Anna van der Voort, Leonie Voorwerk

Background and objectives

The objective of this research program is to develop and improve systemic therapy for patients with early breast cancer and to improve treatment options in (oligo-) metastatic breast cancer. Our studies are in close collaboration with the Dutch Breast Cancer Research Group (BOOG), the EORTC Breast Cancer Group, the Breast International Group (BIG), and Cancer Core Europe. In 2018, we included 160 patients in 12 clinical studies. In addition, the team is involved in optimizing treatment for women with ovarian cancer.

(Neo)adjuvant chemotherapy

The neoadjuvant chemotherapy program is the core of a multidisciplinary research effort to optimize systemic treatment and response prediction. It currently comprises multicenter studies for ER+/HER2- breast cancer (AFTER; NCT00738777, NEOLBC; NCT03283384)), triple negative tumors (SUBITO; NCT02810743) and HER2+ tumors (TRAIN-3). The TRAIN-3 study investigates whether the number of pre-operative chemotherapy cycles can safely be reduced in case of an early radiologic complete remission and builds on the results of TRAIN-2 study, which was recently published in Lancet Oncology. Another major achievement this year was the oral presentation of the 20-years follow-up data of the N4+ study (Rodenhuis et al. NEJM 2003) at ESMO 2018. Overall survival benefit of high dose chemotherapy with autologous stem cell rescue versus standard adjuvant chemotherapy was maintained at 20 years in patients with ≥10 involved axillary lymph nodes, most notably in triple negative breast cancer (TNBC). Long-term toxicity was comparable between both arms, except for more hypertension, dyslipidemia, and dysrhythmias in the high-dose arm.

Metastatic breast cancer

The OLIGO study (NCT01646034), Triple B-study (NCT01898117), and ABC study (NCT02826512) investigate the treatment of patients whose tumours harbour DNA repair defects as interrogated with the BRCA-like test. In 2018, the triple B-study was amended to enable the treatment with anti-PDL1 (atezolizumab) added to the backbone of paclitaxel or platinum-

based chemotherapy in the first- or second-line of treatment for metastatic TNBC. The NKI led international phase Ib/II POSEIDON (NCT02285179) and nationwide SONIA (NCT03155997) studies investigate the optimal use of an isoform selective PI3K inhibition and CDK4/6 inhibition, respectively, added to endocrine therapy in advanced ER+/HER2- breast cancer. The TONIC trial (NCT02499367) is a single center phase II trial in metastatic TNBC, which we initiated to determine the activity of anti-PD1 (nivolumab) after four different immune response induction (low dose doxorubicin, metronomic cyclophosphamide, cisplatin, or radiation) treatments. In 2018 we presented the final clinical data and the first translational data at ASCO suggesting that induction with doxorubicin or cisplatin can result in a more favorable tumor microenvironment and more responses on anti-PD1. 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 synergy between platinum and immune checkpoint blockade in a subgroup of immune-related ILC.

Ovarian cancer

In 2018, two major improvements in the treatment of primary ovarian cancer have been developed, in which the team at the NKI have been closely involved. Firstly, hyperthermic intraperitoneal chemotherapy (HIPEC) added to interval debulking surgery was shown to improve both recurrence-free and overall survival in stage III ovarian cancer. The study that investigated this approach was published in the New England Journal of Medicine and recently awarded with the AVL public impact award. Secondly, adjuvant therapy with olaparib in BRCA mutation carriers following primary treatment for ovarian cancer showed significant improved outcome and this SOLO-1 study was also published in the New England Journal of Medicine.

GASTROENTEROLOGY

Henk Boot, Tineke Buffart, Annemieke Cats, Myriam Chalabi, Jolanda van Dieren, Cecile Grootscholten, Monique van Leerdam, Margot Tesselaar, Wieke Verbeek, Thomas de Wijkerslooth, Linda Henricks, Linda van Veenendaal, Elvira Nuijten, Lisette Al, Berbel Ykema, Esther Toes, Arthur Kooyker, Sonja Levy

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 Gastro-Intestinal cancer

For esophageal cancer several imaging studies are being performed including the evaluation of fiducials, MRI and 4DPET. Furthermore, we are evaluating a watch and wait policy for esophageal cancer. The first studies have been submitted. In 2015, all intended 788 patients with primary resectable gastric cancer were enrolled in the international, randomized, phase III CRITICS study. The results are published in the Lancet Oncology. We are reference center for hereditary diffuse gastric cancer

Mirte Muller PhD student
Rebecca Louhanepessy 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
Tesa Severson PhD student
Tessa van Steenbruggen PhD student
Linde van Veenendaal PhD student
Marit Vermunt PhD student
Sonja Vliek PhD student
Anna van der Voort PhD student
Leonie Voorwerk PhD student
Berbel Ykema PhD student
Michel Hillebrand Technical staff
Matthijs Tibben Technical staff
Marja Merqui-Roelvink Clinical trial manager
Sandra Adriaansz Nurse practitioner
Marjolein Delfos Nurse practitioner i.o.
Emmy Harms Nurse practitioner
Peggy den Hartog-Lievaart Nurse practitioner
Jacoline van der Hek-van Essen Nurse practitioner
Yvonne Hilhorst Nurse practitioner
Marjo Holtkamp Nurse practitioner
Inge Kemper Nurse practitioner
Maria Kuiper Nurse practitioner
Elsbeth van der Laan Nurse practitioner
Nancy Lardenoije Nurse practitioner
Anoesjka Lechner Nurse practitioner
Judith Lijnsvelt Nurse practitioner i.o.
Henk Mallo Nurse practitioner
Suzanne Onderwater Nurse practitioner
Saskia Pulleman Nurse practitioner i.o.
Jana van der Sar Nurse practitioner
Lisette Saveur Nurse practitioner
Margaret Schot Nurse practitioner
Wilma Uyterlinde PhD Nurse practitioner
Marion Zimmerman Nurse practitioner i.o.

Selected publications

SELECTED PUBLICATIONS DEPARTMENT BREAST AND OVARIAN CANCER

Van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HW, Hermans RH, de Hingh IH, van der Velden J, Arts HJ, Massuger LF, Aalbers AG, Verwaal VJ, Kieffer JM, Van de Vijver KK, van Tinteren H, Aaronson NK, Sonke GS. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med 2018;378:230-40

Van Ramshorst MS, van der Voort A, van Werkhoven ED, Mandjes IA, Kemper I, Dezentjé VO, Oving IM, Honkoop AH, Tick LW, van de Wouw AJ, Mandigers CM, van Warmerdam LJ, Wesseling J, Vrancken Peeters MT, Linn SC, Sonke GS. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open label, randomised, phase 3 trial. Lancet Oncol 2018;19:1630-40

Van Rossum A, et al. Adjuvant dose-dense doxorubicin-cyclophosphamide versus docetaxel-doxorubicin-cyclophosphamide for high-risk breast cancer: First results of the randomised MATADOR trial (BOOG 2004-04). Eur J Cancer 2018;102:40-48

SELECTED PUBLICATIONS DEPARTMENT GASTROENTEROLOGY

Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordsmark M, Meershoek-Klein Kranenbarg E, Boot H, Trip AK, Swellengrebel HAM, van Laarhoven HWM, Putter H, van Sandick JW, van Berge Henegouwen MI, Hartgrink HH, van Tinteren H, van de Velde CJH, Verheij M; CRITICS investigators. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol 2018;19:616-628

Rigter LS, Snaebjornsson P, Rosenberg EH, Atmodimedjo PN, Aleman BM, Ten Hoeve J, Geurts-Giele WR; PALGA group, van Ravesteyn TW, Hoeksel J, Meijer GA, Te Riele H, van Leeuwen FE, Dinjens WN, van Leerdam ME. Double somatic mutations in mismatch repair genes are frequent in colorectal cancer after Hodgkin's lymphoma treatment. Gut 2018;67:447-455

Rigter LS, Spaander MCW, Aleman BMP, Bisseling TM, Moons LM, Cats A, Lugtenburg PJ, Janus CPM, Petersen EJ, Roesink JM, van der Maazen RWM, Snaebjornsson P, Kuipers EJ, Bruno MJ, Dekker E, Meijer GA, de Boer JP, van Leeuwen FE, van Leerdam ME. High prevalence of advanced colorectal neoplasia and serrated polyposis syndrome in Hodgkin lymphoma survivors. Cancer 2018

SELECTED PUBLICATIONS DEPARTMENT THORACIC ONCOLOGY

De Langen AJ, Jebbink M, Hashemi SMS, Kuiper JL, de Bruin-Visser J, Monkhorst K, Thunnissen E, Smit EF. Trastuzumab and paclitaxel in patients with EGFR mutated NSCLC that express HER2 after progression on EGFR TKI treatment. Br J Cancer 2018;119:558-564

Quispel-Janssen J, van der Noort V, de Vries JF, Zimmerman M, Lalezari F, Thunnissen E, Monkhorst K, Schouten R, Schunselaar L, Disselhorst M, Klomp H, Hartemink K, Burgers S, Buikhuisen W, Baas P. Programmed death 1 blockade with nivolumab in patients with recurrent malignant pleural mesothelioma. J Thorac Oncol 2018;13:1569-1576

Schunselaar LM, Quispel-Janssen JMMF, Kim Y, Alifrangis C, Zwart W, Baas P, Neefjes J. Chemical profiling of primary mesothelioma cultures defines subtypes with different expression profiles and clinical responses. Clin Cancer Res 2018;24:1761-1770

SELECTED PUBLICATIONS DEPARTMENT CLINICAL PHARMACOLOGY

Groenland SL, van Nuland M, Verheijen RB, Schellens JHM, Beijnen JH, Huitema ADR, Steeghs N. Therapeutic drug monitoring of oral anti-hormonal drugs in oncology. Clin Pharmacokinet 2018

Henricks LM, Lunenburg CATC, de Man FM, Meulendijks D, Frederix GWJ, Kienhuis E, Creemers GJ, Baars A, Dezentjé VO, Imholz ALT, Jeurissen FJF, Portielje JEA, Jansen RLH, Hamberg P, Ten Tije AJ, Droogendijk HJ, Koopman M, Nieboer P, van de Poel MHW, Mandigers CMPW, Rosing H, Beijnen JH, van Werkhoven E, van Kuilenburg ABP, van Schaik RHN, Mathijssen RHJ, Swen JJ, Gelderblom H, Cats A, Guchelaar HJ, Schellens JHM. A cost analysis of upfront DPYD genotype-guided dose individualisation in fluoropyrimidine-based anticancer therapy. Eur J Cancer 2018;107:60-67

Verheijen RB, Yaqub MM, Sawicki E, van Tellingen O, Lammertsma AA, Nuijen B, Schellens JHM, Beijnen JH, Huitema ADR, Hendrikse NH, Steeghs N. Molecular imaging of PgP/BCRP inhibition at the blood brain barrier using elacridar and [11C]erlotinib PET. J Nucl Med 2018;59:973-979

SELECTED PUBLICATIONS DEPARTMENT UROLOGIC ONCOLOGY

Cioni B, Nevedomskaya E, Melis MHM, van Burgsteden J, Stelloo S, Hodel E, Spinozzi D, de Jong J, van der Poel H, de Boer JP, Wessels LFA, Zwart W, Bergman AM. Loss of androgen receptor signaling in prostate cancer-associated fibroblasts (CAFs) promotes CCL2- and CXCL8-mediated cancer cell migration. Mol Oncol 2018;12:1308-1323

Groot HJ, Lubberts S, de Wit R, Witjes JA, Kerst JM, de Jong IJ, Groenewegen G, van den Eertwegh AJM, Poortmans PM, Klümpen HJ, van den Berg HA, Smilde TJ, Vanneste BGL, Aarts MJ, Incrocci L, van den Bergh ACM, Jóźwiak K, van den Belt-Dusebout AW, Horenblas S, Gietema JA, van Leeuwen FE, Schaapveld M. Risk of solid cancer after treatment of testicular germ cell cancer in the platinum era. J Clin Oncol 2018;36:2504-2513

Van Dijk N, Funt SA, Blank CU, Powles T, Rosenberg JE, van der Heijden MS. The cancer immunogram as a framework for personalized immunotherapy in urothelial cancer. Eur Urol 2018

SELECTED PUBLICATIONS DEPARTMENT CLINICAL IMMUNOTHERAPY

Blank CU, Rozeman EA, Fanchi LF, Sikorska K, van de Wiel B, Kvistborg P, Krijgsman O, van den Braber M, Philips D, Broeks A, van Thienen JV, Mallo HA, Adriaansz S, Ter Meulen S, Pronk LM, Grijpink-Ongering LG, Bruining A, Gittelman RM, Warren S, van Tinteren H, Peeper DS, Haanen JBAG, van Akkooi ACJ, Schumacher TN. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med 2018;24:1655-1661

Geukes Foppen MH, Rozeman EA, van Wilpe S, Postma C, Snaebjornsson P, van Thienen JV, van Leerdam ME, van den Heuvel M, Blank CU, van Dieren J, Haanen JBAG. Immune checkpoint inhibition-related colitis: symptoms, endoscopic features, histology and response to management. ESMO Open 2018;3:e000278

Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, Jordan K; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Supplement 4):iv264-iv266

(HDGC) families. The results of surveillance gastroscopies (2005-2015) in non- CDH1 mutation carriers are described in a cohort study.

Lower Gastro-Intestinal 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.nl). Several data have been published including quality aspects and yield of the Dutch program and influence on the CRC stage distribution. 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). Based on the outcome we are now adapting the guidelines. Several studies focus on DPD activity. Genotype-guided dosing resulted in adequate systemic drug exposure and improved safety and was cost-effective. We are involved in translational and clinical studies with targeted and immunotherapy for CRC. The first data about neo-adjuvant Immunotherapy for colon cancer, MMR proficient and deficient has been presented at the ESMO 2018. Remarkable is the fact that a (near) complete response was seen in all MMR deficient colon cancers. Our department has focused on immune related colitis and described endoscopic and histologic findings in correlation with complaints in patients treated with immunotherapy.

Neuroendocrine tumors (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.

THORACIC ONCOLOGY

Paul Baas, Sjaak Burgers, Wieneke Buikhuisen, Maria Disselhorst, Wanda de Kanter, Joop de Langen, Egbert Smit, Willemijn Theelen, Jose Belderbos, Joost Knegjens, Houke Klomp, Koen Hartemink, Kim Monkhorst, Laurel Schunselaar, Annegien Broeks

Background and objectives

The Department of Thoracic Oncology stands for optimizing patient care, performing translation research and introducing new clinical therapy. In 2018 most attention has focused on non-small cell lung cancer and immunotherapy.

Immune checkpoint inhibition

Further developments in the application of immune therapy has led to the implementation of immuno-oncology (IO) treatment together with chemotherapy in the 1th line setting in lung cancer. As one of the first in the Netherlands we have been able to start this combination treatment and disseminate it out to other institutions. New, window of opportunity, studies investigate the combination of IO agents before start of surgery

or chemo-radiation in patients with locally advanced stages. For the translational part much attention has been given to the pharmacodynamics and kinetics of IO compounds. Collaboration with the VUmc is established were 18F of 89ZR labeled monoclonal antibodies against PD1 or PD-L1 compounds have been tested.

Malignant Pleural Mesothelioma (MPM)

In 2018 we initiated the DENIM phase III study in which the effect of disease response of vaccination with dendritic cells is compared to observation after chemotherapy in first line. This study is performed in close collaboration with Erasmus University in Rotterdam. Our INITIATE study (Anti PDL1 + anti CTL4) in patients with recurrent mesothelioma is in press (Lancet Respiratory Medicine). The primary short-term cultures for tumor cells in the PROOF study obtained from pleural fluid has been continued to test for optimal chemotherapy regiments when patients have recurrence of the disease. The Mesoscape Database (ETOP) has now recruited almost 500 patients and analysis are ongoing.

Neuro endocrine tumors (ENETS center of excellence)
We have continued to focus on the diagnosis and treatment of patients with neuro endocrine tumors. Recently, a phase 2 study with a PD1 inhibitor in patient with low grade metastatic neuro endocrine tumors (PDR001) has been finalized. Other studies like the Phase 3 with Lanreotide versus placebo has now been completed.

Targeted agents

We have expanded the panel of gene sequencing already in 2017 and have been able to enter a number of patients in small studies for orphan diseases like met exon 14 skipping deletions, HER2 amplification, ROS1 or RET mutation. We are one of the referral centers in the Netherlands for patients with special mutations. Within the ETOP (European Thoracic Oncology Platform) studies have been initiated for instant looking at the alert study testing Alectinib in patients with red rearrange tumor. Finally, we have entered over 200 patients in the national LEMA study (Early Molecular Assessment) where mutational status is analyzed in all patients presenting with adenocarcinoma.

Small Cell Lung Cancer

A randomized study with lurbenectedin (a tubulin inhibiting agent) with chemotherapy versus chemotherapy alone in second line has finished accrual.

Smoking Cessation

There is an active involvement of a member of our group (W de Kanter), who is leading in national and international committees (IASLC). This allows us to interact with politicians to defer from tobacco lobbyists. A criminal law suit has been initiated in the Netherlands to force the prosecution to file charges against the tobacco companies. However the amount of attention given to this action has led to great awareness. We currently focus on prevention of smoking in adolescents.

CLINICAL PHARMACOLOGY

Neeltje Steeghs, Frans Opdam, Serena Marchetti, Marloes van Dongen, Jan Schellens, Bastiaan Nuijen, Hilde Rosing, Alwin Huitema, Jos Beijnen

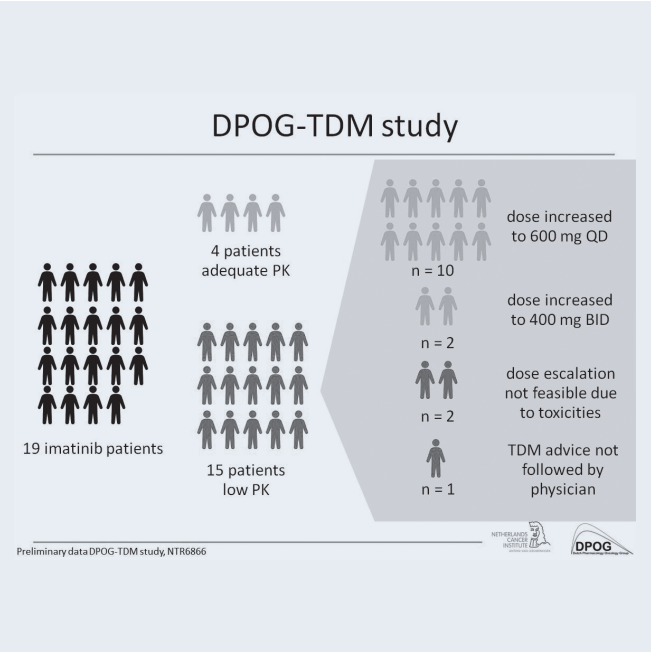
Research activities of the department of Clinical Pharmacology (Steeghs), the department of Pharmacy & Pharmacology (Beijnen) and the division of Pharmacology (group Beijnen/ Huitema) are closely integrated. Currently, we perform 48 phase I/II, pharmacological and proof of concept studies. We recruited 216 new patients this year. In 2018 the main themes of our own investigator-initiated research activities were the personalized dosing of oral anti-cancer drugs, microdosing bioavailability studies and genomic profile selected Phase I/II studies.

Personalized dosing of oral anti-cancer drugs

Oral targeted anti-cancer agents have a complex pharmacological profile, narrow therapeutic index, and a marked pharmacokinetic interpatient variability. Individual patients have a high probability to be either underdosed (>30%) or overdosed (>15%). Therapeutic drug monitoring (TDM), personalized dosing based on measured drug levels, is a well-established method for personalized dosing of drugs. We have started a Therapeutic Drug Monitoring (TDM) project to study and implement TDM for all cancer patients in the country. Over 250 patients have been included so far and were dosed based on their individual drug levels.

Microdosing bioavailability studies

Bioavailability is a measurement of the rate and extent to which the active ingredient or active moiety of a drug is absorbed, reaches the systemic circulation and becomes available at the site of action. The EMA and FDA increasingly request absolute oral bioavailability (ABA) data in humans for new chemical entities. It is ideally studied using a microtracer approach. This can be done by administering a therapeutic dose of the drug via the non-IV route, after which a microtracer (either



radiolabelled drug or stable isotope labeled (SIL) drug) is given via the IV route at 1/100th of therapeutic dose or less than 100 µg at the expected T_{max}. We have vast experience with clinical pharmacokinetic trials to investigate the ABA and ADME properties of drugs.

Genomic profile selected Phase I/II studies

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 lung cancer, pancreatic cancer and colorectal cancer. We initiated a phase II study with AZD1775 in combination with carboplatin for TP53 mutated platinum refractory ovarian cancer patients. Further, we initiated a multinational study (MoTriColor consortium) in which we screen colorectal cancer patient for newly molecular defined subtypes and treat them with specific targeted treatments. And we initiated the Basket of Basket trial within the Cancer Core Europe Consortium to do the same in a pancancer population.

UROLOGIC ONCOLOGY

André Bergman, Martijn Kerst, Michiel van der Heijden, Vincent Dezentje, Jeantine de Feijter, Elsbeth van der Laan, Anoesjka Lechner, Suzanne van der Kolk, Helga Schrijver, Helga Hoogenhout, Rebecca Louhanepessy, Sushil Badrising, Marit Vermunt, Nick van Dijk, Jeroen van Dorp, Hielke-Martijn de Vries

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.

Prostate cancer

Multiple clinical trials in metastasized castration resistant prostate cancer (mCRPC) patients were open for recruitment in 2018, both investigator-initiated and industry-sponsored trials. Investigator-initiated trials included the OSTRICh study, randomizing patients between cabazitaxel and abiraterone or enzalutamide as a second line treatment. Biomarker studies include serum levels of cytokines involved in neutrophil homeostasis and analysis of cfDNA. In the PRESTO study, biopsies of metastatic sites 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. The ROTOR registry aimed to assess the course of pain in a non-study population treated with radium-223. 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.

Bladder cancer

Activity of checkpoint inhibitors in urothelial cancer

An important focus of current research is to bring immunotherapeutics to the pre-operative setting. In January 2018, we have started the NABUCCO trial, in which locoregionally advanced bladder cancer patients are treated with pre-operative combination immunotherapy (ipilimumab / nivolumab). This study will not only provide important clinical data, but will also provide an important biobank of pre- and on-treatment bladder cancer tissue. Using this biobank, we will explore the effects of combined inhibition of the PD1/PDL1 axis and CTLA4 on the tumor-immune microenvironment.

Characterization of urothelial cancer in the neo-adjuvant setting.

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, to test the association between molecular subtypes, chemotherapy response and prognosis in muscle-invasive bladder cancer. Results showed that some tumors assume an immune-infiltrated expression pattern. We will further explore the immunological effects of platinum-based chemotherapy on the bladder cancer microenvironment.

Testicular cancer

The AVL multidisciplinary testicular cancer group (Expert Centre for rare urological diseases) has an ongoing focus on patient treatment, including salvage chemotherapy and robotical laparoscopic surgery and on studies on long-term effects of platinum-containing therapy (cardio-vascular risks and second tumors). In addition, the group works on introducing the sentinal-node procedure in Clinical Stage I testicular cancer

Penile cancer

In 2018, we initiated the PERICLES study. In this study, advanced penile cancer patients are treated with atezolizumab (anti-PDL1). A subset of patients, having loco-regional lymph node metastases, will additionally be treated with radiotherapy.

CLINICAL IMMUNOTHERAPY

John Haanen, Christian Blank, Hans van Thienen, Sofie Wilgenhof, Sandra Adriaansz, Henk Mallo, Elsbeth van der Laan, Wilma Uyterlinde, Judith Lijnsveld, Marieke Groot-Obbink, Marnix Geukes Foppen, Lisette Rozeman, Irene Reijers, Maartje Rohaan, 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 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.

Clinical adoptive T cell transfer program

Based on promising phase I/II feasibility data gathered at our institute and ongoing clinical research in few other centres in the world, 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 the Herlev hospital in Copenhagen, Denmark, and for TIL production with Sanquin blood transfusion services in Amsterdam. The primary objective is improvement in PFS at 6 months. Starting in October 2014, between both institutes a total of 67 patients have been randomized so far. It is the first randomized phase 3 TIL trial worldwide. The vast majority of patients that have been enrolled in this trial have failed 1st line anti-PD-1 treatment. Currently, there is an unmet medical need for patients who have failed anti-PD-1 treatment as the objective response rate of ipilimumab following anti-PD-1 is only 12%. We received financial support from the Dutch Cancer Society to open 2 additional clinical centres to increase accrual. Between 2011 and 2018 we have enrolled 12 patients in a phase I/II trial with T cell receptor (TCR) gene therapy. This trial was one of the first world-wide studying the use of TCR gene modified T cells for the treatment of cancer. HLA-A*0201 positive patients with MART-1 expressing metastatic melanoma, including uveal 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 presented by HLA-A*0201, expressed in 80% of melanomas. The study was stopped in November 2018 and results will be published in 2019.

Immune checkpoint inhibition in melanoma

Anti-CTLA4 (ipilimumab) and anti-PD-1 (nivolumab, pembrolizumab) monotherapies, as well as the combination of ipilimumab plus nivolumab have become standard therapies for metastatic melanoma in the Netherlands. In 2018 both nivolumab and pembrolizumab were approved for adjuvant therapy in stage III melanoma. We published this year the data from our phase I study (Opacin) comparing neoadjuvant versus adjuvant ipilimumab + nivolumab for patients with stage IIIB/C melanoma. We found a high frequency of major pathologic responses after neoadjuvant therapy (pRR, 78%), a stronger expansion of tumor-resident T cell clones in the peripheral blood as compared to adjuvant treatment, and none of the responder relapsing (median follow-up 30 months). However, this high efficacy came at the cost of a grade 3/4 toxicity rate of 90%, hampering a broader application. This has led to the subsequent OpACIN-neo trial, testing two (instead of four) courses ipilimumab + nivolumab using three different schedules. At ESMO 2018 Congress, we presented the results from OpACIN-neo, identifying an equally effective schedule of ipilimumab plus nivolumab (77% pRR), but that was better tolerated (20% grade 3/4 toxicities). Once again only in the group of non-responders relapse have been observed (with a short FU time of 8.3 months). The subsequent PRADO extension cohort aims to confirm the observed response and toxicities in 100 patients and addresses whether a complete lymph node dissection can be omitted in patients achieving a major pathologic response after the neoadjuvant immunotherapy. In addition, we presented the first data from the ImPemBra trial at ESMO 2018 Congress. Based on mouse models (see section IV, Prof Blank) a feasibility phase I/II trial (Impembra) has been started combining anti-PD1 (pembrolizumab) with short-term combination targeted therapy (dabrafenib + trametinib) in BRAF V600 mutated metastatic melanoma patients. This intermittent targeted therapy in addition to PD-1 blockade was better tolerated than continuous combinations, and shall be tested in a subsequent neoadjuvant study for melanoma patients that have a unfavourable baseline biomarker profile, and are thus unlikely respond to the neoadjuvant ipilimumab + nivolumab combination.

Jos Beijnen

Head Division Pharmacology

Harm van Tinteren

Head Division Biometrics

DIVISION PHARMACOLOGY

Jos Beijnen PhD Group leader
Alwin Huitema PhD Academic staff
Bastiaan Nuijen PhD Academic staff
Hilde Rosing PhD Academic staff
Joost van den Berg PhD Academic staff
Cynthia Nijenhuis PhD Academic staff
Thomas Dorlo PhD Academic staff
Jeroen Hendrikx PhD Academic staff
Bart Jacobs PhD Hospital pharmacist-in-training
Lotte van Andel MSc PhD Post-doc
Hedvig Arnamo MSc PhD student
Rene Boosman MSc PhD student
Maaike Bruin MSc PhD student
Maarten van Eijk MSc PhD student
Marie-Rose Flint-Crombag MSc PhD student
Steffie Groenland MSc PhD student
Julie Jansen MSc PhD student
Maikel Herbrink MSc PhD student
Paniz Heydari MSc PhD student
Eveline van Kampen MSc PhD student
Jonathan Knikman MSc PhD student
Sven de Krou MSc PhD student
Laura Kuijsten MSc PhD student
Merel van Nuland MSc PhD student
Semra Palic MSc PhD student
Jeroen Roosendaal MSc PhD student
Ignace Roseboom MSc PhD student
Luka Verrest MSc PhD student
Aurelia de Vries Schultink MSc PhD student
Michel Hillebrand Technical staff
Luc Lucas Technical staff
Matthijs Tibben Technical staff
Abadi Gebretensae Technical staff
Niels de Vries Technical staff
Bas Thijsen Technical staff
Lianda Nan Technical staff
Joke Beukers Technical staff
Nikkie Venekamp Technical staff
Ciska Koopman Technical staff
Joke Schol Technical staff
Maaike Van Zon Technical staff
Rhianne Voogd MSc Technical staff
Saskia Scheij Technical staff

DIVISION BIOMETRICS DEPARTMENT

Harm van Tinteren PhD Group leader
Vincent van der Noort PhD Academic staff
Karolina Sikorska PhD Academic staff
Marta Lopez Yurda PhD Academic staff
Erik van Werkhoven MSc Academic staff
Merel Abbenhuis Technical staff
Aziza Absalah Technical staff
Lisette Al Technical staff
Rebecca Astill PhD Technical staff
Danny Baars Technical staff
Nathalie Barbier Technical staff
Marieke van de Belt Technical staff
Frauwkje Bessels Technical staff
Esther de Boer Technical staff
Mandy Boer Technical staff
Samira van den Bogaard Technical staff
Suzanne Bongers Technical staff
Henk Botma Technical staff
Tineke Bruinsma Technical staff
Heleen Bussing Technical staff
Ruth Cohen Technical staff
Jacques Craenmehr Technical staff
Antonios Daletzakis Technical staff
Sirith Douma Technical staff
Brigitte Dufournij Technical staff
Renske Fles Technical staff
Lindsay Grijpink Technical staff
Yvonne Groot Technical staff
Marjolein van den Haak MSc Technical staff
Florianne Hafkamp Technical staff
Patricia Hagen Technical staff
Christiane Hagenaars Technical staff
Song-Hieng Hau MSc Technical staff
Jolanda Hes Technical staff
Annelies Hiemstra Technical staff
Floor Hogenboom Technical staff
Nienke Hooghiemstra Technical staff
Eduard Ivanov Technical staff
Karin Janmaat Technical staff
Marissa Jansen Technical staff
Nicky Janssens Technical staff
Abi Jayakkumaran Technical staff
Gerda de Jong Technical staff
Josien Kant Technical staff
Karin Kaptijn Technical staff
Astrid Keijser Technical staff
Nawel Khelil Technical staff
Marieke de Kock Technical staff
Danja Koersvelt Technical staff
Lies Kolmschate Technical staff
Tobias Koster Technical staff
Daan Latuihamallo Technical staff

Division of Pharmacology & Biometrics

The division of Pharmacology & Biometrics was founded in 2016. In 2017 and 2018 we organized a symposium to exchange information and tighten mutual cohesion between the Pharmacology and Biometrics departments. Drug research is one of the major themes and what connects us. Our research programs in *Pharmacology* focus on drug manufacturing including cellular immunotherapies, bioanalysis and pharmacokinetics of (anticancer) drugs for both preclinical and clinical projects and in *Biometrics* we focus on collection of clinical data and interpretation.

PHARMACOLOGY

Drug manufacturing

We support >20 mono- and (international) multi-center clinical trials (*e.g.* DRUP, POSEIDON, SUBITO, SENSOR) with drug manufacturing, packaging and distribution. In-house manufacturing of vorinostat capsules and oral solid dispersion tablet formulations of docetaxel (ModraDoc006) and paclitaxel (ModraPac005) is performed for ongoing clinical studies. Research to develop and/or to improve oral formulations of anticancer agents is continued by the introduction in 2019 of a new technique: *hot melt extrusion*. The BioTherapeutics Unit (BTU; headed by pharmacist Joost van den Berg) is the biotech facility from the Antoni van Leeuwenhoek Pharmacy where biotechnological products are developed and manufactured for clinical trials. In 2018, we continued the production of Tumor Infiltrating Lymphocytes (TIL) infusions for metastatic melanoma patients treated in the first multi-center phase III trial with TIL therapy in the world.

BTU has previously produced DNA vaccines for HPV induced malignancies. The second generation of vaccines are currently tested by the Gynaecology department (prof. G. Kenter), and promising results have been observed.

In parallel to current clinical production activities, BTU is preparing itself for future clinical trials. We are aiming to apply TIL therapy in other malignancies. In our collaboration with NEON therapeutics (Cambridge, MA), we develop new T cell therapies directed against patient specific neo-antigens. For this collaboration, large scale optimization runs are currently ongoing. Submission of the Investigational Medicinal Product Dossier (IMPD) is scheduled for mid 2019.

The pharmacy holds a governmental GMP (Good Manufacturing Practice) license for these manufacturing activities of pharmaceutical products.

Bioanalytical method development and implementation in pharmacokinetic studies

In 2018, the bioanalytical laboratory of the department of Pharmacy & Pharmacology continued to support clinical and pre-clinical pharmaceutical research. In collaboration with the Alfred Schinkel group, we studied the pharmacokinetic interactions of several anticancer drugs with multidrug efflux transporters and the multidrug metabolizing enzymes in vitro transport assays and knockout and transgenic mouse models. Plasma pharmacokinetics and tissue distribution of capecitabine, irinotecan, vinorelbine, ribociclib, palbociclib, abamaciclib and galunisertib were measured. Studies are still ongoing, however, preliminary results from these studies provide lots of insights on tissue accumulation, toxicity and systemic exposure, important information for the clinical application of these drugs. For all drugs we have developed and validated bioanalytical assays based on the hyphenated technique of liquid chromatography coupled to tandem mass spectrometry detection (LC-MS/MS).

The mammalian target of rapamycin (mTOR) inhibitor everolimus is used in the treatment of breast cancer, neuroendocrine tumors, and renal cancer. We developed and investigated less invasive sampling techniques, like Dried Blood Spots (DBS) and Volumetric Absorptive Microsampling (VAMS) could facilitate pharmacokinetic studies and personalized dosing based on whole blood concentrations, however, the expected advantage of VAMS over DBS sampling could not be demonstrated. To support a prospective, randomized, pharmacokinetic, crossover trial comparing everolimus 10 mg once daily with 5 mg twice daily, venous whole blood samples were collected and analyzed. The approved 10 mg once-daily dose is associated with considerable adverse effects and it has been suggested that these are associated with the maximum concentration of everolimus. We demonstrated that switching from a once-daily to a twice-daily everolimus dose schedule reduces maximum concentration without negatively impacting the minimum concentration or the area under the plasma concentration-time curve.

SGI-110, also known as guadecitabine, is currently being investigated in a mass balance study. SGI-110 is a prodrug of decitabine, a DNA methyltransferase inhibitor. After cellular uptake and intracellular metabolic activation to decitabine triphosphate, it is incorporated into the DNA where it traps DNA methyltransferases, resulting in reduced 5-methyl-2'-deoxycytidine (5mdC) DNA content. To support the mass balance study we have developed and validated LC-MS/MS assays for the quantification of SGI-110 and decitabine in plasma, whole blood and urine. To investigate the incorporation and its effect on DNA methylation, methods for the total intracellular decitabine triphosphate concentrations, as well as decitabine and 5mdC DNA incorporation relative to 2'-deoxycytidine (2dC) DNA content were developed. A total number of 5 patients were treated in the mass balance study and results indicate that SGI-110 is rapidly metabolized and excreted in urine. The metabolic pathway of SGI-110 has been elucidated and new metabolites have been identified. Moreover, a metabolite profiling study was performed with lurbinectedin (PM01183), a synthetic analogue of the marine derived drug trabectedin (Yondelis®). For this compound faeces is the main route of excretion with a mean total recovery of 91.4 (±11.9)%. The majority of the identities of

Merel Latuihamallo Technical staff
Suzanne Latuihamallo Technical staff
Michiel de Looij Technical staff
Marianne Mahn MSc Technical staff
Ingrid Mandjes MSc Technical staff
Else Meijer Technical staff
Nina Michielsen Technical staff
Gordana Milinovic Technical staff
Lindsey Minnaard Technical staff
Pietje Muller Technical staff
Rick Muusers Technical staff
Gabry van Netten Technical staff
Ruud van der Noll Technical staff
Carla Noordhout Technical staff
Elvira Nuijten Technical staff
Caroline Pauwels Technical staff
Kenneth Pengel PhD Technical staff
Patricia Plasier Technical staff
Loes Pronk MSc Technical staff
Anneke Reinders Technical staff
Jolanda Remmelzwaal Technical staff
Valerie Rhemrev Technical staff
Vénice van Rhijn Technical staff
Sanne van Roekel Technical staff
Jacob Rousseau Technical staff
Lydia Ruiter Technical staff
Aysegül Sari Technical staff
Emmie van Schaffelaar Technical staff
Mariëtte Schrier PhD Technical staff
Helga Schrijver Technical staff
Ernst Smienk Technical staff
Carine Sondermeijer Technical staff
Michiel Sondermeijer Technical staff
Roos Steenhuis Technical staff
Dax Steins Technical staff
Suzan Stijger Technical staff
Adriana Thano Technical staff
Loraine Thompson Technical staff
Alex Torres Acosta Technical staff
Adriaan Touw Technical staff
Ludy Valkenet MD Technical staff
Steven Vanhoutvin PhD Technical staff
Tony van de Velde Technical staff
Maarten Venema Technical staff
Marrit Vermeulen Technical staff
Michel Vergouwen Technical staff
Joëlle Vergroesen Technical staff
Carla Vianen Technical staff
Jeltje de Vries Technical staff
Marjolijn de Waal MSc Technical staff
Anneke Wals Technical staff
Rosa Wartena Technical staff
Tatjana Westphal Technical staff
Lidwina Wever Technical staff
Yvonne Wijnands Technical staff
Els Willemse Technical staff
Janna Winnubst Technical staff
Dayenne de Wit Technical staff
Regina Zucker Technical staff

Selected publications

DIVISION PHARMACOLOGY

Herbrink M, Groenland SL, Huitema ADR, Schellens JHM, Beijnen JH, Steeghs N, Nuijen B. Solubility and bioavailability improvement of pazopanib hydrochloride. Int J Pharm. 2018;544(1):181-190.

Janssen JM, Zwaan CM, Schellens JHM, Beijnen JH, Huitema ADR. Clinical trial simulations in paediatric oncology: A feasibility study from the Innovative Therapies for Children with Cancer Consortium. Eur J Cancer. 2017;85:78-85.

Van Andel L, Rosing H, Tibben MM, Lucas L, Lubomirov R, Avilés P, Francesch A, Fudio S, Gebretensae A, Hillebrand MJX, Schellens JHM, Beijnen JH. Metabolite profiling of the novel anti-cancer agent, plitidepsin, in urine and faeces in cancer patients after administration of (14) C-plitidepsin. Cancer Chemother Pharmacol. 2018;82:441-455.

Rohaan MW, van den Berg JH, Kvistborg P, Haanen JBAG. Adoptive transfer of tumor-infiltrating lymphocytes in melanoma: a viable treatment option. J Immunother Cancer. 2018;6:102.

BIOMETRICS DEPARTMENT

Brok J, Lopez-Yurda M, Tinteren HV, Treger TD, Furtwngler R, Graf N, Bergeron C, van den Heuvel-Eibrink MM, Pritchard-Jones K, Olsen E, de Camargo B, Verschuur A, Spreafico F. Relapse of Wilms' tumour and detection methods: a retrospective analysis of the 2001 Renal Tumour Study Group-International Society of Paediatric Oncology Wilms' tumour protocol database. Lancet Oncol. 2018;19(8); 1072-1081.

Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordsmark M, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (critics): An international, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):616-28

De Ruysscher D, Dingemans AC, Praag J, Belderbos J, Tissing-Tan C, Herder J, Haitjema T, Ubbels F, Lagerwaard F, El Sharouni SY, Stigt JA, Smit E, van Tinteren H, van der Noort V, Groen HJM. Prophylactic Cranial Irradiation Versus Observation in Radically Treated Stage III Non-Small-Cell Lung Cancer: A Randomized Phase III NVALT-11/ DLCRG-02 Study. J Clin Oncol. 2018:10;36(23):2366-2377

Van Ramshorst MS, van der Voort A, van Werkhoven ED, Mandjes IA, Kemper I, Dezentjé VO, Oving IM, Honkoop AH, Tick LW, van de Wouw AJ, Mandigers CM, van Warmerdam LJ, Wesseling JP, Vrancken MJ, Linn SC, Sonke GS. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018;19(12):1630-1640

the metabolites have been elucidated. It was found that the drug undergoes de-alkylation (demethylation), oxidation, aliphatic ring-opening, and loss of water. The chemical formula of several metabolites were confirmed by high resolution and accurate mass spectrometry analysis.

Fluoropyrimidines (capecitabine, 5-fluoro-uracil) can result in severe toxicity, often due to the reduced activity of the metabolic enzyme dihydropyrimidine dehydrogenase (DPD). This is mostly caused by genetic variants in the gene encoding for DPD (*DPYD*). We have performed the bioanalysis for a multicenter prospective study in which more than 1,000 patients were included to investigate the effect of prospective screening for the four most relevant *DPYD* variants on patient safety and subsequent *DPYD* genotype-guided dose individualization in daily clinical care. Prospective *DPYD* genotyping was feasible in routine clinical practice, and *DPYD* genotype-based dose reductions improved patient safety. To further improve fluoropyrimidine treatment, the LC-MS/MS bioanalysis for a study to determine the effect of food intake on uracil and dihydrouracil plasma levels was performed. These levels are a promising marker for DPD activity and for individualizing fluoropyrimidine anticancer therapy and might be used instead of genotyping. Uridine plasma levels showed curves with similar patterns as for uracil. It was shown that both uracil and dihydrouracil levels were higher in fasting state than in fed state. This is hypothesized to be an direct effect of uridine plasma levels, which were previously shown to be elevated in fasting state and reduced after intake of food. These findings show that, when assessing plasma uracil and dihydrouracil levels for adaptive fluoropyrimidine dosing in clinical practice, sampling should be done after overnight fasting to avoid bias caused by circadian rhythm and food effects.
Our therapeutic drug monitoring (TDM) service for the optimization of drug treatment has been extended with anti-hormonal drugs: abiraterone, its active metabolite Δ(4)-abiraterone, anastrozole, bicalutamide, endoxifen, enzalutamide and its active metabolite N-desmethyl enzalutamide, and exemestane. This year we have received more than 5,000 samples for analysis. New state-of-the-art LC-MS/MS equipment is installed in 2019 including a triple Q-TOF instrument (figure 1).

Pharmacokinetic and Pharmacodynamics (PK/PD) modelling and simulation

The modelling and simulation group of the department of Pharmacy & Pharmacology maintains a high performance computational server, part of the NKI Research HPC facility, dedicated to PK/PD modelling and simulation purposes.
The group develops modelling methodologies to relate drug exposure to diverse measures of treatment outcome for both toxicity and efficacy. PK/PD modelling and simulation has been applied to optimize therapy of approved anticancer agents and novel agents used in clinical trials. This research focussed mainly on PK and PD in special patient populations typically underrepresented in clinical trials. The number of elderly treated with anticancer agents is increasing and, therefore, it is of importance to study the impact of older age on the PK and PD of anticancer agents. For paclitaxel it was shown that older age does not have a relevant effect on PK. For pediatric patients we have identified the need for dose adjustments for several compounds, which led in 2018 to the evaluation a novel pediatric model-based dosing regimen for the repurposed anticancer PI3K/Akt inhibitor miltefosine. Furthermore, the effects of pregnancy on the PK of several cytotoxic agent have been explored, in collaboration with the group of Frédéric Amant. A semi-mechanistic physiologically-based PK (PBPK) framework to predict the effects of pregnancy on the PK of these agents based on known physiological changes and dynamics during pregnancy has been developed and is currently validated.

Most kinase inhibitors have a narrow therapeutic index, however, the currently approved dosing paradigm is a "one-size-fits-all" approach. We implemented TDM for these drugs in clinical practice, where plasma concentrations are routinely measured and reported to the treating physician together with a clinical pharmacological review and dosing advice. In 2018 this program was expanded to 33 approved oral anticancer agents including some active metabolites. In this program we reported patients with severe toxicity on the standard dose of pazopanib who could safely and effectively be treated with pazopanib with a up to 8-fold lower dose based on measured plasma levels. Furthermore, it has been shown that elderly treated with kinase inhibitors do not exhibit relevantly higher plasma concentrations or required lower dose intensity. Our program on treatment optimization of the repurposed anticancer PI3K/Akt inhibitor miltefosine for the neglected tropical parasitic disease leishmaniasis has been largely extended, with various clinical PK/PD studies initiated in 2018 in India, Bangladesh, Sudan and Kenya, funded partially through H2020.

BIOMETRICS

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 project 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 2017 until July 2018 about 10.049 tumors are 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 3.500 tumors, of people 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 the period July 2017- June 2018 almost 2.300 patients were registered for this purpose and the demand for new registers 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 patients 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. In 2018, 11.388 patients were added to this register.

Clinical studies and services

The Biometrics Department provides logistic 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 projects. 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 an 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). In 2018 an overall Quality Management System was delivered, based in ICH-GCP(R2) and published on the internal document management system.

The number of studies – approved according to the Medical Research Involving Human Subjects Act (WMO) – open for patient inclusion over the past 5 years is ranging between 230 and 250, while the number of patients registered still increases. About one in every 5 patients who receives treatment in the AVL participates in WMO-studies.

Methodological support to national and international clinical trials

After the successful completion of the TRAIN and TRAIN-2 studies, the research program to investigate possible de-escalation of neoadjuvant chemotherapy was continued. In collaboration with the group of Dr. Gabe Sonke and the Dutch Breast Cancer Research Group (BOOG), the TRAIN-3 study (BOOG 2018-01) was designed. The purpose of the TRAIN-3 study will be to assess whether image-guided de-escalation is possible without compromising event-free survival (EFS) relative to the current standard of care. A particular challenge in the design of this one-arm study was the requirement to

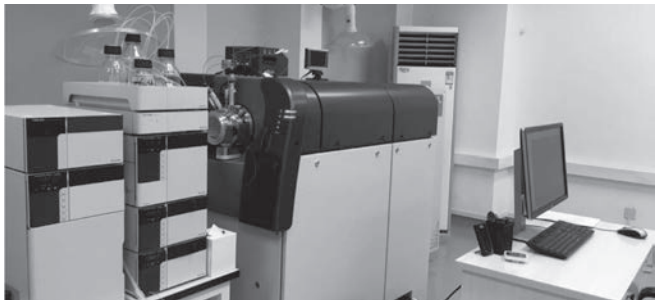


Figure 1: The new Sciex Triple TOF 6600

plan an interim analysis, which allows for stopping the study early if the EFS seems to be worse than expected on the basis of literature. The problem was addressed by assuming that the event rate is fairly constant over time, and recognizing that that the event rate is small enough that the true distribution may be approximated by a Poisson distribution. Because the Poisson distribution function has a closed form, it was then possible to study the operating characteristics of the trial via the behavior of its underlying martingale process using exact methods. This made it possible to choose a stopping boundary which guarantees the safety of the patients in the study, while controlling the significance level and the power of the study. The protocol was recently approved by the ethics committee and the study is expected to be opened in January 2019.

In May 2018 the paper titled 'Chemotherapy versus chemo-radiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial', co-authored by Harm van Tinteren and Karolina Sikorska, was published. In this paper the intention-to-treat (ITT) analysis of the CRITICS trial is presented. CRITICS was a superiority trial aiming to show the benefits of preoperative chemotherapy-curative surgery-postoperative chemoradiotherapy as compared to preoperative chemotherapy-curative surgery-postoperative chemotherapy. In the ITT analysis no superiority was found and the estimates of overall survival were very similar between the arms. However, only about 60% of patients started postoperative treatment. A natural question from the clinical perspective is to perform a so called per protocol analysis in which only those 60% of patients are analyzed. This type of analysis suffers from many flaws and potential sources of bias. We attempted to reduce them by applying several methods intended to deal with confounding such as multivariable Cox model, propensity score analysis and time-dependent inverse probability weighting. Nevertheless, the results are still prone to bias and should be treated with caution by medical readers. Currently a manuscript is drafted from the methodological perspective, which is nevertheless aimed for clinicians, explaining the possible flaws and dangers of the per-protocol analysis. We performed a large simulation study exploring the influence of an unmeasured confounder(s) on the results of per-protocol analyses. We explored the robustness of different analytical methods to unmeasured confounders. The simulated data are as much as possible resembling the CRITICS data. We also discuss the results of a sensitivity analysis exploring how the conclusion of the per-protocol analysis would change if an important confounder has been unmeasured or measured but forgotten in the model. Our goal is to publish this article early 2019.

Over the past few years, the introduction of immunotherapy has radically changed the treatment of advanced stage non-small cell lung cancer (NSCLC). While PD-1 inhibitors Pembrolizumab and Nivolumab yield unprecedented survival benefit in a subgroup of patients, in a majority of patients no tumor-response is seen. Hence there is a clear clinical demand for biomarkers that are able to recognize these non-responders as early as possible, enabling physicians to switch to a different treatment (e.g. chemotherapy) or at at least avoid the costs and side effect of immunotherapy for these patients. However: the demands in terms of specificity on such a marker is high: no one wants to withhold a patient a potentially beneficial treatment. The statistics group of the WA is actively involved in several projects aiming at finding such a biomarker. Candidate biomarkers are developed based on data from thrombocytes (collaboration with VUmc), liquid biopsies (collaboration with AKL and Radboud MC), exhaled breath (collaboration with VUmc), pleural effusion and PET-scan data. Besides we are working with the AKL on the development of an ICT infrastructure and tools for data visualizing that aim to simplify the use of lab data collected in routine clinical care for biomarker development. Both training and development and the evaluation and validation of biomarkers have a strong statistical component. Various statistical and machine learning techniques are employed to condense high-dimensional measurement data into a simple classifier distinguishing prospective responders from non-responders. Translating these classifiers into a form that enables predicting the response or non-response of a single patient without access to the entire training dataset is often an additional mathematical challenge. In the validation phase, the study design is interesting as the relative importance of the two different types of mistakes that each marker will inevitably make (predicting that a patient will respond when in reality he will not and vice versa) as well as the amount of uncertainty we are willing to accept in our estimates of their frequency, vary from case to case based on the relative proportion of each group, the availability of alternative treatments and the invasiveness of the data collection needed for the prediction, among other consideration. An invaluable tool in both development and validation of these markers has been the NVALT Registry, established in 2016 and maintained by the WA.

Since 2015, the department provides statistical services to the area of Innovative Therapies for Children with Cancer (ICTT) of the Princess Máxima Center (PMC). The PMC (prof. CM Zwaan) is leading in a few international phase I/II studies with novel drugs such as Bosutinib for chronic myeloid leukemia, Inotuzumab Ozogamicin as a single agent and in combination with chemotherapy for CD22-positive relapsed/refractory acute lymphoblastic leukemia and Crizotinib for ALK, ROS1 or MET positive malignancies. These projects use rule-based as well as model-based designs for dose-escalation, such as escalation with overdose control (EWOC), as well as a longitudinal dose-time-toxicity model to integrate data from all courses to help determine the recommended phase II dose level. Additional projects include, among others, iTHER and iTHER 2.0, that attempt to improve the treatment of relapse in pediatric cancer with no available curative options by implementing a pediatric cancer precision medicine program. Another initiative with the PMC is the organisation of the data collection of the SIOP-Renal Tumor Study Group. In 2018 the department has developed the database, including a `trusted-third-party' solution, for the upcoming world-wide study that will be launched in 2019.

One of the collaborations of the Biometrics department at the NKI is with BOOG is the Stop&Go study. This open randomized phase III study compares 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 of patients with HER2/neu negative, incurable, metastatic or unresectable locally advanced breast cancer. In the first line of treatment, the intermittent arm was

not found to be non-inferior to the continuous arm (Claessens et al., 2018). At the moment, a manuscript concerning results for the second line of treatment is in preparation, where the statistical analyses account for imbalances in the randomization among those patients going on to the second line.

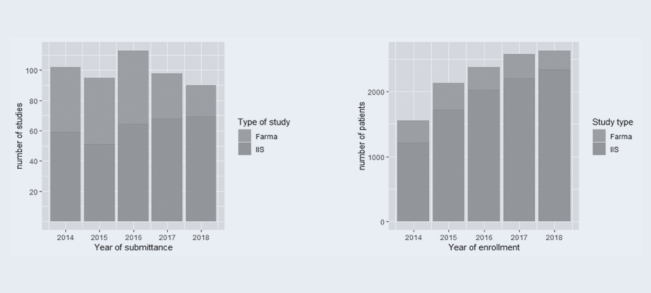


Figure 2

Number of WMO-studies open for inclusion over the past 5 years

Number of patients enrolled in WMO-studies over the past 5 years

Jan-Jakob Sonke

Head (ad int.) Division Radiation Oncology

Jan-Jakob Sonke PhD Head (ad int.)
Berthe Aleman MD PhD Academic staff
Abrahim Al-Mamgani MD PhD Academic staff
Harry Bartelink MD PhD Academic staff
José Belderbos MD PhD Academic staff
Monique Bloemers MD Academic staff
Gerben Borst MD PhD Academic staff
Maarten Buiter Academic staff
Eugène Damen PhD Academic staff
Luc Dewit MD PhD Academic staff
Judi van Diessen MD Academic staff
Paula Elkhuizen MD PhD Academic staff
Marloes Frantzen-Steneker PhD Academic staff
Rick Haas MD PhD Academic staff
Olga Hamming-Vrieze MD Academic staff
Uulke van der Heide PhD Academic staff
Edwin Jansen MD PhD Academic staff
Tomas Janssen PhD Academic staff
Jeroen van de Kamer PhD Academic staff
Joost Knegjens MD Academic staff
Folkert Koetsveld PhD Academic staff
Joos Lebesque MD PhD Academic staff
Anton Mans PhD Academic staff
Luc Moonen MD PhD Academic staff
Ben Mijnheer PhD Academic staff
Anke van Mourik PhD Academic staff
Arash Navran MD Academic staff
Floris Pos MD PhD Academic staff
Peter Remeijer PhD Academic staff
Nicola Russell MD PhD Academic staff
Govert Salverda MD Academic staff
Eva Schaake MD PhD Academic staff
Christoph Schneider PhD Academic staff
Astrid Scholten MD PhD Academic staff
Baukelien van Triest MD PhD Academic staff
Conchita Vens PhD Academic staff
Marcel Verheij MD PhD Academic staff
Wouter Vogel MD PhD Academic staff
Francine Voncken MD Academic staff
Iris Walraven PhD Academic staff
Terry Wiersma MD Academic staff
Thelma Witteveen MD Academic staff
Frits Wittkämper PhD Academic staff
Mila Donker MD PhD Academic staff
Renske de Jong MD PhD Academic staff
Marlies Nowee MD PhD Academic staff

Romy van Amelsfoort MD Clinical resident, PhD student
Anouk Trip MD PhD Clinical resident, PhD student
Sophie Bosma MD Clinical resident, PhD student
Jos Elbers MD Clinical resident, PhD student
Zeno Gouw MD Clinical resident, PhD student
Rosemarie de Haan MD Clinical resident, PhD student
Eline Hessen MD Clinical resident, PhD student
Jolien Heukelom MD Clinical resident, PhD student
Jules Lansu MD Clinical resident, PhD student
Femke van der Leij MD Clinical resident, PhD student
Pieter de Veij Mestdagh MD Clinical resident, PhD student
Charlotte Deijen MD Clinical resident
Jan Groenewegen MD Clinical resident
Carmen Liskamp MD Clinical resident
Barbara Rijksen MD Clinical resident
Quinten Telkamp MD Clinical resident
Erik van der Bijl PhD Physics resident
Anne Lisa Wolf PhD Physics resident
Milena Smolic PhD Physics resident
Petra van Houdt PhD Associate staff scientist
Jonas Teuwen PhD Associate staff scientist
Masudur Al Arif PhD Post-doc
Roeland Dilz PhD Post-doc
Paul Essers PhD Post-doc
Martin Fast PhD Senior post-doc
Ghazaleh Ghobadi PhD Post-doc
Patrick Gonzalez PhD Post-doc
Rob de Graaf PhD Post-doc
Brent Huisman PhD Post-doc
Takahiro Kanehira PhD Post-doc
Artem Khmelinskii PhD Post-doc
Karen Kiers PhD Post-doc
Simon van Kranen PhD Post-doc
Matthew La Fontaine PhD Post-doc
Kees Landheer PhD Post-doc
Albert Licup PhD Post-doc
Gordon Lim PhD Post-doc
Lotte Lutkenhaus PhD Post-doc
Scott Marshall PhD Post-doc
Jasper Nijkamp MSc PhD Post-doc
René van Oers PhD Post-doc
Igor Olaciregui-Ruiz PhD Post-doc
Pavlos Papaconstadopoulos PhD Post-doc
Roel Rozendaal PhD Post-doc
Stijn van der Schoot PhD Post-doc
Barbara Stam MSc PhD Post-doc
Aldemar Torres Valderrama PhD Post-doc
Gijs van der Veen PhD Post-doc
Steven van de Water PhD Post-doc
Marnix Witte PhD Post-doc
Wouter van den Wollenberg PhD Post-doc
Geert Wortel PhD Post-doc
Ahmed Bani Yassien PhD student
Chris Beekman PhD student
Catarina Dinis Fernandes PhD student
Roelant Eijgelaar PhD student
Elselien Frijlink PhD student
Beatrix Gomez Solsona PhD student

Division of Radiation Oncology

The research activities within the division of Radiation Oncology are clustered within three of the five institution wide themes: personalized radiotherapy, image guided radiotherapy and survivorship. Most research projects have a multi-disciplinary character, combining clinical, physics, biology and/or epidemiology and a strong focus on translational research and innovation.

Marcel Verheij, the former chair of our department and head of division of Radiation Oncology has recently moved to Nijmegen as the chair of the department of Radiation Oncology of the Radboud University Medical Center in Nijmegen. Per March 1, 2019, Corry Marijnen has been appointed as the new chair of the department of Radiation Oncology and head of the division of Radiation Oncology.

In June 2018 we treated our first patient on the ICON Gamma Knife, a stereotactic radiosurgery system equipped with a CBCT to facilitate frameless and fractionated treatments. On July 5 and 6 we organized a symposium, the art of ART, with internationally renowned speakers covering a broad spectrum of topics on adaptive radiotherapy followed by the inaugural speech titled "Radiotherapy and the art of continuous learning" by Jan-Jakob Sonke. In September 2018, we treated the first patient on our Elekta Unity MR-Linac system.

Personalized Radiotherapy

Personalized radiotherapy aims to individualize treatment through the use of genetic profiling and biology driven imaging for patient selection and the use of targeted agents during radiotherapy. The ongoing and future research addresses 1) novel insights in the irradiation response of tumors, 2) better patient selection for better individualized treatment management, and 3) optimization of combined-modality-targeted therapeutics to increase the therapeutic window. Our research follows the bench to bedside approach with the focus on the clinical needs and opportunities in our daily clinical practice. Importantly, we initiated new and promising collaborations with other research groups to use state-of-the-art pre-clinical tools and to enable innovative translational studies contributing to the personalized radiotherapy treatment approach.

Preclinical research

Modulation of targeted agents to optimize the radiotherapy outcome

Our preclinical studies aim to optimize the timing and duration of targeted agents in relation to the RT in glioblastoma. Interestingly, the start of adjuvant immunotherapy did improve the survival of mice in contrast to concurrently started IT. In collaboration with the Akkari group we further study the sequence and timing of immunotherapy and fractionated radiotherapy to optimize the radiotherapy outcome.

Another strategy to improve the radiotherapy outcome for glioblastoma patients is to increase the mitotic fraction in the tumor which is most radiosensitive cell cycle phase. Previous clinical attempts failed due to cytotoxicity and inappropriate timing. In collaboration with the van Tellingen group we observed recently both *in vitro* and *in vivo* very promising results and are currently working on the introduction of this concept into the clinic.

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 Department of Head and Neck Surgery and Oncology. In preliminary studies these showed promise, identifying a subgroup of patients with different outcome parameters that warrant validation in an independent cohort.

Clinical research

PARP inhibitors in combination with radiotherapy

PARP inhibitors are currently evaluated in combination with radiotherapy and/or chemotherapy. As sensitizers, PARP inhibitors are active at very low concentrations therefore requiring highly sensitive pharmacodynamic (PD) assays. Current clinical PD-assays partly fail to provide such sensitivities. Our department developed a valuable and clinically implementable PD-assay for such combination purposes and provides proof of clinically relevant cellular PARP inhibitory activities at low daily olaparib doses.

Individualizing preoperative radiation for sarcoma patients

Opposed to myxoid liposarcomas, in other sarcoma subtypes pathologists frequently report an absence of treatment response with high percentages of remaining viable tumor cells. Increasing radiation dose in patients that still have to undergo definitive surgery is probably not clinically feasible. Obviously, investigations into radiation sensitizers maintaining radiation dose are warranted and angiogenesis inhibitors seem logic candidates. After completing a phase I study on the combination with pazopanib, (NCT01985295), in 2018 we have confirmed our prior observation of a high pathological complete remission rate in the subsequent phase II study (NCT02575066) investigating the phase I recommended dose of 25 x 2 Gy radiotherapy and once-daily 800 mg pazopanib, such that the trial could be amended to continue with a lower radiation dose (18 x 2 Gy), while maintaining pazopanib dose (not yet published).

Survivorship

In the last decades, cancer treatments have improved significantly, leading to improved cure rates. Consequently, increasing numbers of cancer survivors are at risk of developing (late) adverse effects, which in turn may affect quality of life (QOL) and long-term survival. Therefore, treatment individualization and optimization to decrease adverse event risk, as well as early detection and monitoring strategies of adverse events are warranted.

Natasja Janssen PhD student
Celia Juan de la Cruz PhD student
Edzo Klawer PhD student
Ernst Kooreman PhD student
Maria Lambrecht PhD student
Tessa van de Lindt PhD student
Kai Lønning PhD student
Vineet Mohan PhD student
Karin Ortega Marin PhD student
Kleopatra Pirpinia PhD student
Angjelina Protik PhD student
Marcel van Schie PhD student
Lukas Schröder PhD student
Paul Slangen PhD student
Bruno Soares Vieira PhD student
Uros Stankovic PhD student
Iban Torres Xirau PhD student
Barry Doodeman Physician assistant
Marcel Jonker Physician assistant
Robin Kalisvaart Physician assistant
Margriet Kwint Physician assistant
Cherita Sombroek Physician assistant
Sandra Vreeswijk Physician assistant
Gerbert Vrijenhoek Physician assistant
Corine Veenstra Physician assistant
Hester Visser Physician assistant
Anja Betgen MSc Technical staff
Suzanne van Beek Technical staff
Natascha Bruin Technical staff
Casper Carbaat Technical staff
Mariska Geldorp Technical staff
Di Geng Technical staff
Emmy Lamers Technical staff
Wai Kong Mok Technical staff
Thi Minh Anh Nguyen Technical staff
Priyanka Ojha Technical staff
Vivian van Pelt Technical staff
Lennert Ploeger PhD Technical staff
Mohsen Rahimimoghaddam Technical staff
Maddalena Rossi MSc Technical staff
Georgios Sotiropoulos Technical staff
Evalien Veldhuijzen Technical staff

Selected publications

Barazas M, Gasparini A, Huang Y, Küçükosmanoğlu A, Annunziato S, Bouwman P, Sol W, Kersbergen A, Proost N, de Korte-Grimmerink R, van de Ven M, Jonkers J*, Borst GR*, Rottenberg S*. Radiosensitivity is an acquired vulnerability of PARPi-resistant BRCA1-deficient tumors. Cancer Res. 2018

Beekman C, van Triest B, van Beek S, Sonke JJ, Remeijer P. Margin and PTV volume reduction using a population-based library of plans strategy for rectal cancer radiotherapy, Med Phys. 2018;45(10):4345-4354

Boekel NB, Jacobse JN, Schaapveld M, Hooning MJ, Gietema JA, Duane FK, Taylor CW, Darby SC, Hauptmann M, Seynaeve CM, Baaijens MHA, Sonke GS, Rutgers EJT, Russell NS, Aleman BMP*, van Leeuwen FE*. Cardiovascular disease incidence after internal mammary chain irradiation and anthracycline-based chemotherapy for breast cancer. Br J Cancer. 2018;119(4):408-418

Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordsmark M,Meershoek-Klein Kranenbarg E, Boot H, Trip AK, Swellengrebel HAM, van Laarhoven HWM, Putter H, van Sandick JW, van Berge Henegouwen MI, Hartgrink HH, van Tinteren H, van de Velde CJH, Verheij M; CRITICS investigators. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomized phase 3 trial. Lancet Oncol. 2018;19:616-628

De Haan R, Pluim D, van Triest B, van den Heuvel M, Peulen H, van Berlo D, George J, Verheij M, Schellens JHM, Vens C. Improved pharmacodynamic (PD) assessment of low dose PARP inhibitor PD activity for radiotherapy and chemotherapy combination trials. Radiother Oncol. 2018

De Veij Mestdagh PD, Janssen T, Lamers E, Carbaat C, Hamming-Vrieze O, Vogel WV, Sonke JJ, Al-Mamgani A. SPECT/CT-guided elective nodal irradiation for head and neck cancer: Estimation of clinical benefits using NTCP models. Radiother Oncol 2018

Fast M, van de Schoot A, van de Lindt T, Carbaat C, van der Heide U, Sonke JJ. Tumor trailing for liver SBRT on the MR-Linac. Int J Radiat Oncol Biol Phys. 2018

Haas RL, Gronchi A, van de Sande MAJ, Baldini EH, Gelderblom H, Messiou C, Wardelmann E, Le Cesne A. Perioperative management of extremity soft tissue sarcomas. J Clin Oncol 2018;36:118-124

Haas RL, Baldini EH, Chung PW, van Coevorden F, DeLaney Th. Radiation Therapy in Retroperitoneal Sarcoma Management. J Surg Oncol 2018;117:93-98

Jacobse JN, Duane FK, Boekel NB, Schaapveld M, Hauptmann M, Hooning MJ, Seynaeve CM, Baaijens MHA, Gietema JA, Darby SC, van Leeuwen FE, Aleman BMP*, Taylor CW*. Radiation Dose-Response for Risk Of Myocardial Infarction In Breast Cancer Survivors. Int J Radiat Oncol Biol Phys. 2018

Mijnheer B, Jomehzadeh A, González P, Olaciregui-Ruiz I, Rozendaal R, Shokrani P, Spreeuw H, Tielenburg R, Mans A. Error detection during VMAT delivery using EPID-based 3D transit dosimetry. Phys Med. 2018;54:137-145

Monninkhof EM, van Loon JWL, van Vulpen M, Kerkmeijer LGW, Pos FJ, Haustermans K, van den Bergh L, Isebaert S, McColl GM, Jan Smeenk R, Noteboom J, Walraven I, Peeters PHM, van der Heide UA. Standard whole prostate gland radiotherapy with and without lesion boost in prostate cancer: Toxicity in the FLAME randomized controlled trial. Radiother Oncol. 2018;127(1):74-80

Olaciregui-Ruiz, R. Rozendaal, B. Mijnheer, A. Mans. Site-specific alert criteria to detect patient-related errors with 3D EPID transit dosimetry. Medical Physics 2019;46,45

Torres-Xirau I, Olaciregui-Ruiz I, Baldvinsson G, Mijnheer BJ, van der Heide UA, Mans A. Characterization of the a-Si EPID in the unity MR-linac for dosimetric applications. Phys Med Biol. 2018;63(2):025006

Van de Lindt T, Sonke J-J, Nowee M, Jansen E, van Pelt V, van der Heide U, Fast M. A Self-Sorting Coronal 4D-MRI Method for Daily Image Guidance of Liver Lesions on an MR-LINAC. Int J Radiat Oncol Biol Phys. 2018

Van Diessen J, De Ruysscher D, Sonke JJ, Damen E, Sikorska K, Reymen B, van Elmpt W, Westman G, Fredberg Persson G, Dieleman E, Bjorkestrand H, Faivre-Finn C, Belderbos J. The acute and late toxicity results of a randomized phase II dose-escalation trial in non-small cell lung cancer (PET-boost trial). Radiother Oncol. 2018

Velikova G, Williams LJ, Willis S, Dixon JM, Loncaster J, Hatton M, Clarke J, Kunkler IH, Russell NS; MRC SUPREMO trial UK investigators. Quality of life after postmastectomy radiotherapy in patients with intermediate-risk breast cancer (SUPREMO): 2-year follow-up results of a randomised controlled trial. Lancet Oncol. 2018;19(11):1516-1529. Erratum in: Lancet Oncol. 2018;19(12):e668

Verhagen CVM, Vossen DM, Borgmann K, Hageman F, Grénman R, Verwijs-Janssen M, Mout L, Kluin RJC, Nieuwland M, Severson TM, Velds A, Kerkhoven R, O'Connor MJ, van der Heijden M, van Velthuysen ML, Verheij M, Wreesmann VB, Wessels LFA, van den Brekel MWM, Vens C. Fanconi anemia and homologous recombination gene variants are associated with functional DNA repair defects in vitro and poor outcome in patients with advanced head and neck squamous cell carcinoma. Oncotarget. 2018;9:18198-213

* authors contributed equally

Identification of risk groups at increased risk of treatment related adverse events

In a Dutch hospital-based cohort of 14,645 breast cancer (BC) patients, we found that women treated with anthracycline-based chemotherapy and internal mammary irradiation (in an older era) with a considerable mean whole heart dose (MWHD) have a substantial increased incidence of several Cardiovascular diseases. Screening may be appropriate for some BC patient groups. Furthermore, a case-control study (183 cases and controls) nested within a cohort of BC survivors showed that myocardial infarction rate after radiation for BC increased linearly with MWHD. This result will be used in future risk prediction models.

Treatment individualization and optimization

An international, randomized, controlled trial (SUPREMO trial) was performed (2006-2013; n=1,688) to define the role of radiotherapy in intermediate risk breast cancer patients. The two-year results of the QOL sub-study showed that compared to patients who were only treated with surgery, patients receiving postmastectomy radiotherapy reported slightly worse chest-wall symptoms but the difference was small and of uncertain clinical significance. Furthermore, symptoms improved from year 1 to 2. These reassuring results will facilitate shared decision making while awaiting the survival results (primary endpoint).

Radiotherapy for locally advanced non-small lung cancer (LA-NSCLC) may cause severe esophageal and/or pulmonary toxicity. The PET-boost randomized phase II trial (NCT01024829) investigated dose-escalation to the entire primary tumor or redistributed to regions of high pre-treatment FDG-uptake in inoperable non-small cell lung cancer (NSCLC) patients. The toxicity results of the PET-boost trial revealed that hypofractionated dose-escalation to the primary tumor, but not the lymph nodes, is associated with higher acute and late toxicities compared to conventional chemoradiotherapy.

Accurate monitoring of adverse event development

Recent trials showed that the use of patient reported outcomes (PROs) to monitor symptoms during and after cancer treatment does not only improve adverse event management but also significantly improves QOL and overall survival. These promising results emphasize the increasingly important role of the PRO symptom monitoring tools and the need to implement these tools within clinical practice. To implement PRO symptom monitoring, we successfully translated and linguistically validated the Dutch version of the PRO-CTCAE, which is now publicly available (https://healthcaredelivery.cancer.gov/pro-ctcae/pro-ctcae_dutch.pdf).

Image Guided Radiotherapy

Spatiotemporal inter- and intra-tumor variability challenge optimal treatment selection and delivery. Imaging allows to quantify such variability non-invasively. Image guided radiotherapy is the process of image acquisition, image processing and treatment modification for optimal treatment selection and delivery. Our image guided research activities span a broad range of disease sites and all major imaging modalities.

Adaptive Radiotherapy

Day-to-day shape variation in the rectum CTV results in considerable geometric uncertainties during rectal cancer radiotherapy. The purpose of this study was to increase the accuracy of treatment delivery by building a population-based library of planning CTVs for rectal cancer patients and to evaluate its potential for rectum PTV margin and PTV volume reduction. We created signed distance maps from the planning rectum CTV to each of the repeat CTVs to create the library of nine planning CTVs. For each of the repeat CTVs the best fitting CTV structure in the library was automatically selected and residual distance maps were calculated from which a new PTV margin was constructed. Residual errors were found to decrease with the number of plans in the library, but adding more than five plans yields negligible further error reduction. Margin reduction of up to 50% was achieved at the upper-anterior site of the mesorectum. In conclusion, a library of plans strategy for rectal cancer based on population statistics is feasible and results in a considerably reduced average rectum PTV volume compared to conventional radiotherapy.

MRI-guided radiotherapy

To improve the precision of dose delivery in the clinic, the department of Radiation Oncology has started MRI-guided radiotherapy with the Elekta Unity system. The department participates in the MR-linac consortium to further develop the methodology and conduct joint clinical trials. The NKI leads the consortium tumor site groups on rectal cancer and oligo-metastases.

Building on the experience gained with cone-beam CT-guided radiotherapy, we are developing methods to make optimal use of the on-line imaging capacity of the MR-linac. For treatment of rectal cancer, library-of-plans are generated that allow us to select an optimal plan for the anatomy of a given day. For treatment of cancers in the abdomen, a 4D-MRI technique was developed from which the mid position of the tumor during breathing motion can be derived, as well as the amplitude of the motion. We intend to use this first for patients with liver cancer. As the time-averaged position can drift during irradiation, this potentially results in deterioration of target coverage. A continuous adjustment of beam apertures in a process called trailing, can restore target coverage. To test the feasibility of these and other techniques, we have started the Umbrella-II study. While the regulatory environment has become challenging, we aim to continue to bring these novel technologies to routine clinical care.

As the imaging performance of integrated MR-Linac systems is critical for their application, within the MR-linac consortium a comprehensive commissioning protocol was developed that combines standard MRI performance measurements with dedicated hybrid tests that specifically assess the interactions between the Linac and the MRI system. Importantly, the homogeneity of the static magnetic field of the scanner is not influenced at all by the accelerator mounted on the gantry around the MRI. The results show that high-quality MR imaging is feasible during irradiation and while the gantry is moving around the patient. In the absence of guidelines for commissioning MR-linac systems, the test results from 4 consortium centers provide initial bench mark data for future MR-linac installations.

Now that the MR-linac is used clinically, we will start clinical trials to investigate the potential benefit for a range of patient groups. To accelerate the technical and clinical development of MR-guided radiotherapy and facilitate the evidence-based introduction of the MR-linac into clinical practice, the MR-linac consortium has initiated the Momentum trial and project. Technical and clinical data are gathered to develop further functionality and evaluate treatment outcomes.

EPID Dosimetry

Systems for pre-treatment and in vivo dosimetric QA of radiation treatments are traditionally commissioned without knowledge of their sensitivity to clinically relevant errors. In this work, we developed a framework in which virtual dose reconstructions is combined with synthetic patient data allows to assess the sensitivity of our 3D EPID transit dosimetry method to patient-related variations. Translation and rotation patient setup errors and uniform contour changes were studied for 104 VMAT plans of 4 treatment sites. The detectability of each introduced error is specific to the treatment site and indicator used. The area under the curve (AUC) of the receiver operating characteristic curve (ROC) was >0.8 for 3 out of 4 sites. Optimal alert criteria were determined to ensure excellent detectability for each combination of error type and indicator.

Last year, we have presented a characterization of the EPID positioned on the MR-linac for portal dosimetry applications. This year, the next step towards in vivo portal dosimetry was taken by demonstrating the possibility to perform 2D portal dosimetry on the MR-linac. Our conventional back-projection algorithm was adapted for the MR-linac geometry. It was commissioned using absolute dose values obtained from ionization chamber (IC) array measurements. Furthermore, a method was presented to correct for the (gantry-angle dependent) influence of the couch, bridge and cryostat. Dosimetric verification of 25 IMRT beams showed excellent agreement between IC array measurements and EPID-based 2D dose distributions reconstructed at 10 cm depth in a phantom at isocenter.

Individualizing irradiation treatment for Head and Neck patients

The SPECT-guided elective unilateral nodal irradiation lead by Dr. Al-Mamgani was completed in January 2018. In this proof-of-concept study, 50 patients with T1-3N02b head and neck squamous cell carcinoma limited to the midline were treated electively to one side of the neck instead of the current standard of care where patients with these tumors are electively treated to both sides of the neck in order to reduce the risk of contralateral recurrence. The preliminary results are very promising. After a median follow-up of 12 months, only one patient (2%) developed contralateral regional failure after unilateral elective irradiation. Furthermore, the severity, frequency and duration of different troublesome acute and late radiation-related toxicities such as the need for tube feeding and xerostomia were significantly reduced, compared to the historical cohort treated to both sides of the neck at our institute.

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. We analyzed the toxicity up to two years after treatment and found that the focal boost did not result in an increase in GU and GI toxicity when compared to the standard treatment. This suggests that the described focal dose escalation technique is safe and feasible. The primary endpoint, 5-year biochemical failure free survival, will be reached in 2020.

Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS)

This investigator-initiated, open-label, randomized phase 3 trial enrolled 788 patients to compare perioperative chemotherapy with preoperative chemotherapy and postoperative chemoradiotherapy in patients with resectable gastric adenocarcinoma. Postoperative chemoradiotherapy did not improve overall survival compared with postoperative chemotherapy in patients with resectable gastric cancer treated with adequate preoperative chemotherapy and surgery. In view of the poor postoperative patient compliance in both treatment groups, future studies should focus on optimizing preoperative treatment strategies.

Theo Ruers

Head Division Surgical Oncology

BOARD

Theo Ruers MD PhD Division Head
Henk van der Poel MD PhD Academic staff
Christianne Lok MD PhD Academic staff

SURGICAL ONCOLOGY

Geerard Beets MD PhD Head
Arend Aalbers MD Academic staff
Alexander van Akkooi MD PhD Academic staff
Marie-Jeanne Baas-Vrancken Peeters MD PhD Academic staff
Frits van Coevorden MD PhD Academic staff
Frederieke van Duijnhoven MD PhD LLM Academic staff
Koen Hartemink MD PhD Academic staff
Winan van Houdt MD PhD Academic staff
Houke Klomp MD PhD Academic staff
Niels Kok MD PhD Academic staff
Koert Kuhlmann MD PhD Academic staff
Hester Oldenburg MD PhD Academic staff
Marianne Piek-den Hartog MD Academic staff
Iris van der Ploeg MD PhD Academic staff
Theo Ruers MD PhD Academic staff
Emiel Rutgers MD PhD Academic staff
Johanna van Sandick MD PhD Academic staff
Xander Veenhof MD PhD Academic staff
Michel Wouters MD PhD Academic staff
Miranda Kusters MD PHD Temporary staff
Nienke Dols MD PhD Temporary staff
Marjolein Schrijver PhD Fellow
Karlijn Woensdregt MD Fellow
Danny Evers MD PhD Fellow
Tjeerd Aukema MD PhD Fellow
Karla Martin Telez PhD Fellow
Behdad Dasht Bozorg Post-doc
Matteo Fusaglia Post-doc
Harald Groen Post-doc
Wout Heerink Post-doc
Denise Hilling Post-doc
Jasper Nijkamp Post-doc
Anouk Post Post-doc
Lisanne Baltussen PhD student
Stephanie Blankenstein PhD student
Lisanne de Boer PhD student
Susan Brouwer de Koning PhD student
Luuk Buijs PhD student
Chris Dickhoff MD PhD student
Lotte Elshof PhD student
Roeland Eppenga PhD student
Viola Franke PhD student
Matthijs van Gool PhD student
Eric Heeg PhD student
Hester Haak PhD student
Britt Hupkens PhD student
Natasja Janssen PhD student
Pieter Joosten PhD student
Esther Kho PhD student
Willem Koemans MD PhD student
Esther Kok PhD student
Rosa van der Kraaij MD PhD student
Niels Langhout PhD student
Ariane van Loevezijn PhD student
Max Madu PhD student
Marieke van der Noordaa PhD student
Julianne de Ruiter PhD student
Marit van der Sande PhD student
Bram Schermers PhD student
Jasper Smit PhD student
Pauline Spronk PhD student
Erik Tanis PhD student
Suzana Teixeira PhD student
Niels Vos MD PhD student
Maxime van der Valk PhD student
Eva Huis in 't Veld PhD student
Lisa van der Woude PhD student
Dick Sterenborg Physicist
Ruben van Veen Technical physician

HEAD AND NECK ONCOLOGY AND SURGERY

Michiel van den Brekel MD PhD Head
Fons Balm MD PhD FRCS FACS Academic staff
Marc van Beurden MD PhD Academic staff
Frans Hilgers MD PhD Academic staff
Gwen Honnef DDS Academic staff
Baris Karakullukcu MD PhD Academic staff
Martin Klop MD PhD Academic staff
Menno Krap DDS Academic staff
Peter Lohuis MD PhD Academic staff
Pim Schreuder MD DDS Academic staff
Ludi Smeele MD DDS PhD Academic staff
Bing Tan MD PhD Academic staff
Corina van As-Brooks PhD Academic staff
Lilly-Ann van der Velden MD PhD Academic staff
Charlotte Zuur MD PhD Academic staff
Luc Karssemakers MD Fellow
Marjolijn Oomens MD Fellow
Thomas Pézier MD PhD Fellow
Joan Birkhoff PDT coordinator
Ann-Jean Beck MD PhD student
Danique Berger MD PhD student, resident
Amy Dohmen MD PhD student
Charlotte Duinkerken MD PhD student
Jos Elbers MD PhD student
Roel Henneman MD PhD student
Kilian Kappert MSc PhD student
Rebecca Karsten MD PhD student
Liset Lansaat MsC PhD student
Maartje Leemans MSc PhD student
Inge Oskam MD PhD student
Ellen Passchier MsC PhD student
Marije Petersen MD PhD student

Division of Surgical Oncology

IMAGE GUIDED SURGERY

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-operatively. 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 Universities 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. In 2018 we developed our own spectroscopy hardware to allow research activities independent form industry. We published for the first time that the technique can be used seamlessly in the current workflow for breast cancer diagnosis. Breast cancer malignancies could be detected with an accuracy of over 95%. We will further concentrate to incorporate the developed technology into surgical tools and started a STW project in 2018 to further develop this technology in combination with ultrasound as well. In a second project we aim to improve the balance between radical surgery and preventing morbidity in extensive surgery, by bringing innovative navigation technology to the OR. We introduced the first in world electromagnetic navigation system for abdominal and pelvic surgery. 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. In 2018 we published the first in man navigation study for abdominal tumor tracking. 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 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.

SURGICAL ONCOLOGY

Patient care and clinical research is largely organized in subunits who work in multidisciplinary teams: breast, melanoma, sarcoma, thoracic tumours, upper gastro-intestinal, and a combined unit of lower gastro-intestinal, liver, and colorectal peritoneal metastases. The goal of our research is twofold: to improve the survival for patients with more advanced disease, and to improve the quality of life of all patients by minimizing the side-effects and trauma of oncological treatment. A first common theme is to explore better combinations of systemic therapy, radiotherapy and surgery, and to incorporate the

recent advances in immunotherapy. These therapies are increasingly applied in a neo-adjuvant setting, and with a focus on a better assessment of the response it becomes possible to individually tailor the extent of the surgery to the type response. Some well-responding tumours can be removed with less extensive surgery, and in some patients, surgery can be omitted altogether. Some very advanced unresectable tumours may become resectable after neoadjuvant therapy. A second common theme is the technical development and clinical use of intra-operative imaging and tissue differentiation techniques that allow more precise identification of tumour tissue, allowing both a better complete removal of the tumour and sparing of non-involved tissues.
The department of surgery has initiated many phase I and II trials, and is participating in multicenter phase III trials, some of which have been initiated by NKI-AVL. In addition to the surgical staff, over 40 researchers were associated with the department. In 2018 this resulted in close to 200 publications in peer reviewed journals, 6 PhD theses, and regular media coverage.

Upper GI cancer

Translational research focusses on the identification of genetic patterns based on copy number variation in relation to treatment response of the tumour, immune activity, and patients' survival. The results of the multicenter clinical NKI-AVL study on (neo)-adjuvant multimodality treatment in gastric cancer was internationally well recognized with a major Lancet Oncology publication. Ongoing studies in this field are further investigating the role of multimodality neo-adjuvant treatment, e.g. neoadjuvant chemoradiotherapy and immunotherapy for gastric cancer and a surgery-as-needed protocol for oesophageal cancer. An ongoing clinical and research focus is on the role of hyperthermic intraperitoneal chemotherapy (HIPEC) in gastric cancer patients with peritoneal metastases.

Thoracic surgery

Clinical innovations in surgical treatment for NSCLC include minimally invasive surgical techniques such as 3D-video assisted thoracoscopic surgery (VATS), robotic surgery and segmental resections. Scientific research focusses on multimodality treatment, including the role of chemoradiation followed by surgery and the role of neoadjuvant and adjuvant immunotherapy and targeted therapies in combination with surgery. There are ongoing studies on response evaluation after chemoradiotherapy and immunotherapy. Another research focus is on the role of Tumor Infiltrating lymphocytes (TIL) therapy and organoids.

Colorectal – Liver – Peritoneal metastases

In both rectal cancer and liver tumours there are many ongoing intraoperative imaging studies. In rectal cancer NKI-AVL has established itself as a world leader in organ preservation, with a major publication in the Lancet. The program is continuously expanded with ongoing multicenter trials, and with now a fully operational contact radiotherapy device. The concept of neo-adjuvant immunotherapy is tested in an exploratory study in colonic cancer, and a new trial for rectal cancer is expected to start in 2019. For liver metastases the concept of adjuvant intra-arterial chemotherapy is tested in a phase II trial, expected to lead to a phase III trial in 2019. Advanced MR imaging studies are continued in the field of rectal cancer and peritoneal

Matthijs Valstar MD PhD student
Martijn van der Heijden MD PhD student
Manon van der Laaken MSc PhD student
Anne van der Leun MSc PhD student
Tessa van Doeveren PhD student
Simone van Dijk MD PhD student
Michel van Harten MD PhD student
Klaske van Sluis PhD student, SLP
Joris Vos MD PhD student
Luuk Voskuilen MSc PhD student
David Vossen MSc PhD student
Judith Zecha MD PhD student
Lisette van der Molen PhD Post-doc, SLP
Maarten van Alphen MSc Post-doc
Rob van Son PhD Post-doc
Robert van Veen PhD Post-doc
Renske Fles MSc Research coordinator
Wim Vallenduuk Research staff
Gili Yaron Research staff

UROLOGY

Simon Horenblas MD PhD Head
Henk van der Poel MD PhD Academic staff
Bas van Rhijn MD PhD Academic staff
Axel Bex MD PhD Academic staff
Esther Wit, MD Academic staff
Kees Hendricksen MD PhD Academic staff
Pim van Leeuwen MD PhD Academic staff
Roderick de Bruijn MD Fellow
Teele Kuusk MD Fellow
Oscar Brouwer MD PhD AIOS
Max Bruins MD AIOS
Rianne Lammers MD PhD AIOS
Tessa van Ginkel MD AIOS
Sarah Ottenhof MD Research physician
Charlotte Voskuilen MD Research physician
Hielke-Martijn de Vries MD Research physician

GYNAECOLOGY

Frédéric Amant MD PhD Head
Marc van Beurden MD PhD Academic staff
Monique Brood MD Academic staff
Christianne Lok MD PhD Academic staff
Willemien van Driel MD PhD Academic staff
Henry Zijlmans MD PhD Academic staff
Nienke van Trommel MD PhD Academic staff
Hans Trum MD PhD Academic staff
M.J. Rijken Fellow

PLASTIC AND RECONSTRUCTIVE SURGERY

Leonie Woerdeman MD PhD Head
Marieke van der Berg MD Academic staff
Marin Citges MD Academic staff
Joris Hage MD PhD Academic staff
Marije Hoornweg MD PhD Academic staff
Martine van Huizum MD Academic staff
Brigitte Drost MD Academic staff

DERMATOLOGY

Marianne Crijns MD PhD Head
Germaine Relyveld MD PhD Academic staff
Biljana Zupan-Kajcovski MD Academic staff
Soe Janssens MD PhD Academic staff

ANESTHESIOLOGY

Sandra Huissoon MD Head
Aletta Houwink MD Academic staff
Anita Rothengatter-Ophof MD Academic staff
Bart Schieveld MD Academic staff
Christoph Hahn MD PhD Academic staff
Esther Wolthuis MD PhD Academic staff
Herlina Hakim MD Academic staff
Ingeborg Vergouwe MD Academic staff
Julia ten Cate MD Academic staff
Karin Ariese MD Academic staff
Katina Efthymiou MD Academic staff
Lenie Hulshoff MD Academic staff
Liang Tjoa MD Academic staff
Marloes Bolman MD Academic staff
Michael Šrámek MD PhD Academic staff
Mischa Simon MD PhD Academic staff
Peter Schutte MD Academic staff
Sannine Buma MD Academic staff
Tom Leuverink MD Academic staff
Vivian Winia MD Academic staff

Selected publications

Bex A, Mulders P, Jewett M, Wagstaff J, van Thienen JV, Blank CU, van Velthoven R, Del Pilar Laguna M, Wood L, van Melick HHE, Aarts MJ, Lattouf JB, Powles T, de Jong IJ, Rottey S, Tombal B, Marreaud S, Collette S, Collette L, Haanen J. Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients with Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. JAMA Oncol. 2018

Blank CU, Rozeman EA, Fanchi LF, Sikorska K, van de Wiel B, Kvistborg P, Krijgsman O, van den Braber M, Philips D, Broeks A, van Thienen JV, Mallo HA, Adriaansz S, ter Meulen S, Pronk LM, Grijpink-Ongering LG, Bruining A, Gittelman RM, Warren S, van Tinteren H, Peeper DS, Haanen J, van Akkooi ACJ, Schumacher TN. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med. 2018;24(11):1655-1661

Buma S, van Klinken M. Hospitalizations in cancer patients in the last three months of life. 10th World Research Congress of the European Association for Palliative Care (EAPC 2018). Palliative Medicine, 32(1_suppl), 3–330

Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordsmark M, Meershoek-Klein Kranenbarg E, Boot H, Trip AK, Swellengrebel HAM, van Laarhoven HWM, Putter H, van Sandick JW, van Berge Henegouwen MI, Hartgrink HH, van Tinteren H, van de Velde CJH, Verheij M. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):616-628

De Boer LL, Bydlon TM, van Duijnhoven F, Vranken Peeters MTFD, Loo CE, Winter-Warnars GAO, Sanders J, Sterenborg HJCM, Hendriks BHW, Ruers TJM. Towards the use of diffuse reflectance spectroscopy for real-time in vivo detection of breast cancer during surgery. J Transl Med. 2018;16(1):367

De Haan J, Verheecke M, van Calsteren K, van Calster B, Shmakov RG, Mhallem Gziri M, Halaska MJ, Fruscio R, Lok CAR, Boere IA, Zola P, Ottevanger PB, de Groot CJM, Peccatori FA, Dahl Steffensen K, Cardonick EH, Polushkina E, Rob L, Ceppi L, Sukhikh GT, Han SN, Amant F; International Network on Cancer and Infertility Pregnancy (INCIP). Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. Lancet Oncol. 2018;19(3):337-346

Eskes M, Balm AJM, van Alphen MJA, Smeele LE, Stavness I, van der Heijden F. Simulation of facial expressions using person-specific sEMG signals controlling a biomechanical face model. Int J Comput Assist Radiol Surg. 2018;13:47-59

Janssen NNY, van la Parra RFD, Loo CE, Groen EJ, van den Berg MJ, Oldenburg HSA, Nijkamp J, Vrancken Peeters MTFD. Breast conserving surgery for extensive DCIS using multiple radioactive seeds. Eur J Surg Oncol. 2018;44(1):67-73

Hage JJ, Lange M, Zijlmans HJ, van Beurden M. Repeated use of gluteal fold flaps for post-oncologic vulvoperineal reconstruction. Ann Plast Surg. 2018;80(6):648-652

Lansaat L, van der Noort V, Bernard SE, Eerenstein SEJ, Plaat BEC, Langeveld TAPM, Lacko M, Hilgers FJM, de Bree R, Takes RP, van den Brekel MWM. Dutch Head and Neck Society. Predictive factors for pharyngocutaneous fistulization after total laryngectomy: a Dutch Head and Neck Society audit. Eur Arch Otorhinolaryngol. 2018;275:783-94

Mureau MAM, van der Hulst RRWJ, Woerdeman LAE, van Turnhout AAWM, Posch NAS, Menke-Pluijmers MBE, Luiten EJT, Westenberg AH, Gopie JP, Zonderland HM, Westerhof M, Krol-Warmerdam EMM. Dutch breast reconstruction guideline. J Plast Reconstr Aesthet Surg. 2018;71(3):290-304

Neto AS, Juffermans NP, Hemmes SNT, Carmen S. V. Barbas CSV, Wolthuis EK, Schultz MJ et al. Interaction between peri-operative blood transfusion, tidal volume, airway pressure and postoperative ARDS: an individual patient data meta-analysis. Ann Transl Med 2018;6(2):23

Nijkamp J, Kuhlmann KFD, Ivashchenko O, Pouw B, Hoetjes N, Lindenberg MA, Aalbers AGJ, Beets GL, van Coevorden F, KoK N, Ruers TJM. Prospective study on image-guided navigation surgery for pelvic malignancies. J Surg Oncol. 2018

Ottenhof SR, Djajadiningrat RS, Thygesen HH, Jakobs PJ, Jóźwiak K, Heeren AM, De Jong J, Sanders J, Horenblas S, Jordanova ES. The Prognostic Value of Immune Factors in the Tumor Microenvironment of Penile Squamous Cell Carcinoma. Front Immunol. 2018 Jun 11;9:1253

Srámek M. Compendium Anaesthesia in Surgical Oncology, version 1.8. ISBN: 978-90-824409-0-4

Van Baal JOAM, van Noorden CJF, Nieuwland R, Van de Vijver KK, Sturk A, van Driel WJ, Kenter GG, Lok CAR. Development of peritoneal carcinomatosis in epithelial ovarian cancer: a review J Histochem Cytochem. 2018;66(2):67-83

Van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, Habr-Gama A, Perez RO, Renehan AG, van de Velde CJH, Consortium I. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet. 2018;391(10139):2537-254

Van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, de Hingh IHJT, van der Velden J, Arts HJ, Massuger LFAG, Aalbers AGJ, Verwaal VJ, Kieffer JM, Van de Vijver KK, van Tinteren H, Aaronson NK, Sonke GS. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. N Engl J Med. 2018;378(3):230-240

metastases. New studies on the use of liquid biopsies in primary and metastatic colorectal cancer have been explored and will be initiated.

Breast

The breast cancer group focuses their main research activities on three programs. The first is personalized breast cancer treatment with the goal to de-escalate breast cancer treatment. In close collaboration with the radiology and pathology divisions, we work on trials investigating which patients are eligible for active surveillance instead of local treatment both in the primary surgery setting and in the neo-adjuvant systemic treatment setting. Together with the Division of Medical Oncology we work on multicenter trials to personalize (neoadjuvant) systemic treatment based on response prediction and monitoring.
The second research focus is on the development of 'shared decision making' programs for breast cancer patients. Our third research focus is on outcome of breast cancer care; we actively participate in the NBCA and in close collaboration with the division of quality of care we invest in research focused on both the long term psychological and physical outcome of breast cancer care.

Melanoma and skin tumours

Together with the Division of Medical Oncology the melanoma unit has invested in the development of new neo-adjuvant therapies in stage III disease, allowing a reduction of the extent of surgery. Other areas of interest have been the treatment and outcome of Merkel Cell Carcinoma (MCC), and loco-regional therapies such as oncolytic viruses. In all these areas our unit has established itself as leaders in the field with high-ranking publications in NEJM, Lancet and Nat Med.

Soft tissue tumours

The sarcoma unit focusses their research activities on three programs. The first is the development of (international) neo-adjvuant trials for angiosarcoma and retroperitoneal sarcoma. The second is the development of a multi-disciplinary translational research collaboration on the prediction of response to neo-adjuvant systemic therapy, radiotherapy and isolated limb perfusion, and on exploring new therapeutic options. The third is outcome research on different surgical strategies in DFSP, angiosarcoma and retroperitoneal sarcoma.

HEAD AND NECK SURGERY AND ONCOLOGY

The department is active in clinical and translational research. In 2018 there were several highlights.

In April Lisette van der Molen PhD, Speech and Linguist Pathologist and one of the founders of the first head and neck rehabilitation program in the world, received the national Michel Keijzerfonds Price (of the head and neck cancer patients' society) for the clinically most significant PhD thesis in the last 10 years.
In October Martijn van der Heijden has received the first price for the best scientific presentation at the 6th World Conference of the IFHNOS in Buenos Aires for his work on epithelial-mesenchymal transition.

Michiel van den Brekel became an honorary member of the German ENT society.

The head and Neck Co-operative Group organised the Annual Scientific Day of the Dutch Head and Neck Society on the theme: Breaking Barriers in Head and Neck Care. Major topics were: image guided treatments, patient centered care and immunotherapy.

Several research projects published important articles. Several studies on quality of care in laryngectomy surgery and rehabilitation were published. The phase one study on induction immunotherapy before surgery (IMCISION), led by C.L Zuur was completed. The results were very promising with several major responses. A phase 2 study has been started. Also, a study on combining immunotherapy with cetuximab and radiotherapy, led by JP de Boer was finished with promising results. The SPECT-guided elective unilateral (instead of bilateral) elective nodal irradiation lead by Al-Mamgani was completed in January 2018 and the preliminary results are very promising. A phase 2 will start shortly. The Virtual Therapy Group published on the simulation of facial expressions using person-specific sEMG signals controlling a biomechanical face model. This is an important step in the project on personalized prediction of functional defects after head and neck cancer treatment.

UROLOGY

In 2018 science on the department of urology covered both clinical and preclinical studies. The most important prominent will be addressed by tumor-working group.

Bladder cancer

Bladder sparing treatment options

Urothelial non-muscle invasive carcinoma is being treated with intravesical hyperthermia using mitomycine-C (HIVEC). HIVEC treatment is an option for patients unresponsive to BCG instillations for whom cystectomy is often considered. In a collaboration with the VU-medical center we showed that for muscle invasive smaller bladder cancers brachytherapy using both open and robot brachy-loops implantation was found a viable option for bladder preservation. A retrospective analysis of patients from the world-wide largest cohorts on prostate-sparing cystectomy the functional outcome data were superior to cysto-prostatectomy series without compromising oncological outcome.

Chemotherapy

A retrospective analysis revealed improved outcome of neoadjuvant chemotherapy and cystectomy in particular in cT4 bladder cancer. In a prospective phase II study with cisplatin-based chemotherapy, the EGFR inhibitor panitumumab and radiotherapy a 94% complete response rate was obtained with 4 patients experiencing local recurrence during 34 months of follow up.

Renal cancer

The group from Axel Bex has finalized a multicenter randomized trial on the use of cytoreductive nephrectomy (CN) showing the

Verhagen CVM, Vossen DM, Borgmann K, Hageman F, Grénman R, Verwijs-Janssen M, Mout L, Kluin RJC, Nieuwland M, Severson TM, Velds A, Kerkhoven R, O'Connor MJ, van der Heijden M, van Velthuysen ML, Verheij M, Wreesmann VB, Wessels LFA, van den Brekel MWM, Vens C. Fanconi anemia and homologous recombination gene variants are associated with functional DNA repair defects in vitro and poor outcome in patients with advanced head and neck squamous cell carcinoma. Oncotarget. 2018;9:18198-213

Young-Afat DA, Hoornweg MJ, van Huizum MA. Autologous breast reconstruction in sickle cell trait: A fine line between success & failure. Breast J. 2018;24(2):193-195

delayed CN did not improve progression free survival but may improve overall survival. Survival in patients with microscopic sentinel node metastases during nephrectomy is long.

Penile cancer

PDL1 expression in penile cancer was found associated with poor outcome. These observations have led to the initiation of the PERICLES trial where atezolizumab is combined with radiotherapy for patients with advanced penile cancer.

Prostate cancer

Active involvement of patients in treatment decision making was found to improve outcome in a prospective national trial. MRI anatomical imaging allows personalized prediction of functional outcome after prostatectomy. 68Ga-PSMA PET imaging was found predictive of outcome after prostatectomy. Ultrasensitive PSA analyses after prostatectomy allow multiparameter prediction of biochemical recurrence intervals.

GYNAECOLOGY

Center for Gynecologic Oncology Amsterdam (CGOA)

The integration of the clinical groups at the NKI-AVL and Amsterdam UMC into Center for Gynecologic Oncology Amsterdam was further structured. Interdisciplinary teams with members from both locations are now established per organ. The teams aim to facilitate guideline writing, conduct clinical and translational research, contribute to teaching and collaborate on (inter)national level.

In addition, in 2019 we will focus on overarching projects we considered as pivotal in an academic clinical setting. We developed a strategic plan for 2019. The ultimate goal remains to install CGOA on one location in Amsterdam.

Ovarian carcinoma

Ovarian carcinoma is a disease with a high mortality due to the fact that symptoms are present when the disease has spread to the abdomen. In 2018, a large clinical trial evaluating the effect of adding HIPEC to the interval cytoreductive surgery was published. It showed that HIPEC improves overall survival with almost one year. Advanced disease with extensive peritoneal carcinomatosis is difficult to treat and more knowledge about the peritoneum is indispensable. Another method to improve patient outcome, is early detection of ovarian cancer. Research in serum and molecular biomarkers can contribute to this. Ovarian carcinoma is a heterogenous disease with different histological subtypes. Research to clinical characteristics and molecular background of ovarian cancer and the subtypes is another focus of research.

Endometrial cancer

Endometrial cancer is the most common gynecological malignancy in high-income countries. Although the overall prognosis is relatively good, high-grade endometrial cancers tend to recur. Our focus is to develop a risk stratification based on molecular and other tumor characteristics and imaging that helps us to identify patients with extra uterine disease. Minimal invasive surgery including the studies with sentinel node biopsy are ongoing. We contribute in the development of European (ESMO) and national guidelines (oncoline)

Cervical Cancer

Cervical cancer affects 700 women in the Netherlands on an annual basis. On third of these women are younger than 40 years and a significant part of these women still have a child wish. Current treatment modalities to preserve fertility in early stage cervical cancer consist of an operation with poor pregnancy outcomes. In 2018, we started an observational trial for treatment with chemotherapy to reduce the size of the tumor enabling less radical surgery. We expect the number of women who will be able to carry a child after this increases by 5-fold. Besides, we aim to improve the current procedure to screening for cervical cancer by introduction of molecular markers as a triage test in hrHPV positive women in urine and cervical scrapes because many women do not attend the screening program, possibly because of fear for a gynecological examination.

Vulva

Vulvar cancer is a relatively uncommon disease. Surgery is treatment of choice, causing frequently postoperative morbidity in patients with high stage disease. An alternative treatment, starting with neo adjuvant chemotherapy, could reduce tumour size, thereby diminishing the chance for morbidity. In case of lymph node metastases, prognosis is worse. Tumor-derived factors are an important factor in these metastases and we investigate how this mechanism works and determine if immunotherapeutic strategies could be useful. Also, pre-malignant vulvar disease is investigated to determine optimal treatment.

Cancer and pregnancy

On behalf of the International Network on Cancer Infertility and Pregnancy, we reported on the evolution of clinical management over 20 years. We observed a trend towards more chemotherapy administration during pregnancy resulting in less terminations and less prematurity. Chemotherapy administration itself was associated with small for gestational age babies and admission at the neonatal intensive care unit, emphasizing the need for management in high risk obstetric units.

Gestational Trophoblastic Disease

Gestational trophoblastic disease (GTD) is a heterogeneous group of disorders characterized by abnormal proliferation of trophoblastic tissue. Since GTD is a rare disease, little evidence is available from randomized controlled trials on optimal treatment and follow-up. In Amsterdam, the ATT (Amsterdam Trophoblastic Team) was founded in 2018, to advice on treatment and follow up of GTD. We cooperate with the EOTTD (European Organisation for Treatment of Trophoblastic diseases) and ISSTD (international Society for the Studies on Trophoblastic Disease). In 2018, we started an RCT on providing digital information for these patients. We are also finetuning therapy for very rare subtypes of GTD.

PLASTIC AND RECONSTRUCTIVE SURGERY

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 NKI-AVL Division of Psychosocial Research and Epidemiology, as well as 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. Women who find out after such therapy that they are carrier of a BRCA germ line mutation may still opt for prophylactic bilateral ablative surgery. Because the conservingly treated breast has been previously irradiated, the prophylactic completing ablation is usually performed in a non-skin sparing fashion and possible breast reconstruction may, then, done only secondarily.

Immediate breast reconstruction has been shown to psychologically support women who undergo ablative surgery. We therefore performed 28 prophylactic combined completing skin-sparing mastectomies and implant-based immediate reconstruction. To prevent radiation-induced complications, the implant was covered with the latissimus dorsi muscle. Because this leads to satisfactory results with no increase of oncological risk, we now advocate to contemplate apply this combined approach rather than opting for delayed, secondary breast reconstruction.

Because of the associated high recurrence rate, future reconstructive options should be reckoned with during surgical treatment of primary or recurrent (pre)malignant vulvoperineal lesions. One of the claimed, but never proven advantages of the gluteal fold flap is the possibility of repeated use of the flap in case of recurrence.

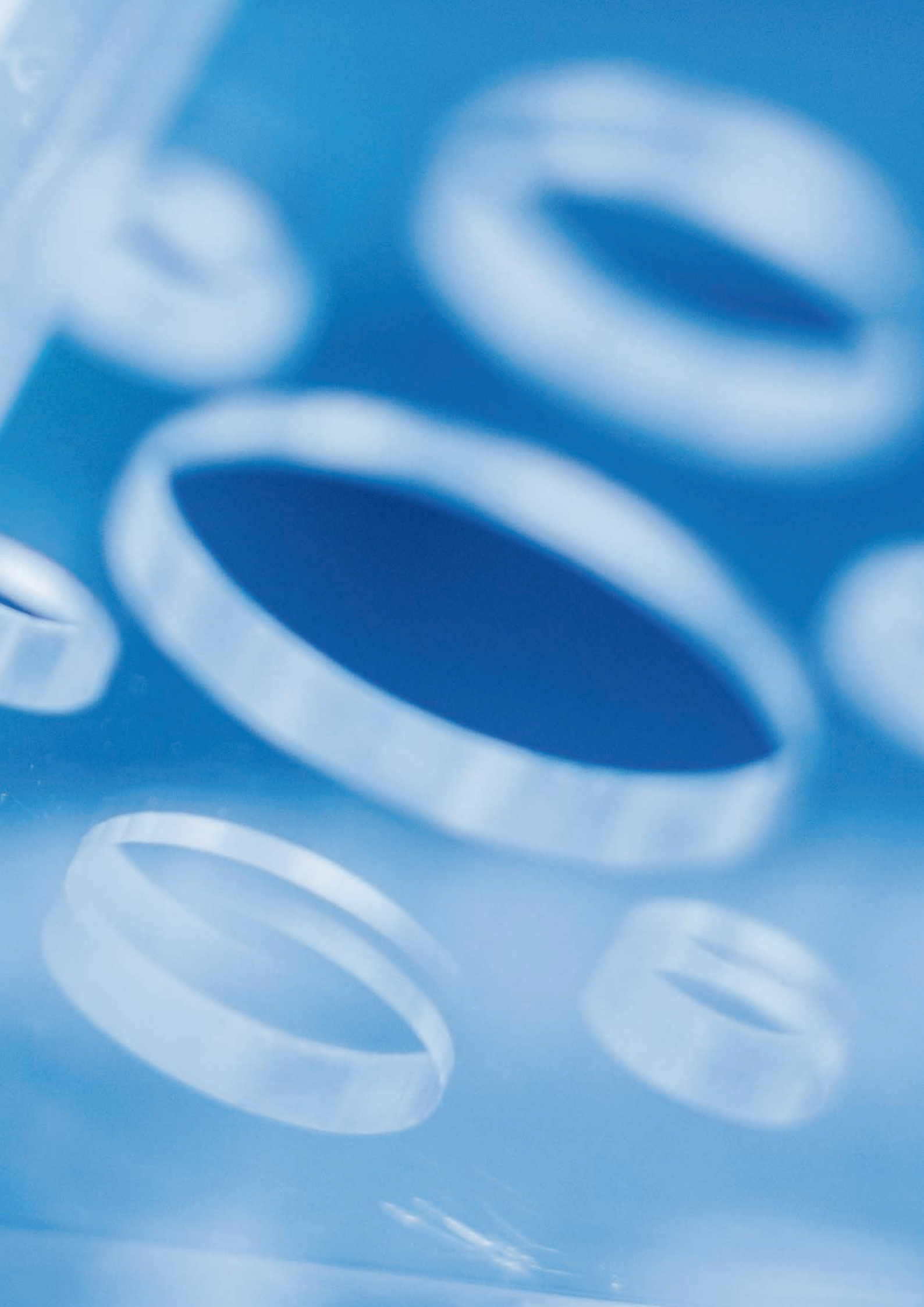
A mean of 27 months after initial use, 10 subcutaneously pedicled or perforator-based V-Y advancement or propeller-rotation flaps were elevated from previously used gluteal fold flaps in 9 women presenting with recurrent vulvoperineal (pre) malignancy. Five of these women had undergone radiotherapy prior to flap reuse. Although short-term complications were observed in 3 women, all flaps survived and healed completely. With this series, we showed the feasibility of successful reuse of subcutaneous pedicled or perforator-based gluteal fold flaps for repeated vulvoperineal reconstruction, both in non-irradiated and irradiated women.

ANESTHESIOLOGY, INTENSIVE CARE MEDICINE AND PAIN MEDICINE

The principal aim of our department is to deliver the highest standard of anesthesiological, intensive care and pain therapy and to continually work on the development of best practices in everyday patient care.

In 2018 there has been ongoing work on a comprehensive review on the effects of anesthetics on cancer recurrence and patient outcome.
In the supportive care department, a prospective study investigating an intervention to decrease hospital admissions at the end of life is currently running.
Furthermore, clinical studies in the surgical field involve optimal treatment after prostatectomy and breast cancer surgery.


Bo® AX



Technology Transfer Office

Koen Verhoef

Head Technology Transfer Office

Koen Verhoef Manager
Marije Marsman Senior business developer
Tim Moser Senior business developer
Anje Raven Business developer
Hylke Galama Senior legal counsel
Marin Hubertus Legal counsel
Stephanie de Meza Legal counsel

The Technology Transfer Office (TTO) of the NKI 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. To this end, it has established a contracts database that is used to maintain an overview of existing rights and obligations to third parties and monitor the performance of contractual arrangements.
In addition, TTO is charged with advancing the application of NKI research results in healthcare. One of the major aims of the Netherlands Cancer Institute is to see its scientific breakthroughs being turned into novel products and services that benefit cancer patients and their families. On occasion, NKI applies for patent protection for promising new technology developed within the institution as a means to attract investment from companies for new product development. TTO manages the patent portfolio and other intellectual property assets of the institute and actively engages with life science/healthcare companies and investors who have the commitment and resources to bring our innovations to the market.
In addition, TTO also handles all consultancy agreements for the institute and has a sizeable portfolio of research materials which it licenses to industry.

SELECTED HIGHLIGHTS FOR 2018

Collaboration agreement with the Princess Máxima Centre

Starting November 1st 2018, NKI has entered into a collaboration agreement with the Princess Máxima Centre (PMC) on Technology Transfer. In particular, the NKI TTO will assist the PMC with drafting, reviewing and negotiating research-related contracts, as well as provide advice on valorization issues, in particular around the commercial potential of inventions coming out of the PMC's research groups and the optimal way of progressing these to the clinic.
PMC has employed a legal counsel who is supervised by senior staff in and is part of the NKI tech transfer team. Both parties anticipate a long-standing and durable relationship. Once the tech transfer function within the PMC has sufficiently developed, it may be possible for PMC-based tech transfer staff to support activities within NKI as well.

Oncode Institute

Oncode Institute is an independent research institute with a mission to create impact in the lives of cancer patients. It has three cornerstones: excellent research, intensive cooperation and bringing new treatments faster into the clinic. Over the course of 2018, Oncode Institute has appointed a team of valorization experts to help build on and further develop research results from the various Oncode teams and, in doing so, aim to eventually increase the quality of life of patients.
The NKI TTO has supported Oncode Institute in 2018 as it built up its Valorization Team by continuing to provide support to the NKI research groups that are affiliated with Oncode. Since then, two NKI TTO team members are seconded for part of their time to Oncode, working one day per week out of Oncode's offices in Utrecht. In addition, the legal team within the NKI TTO provides advice to Oncode on legal matters. Formalization of this arrangement is expected early 2019.

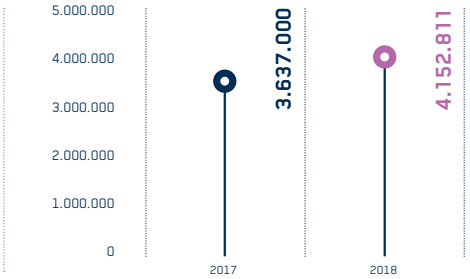
SPIN-OFF COMPANY FOUNDED IN 2018

SlideScore

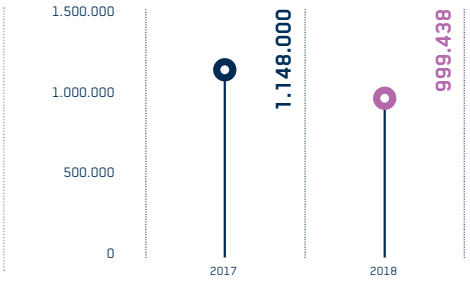
SlideScore (www.slidescore.com) was founded by Jan Hudecek, a scientific programmer with the Research IT group at NKI, who – learning about the frustration of pathologists around their experiences with standard software solutions that are bundled with digital slide scanners – developed an intuitive, easy to use and online platform for scoring pathology slides. By working with pathologists at the Netherlands Cancer Institute during development, he obtained crucial feedback that allowed him to finetune the software to match the end-users needs.
The company was founded in Q2 of 2018 and a license agreement was agreed with NKI later in the year. Thus far, more than 400,000 answers have been submitted to the platform, which is growing very rapidly through positive referrals among pathologists.

TTO 2018 IN NUMBERS*

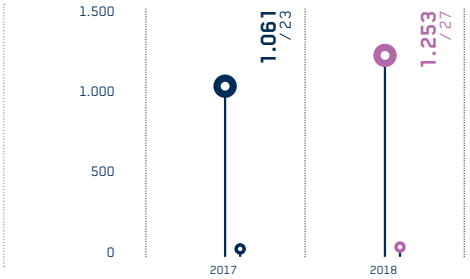
License income:
€ 4.152.811



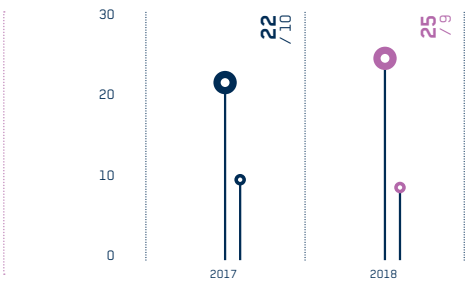
Freely disposable income from commercial research and consulting:
€ 999.438



In total, 1253 contracts were negotiated and executed in 2018, of which 27 were license agreements.



TTO received 25 invention disclosures and filed 9 priority patent applications in 2018.



* some numbers are still provisional at this stage as financial records for 2018 are still to be finalized.

Research facilities

Modern day biomedical research depends on expensive equipment and extensive experience with very specialized techniques. Individual researchers need to use a wide range of techniques for their work. It is impossible for anyone to master them all or to be given the budget to buy all the equipment they are likely to need. The NKI has resolved this problem and used its funding in the most efficient way by creating dedicated, centralized technology (core) facilities that serve the whole Institute. These research facilities play an essential role in almost all research performed at the NKI.

The facilities of the NKI are offered free of charge to NKI-researchers. In some cases, the costs of consumables are charged to the project budget of the group. There is in principle no restriction on the amount of time one can utilize a certain facility. When extensive support from a facility is required, this is discussed beforehand and group leaders transfer some of their budget to the facility in order to finance the support (e.g. for recruitment of extra staff). In 2018 we published an internal guideline for recognition of the contribution of personnel at research facilities in publications. Most facilities of the NKI are supervised by a user committee. The Research Council installs these user committees, which consist of faculty members and postdocs, PhD students and/or technicians. The user committees meet at least once a year and they see to the quality of the service provided by the facility and make sure that the facility caters to the need of the researchers. They also review requests for new equipment for the facility. The head of the facility and the director of operations are invited to the user committee meetings.

The research facilities of the NKI are presented on the next pages. In addition to those facilities we also provide the researchers with the following facilities:

- sequencing facility performing DNA sequence and fragment analysis for users in the research divisions and the DNA-diagnostics laboratory of the Department of Human Pathology. The Sequencing Facility has an important role in the diagnostic analysis of patient samples. Its procedures and protocols are therefore accredited by the CCKL. Researchers from all divisions make use of the service provided by the facility. The facility is equipped with a 3730 DNA analyzer capillary sequence machine, which can handle up to 96 samples simultaneously, and a 3500xL Genetic Analyzer capillary sequence machine. The sequence facility handled approximately 46,000 samples;
- electron microscopy support for staff members of the NKI and for others through collaborations with NKI staff. The facility performs the whole procedure from fixation until the generation of the final pictures, from tissues to proteins. The facility is supervised by a facility committee and supported by colleagues from the AMC EM-group for EM-related backup. The NKI has no EM of its own anymore; we now buy time on the EMs at the AMC. The most frequently used techniques are Immuno-EM on tokuyasu cryosections for localization of proteins within cells, negative staining and cryo-EM for visualization of large proteins or protein complexes. The AMC EM is used for quality checking of cryo-EM grids before going to the high-end EMs at NECEN. We offer IT support for the development of software and databases;
- library with dedicated support for data management and literature searches and providing access to a large collection of electronic journals and books;
- cryogenic storage of cells and tissues in a centralized liquid nitrogen storage facility;
- culture labs at different containment levels;
- dedicated labs for working with radionuclides or carcinogens;
- technical workshop that can make modifications to existing equipment or develop new tools;
- glassware cleaning.

Proteomics Facility

Maarten Altelaar

Head Proteomics Facility

Maarten Altelaar PhD Head
Onno Bleijerveld PhD Senior post-doc
Liesbeth Hoekman BSc Technical staff

Selected publications

Simonetta M, de Krijger I, Serrat J, Moatti N., Fortunato D, Hoekman L, Bleijerveld OB, Altelaar AFM, Jacobs JJL. H4K20me2 distinguishes pre-replicative from post-replicative chromatin to appropriately direct DNA repair pathway choice by 53BP1-RIF1-MAD2L2. Cell Cycle 2018;17(1):124-36

Spel L, Nieuwenhuis J, Haarsma R, Stickel E, Bleijerveld OB, Altelaar M, Boelens JJ, Brummelkamp TR, Nierkens S, Boes M. Nedd4-Binding Protein 1 and TNFAIP3-Interacting Protein 1 control MHC-1 display in neuroblastoma. Cancer Res 2018;78(23):6621-31

Stelloo S, Nevedomskaya E, Kim y, Hoekman L, Bleijerveld OB, Mirza T, Wessels LFA, van Weerden WM, Altelaar AFM, Bergman AM, Zwart W. Endogenous androgen receptor proteomic profiling reveals genomic subcomplex involved in prostate tumorigenesis. Oncogene 2018;37(3):313-22

The Proteomics Facility started its activities in July 2013 aided by the NWO project Proteins@Work, part of the National Roadmap Large-scale Research Facilities of the Netherlands, and provides proteomics services to all researchers within the NKI. Occasionally, projects are also run for researchers outside the institute that do not have the experience and/or equipment available. Since July 2018 the Proteomics Facility became a permanent facility within the Institute. As of yet, over 330 proteomics experiments have been performed for (ongoing) projects of more than 20 research groups within the NKI.

Equipment

Our Facility operates a Thermo Orbitrap Fusion hybrid mass spectrometer equipped with a Proxeon nLC1000 nano-LC system for LC-MS/MS-based peptide/protein identification and quantification. Aided by funding from the NWO X-Omics Initiative, we just purchased a second, state-of-the-art Thermo Q Exactive HF-X hybrid Quadrupole-Orbitrap mass spectrometer with a Proxeon nLC1200 nano-LC system which will be installed in early 2019. Depending on sample complexity and when required, samples are pre-fractionated at the protein level by SDS-PAGE, or at the peptide level using a dedicated offline High-pH HPLC fractionation system (Agilent 1200) in order to increase depth of proteome coverage.

Proteomics

Projects to which the NKI Proteomics Facility has provided their services include mostly immunoprecipitation experiments aimed at unraveling protein-protein interactions, global proteome profiling of cell lines and post-translational modification-focused profiling such as protein phosphorylation and ubiquitination. In 2018 we performed over 60 proteomics experiments for 19 research groups. We saw a slight increase in requests for targeted protein quantitation using parallel reaction monitoring (PRM).

Our efforts have contributed to several publications. In a publication by the Zwart lab, combination of proteomic and genomic data revealed subclasses of Androgen Receptor (AR) transcriptional complexes, differentiating normal AR behavior from the oncogenic state. With the Jacqueline Jacobs lab, identification of MAD2L2 protein interactors aided in the discovery that 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 DNA double-strand breaks, to engage the correct DNA repair pathway. Furthermore, in a collaboration between the Brummelkamp lab and the Translational Immunology Laboratory of UMC Utrecht, proteomics provided a valuable insight into the mechanism by which N4BP1 controls MHC-1 display in neuroblastoma.

Roderick Beijersbergen

Head Robotics and Screening Center

Roderick Beijersbergen PhD Head
Cor Lieftink MSc Bioinformatician
Ben Morris Technical staff

Selected publications

Matlung HL, Babes L, Zhao XW, van Houdt M, Treffers LW, van Rees DJ, Franke K, Schornagel K, Verkuijlen P, Janssen H, Halonen P, Lieftink C, Beijersbergen RL, Leusen JHW, Boelens JJ, Kuhnle I, van der Werff Ten Bosch J, Seeger K, Rutella S, Pagliara D, Matozaki T, Suzuki E, Menke-van der Houven van Oordt CW, van Bruggen R, Roos D, van Lier RAW, Kuijpers TW, Kubes P, van den Berg TK. Neutrophils Kill Antibody-Opsonized Cancer Cells by Trogoptosis. Cell Rep. 2018;23(13):3946-3959

Serresi M, Siteur B, Hulsman D, Company C, Schmitt MJ, Lieftink C, Morris B, Cesaroni M, Proost N, Beijersbergen RL, van Lohuizen M, Gargiulo G. Ezh2 inhibition in Kras-driven lung cancer amplifies inflammation and associated vulnerabilities. J Exp Med. 2018;215(12):3115-3135

Wang C, Jin H, Gao D, Wang L, Evers B, Xue Z, Jin G, Lieftink C, Beijersbergen RL, Qin W, Bernards R. A CRISPR screen identifies CDK7 as a therapeutic target in hepatocellular carcinoma. Cell Res. 2018;28(6):690-692

Robotics and Screening Center

The NKI Robotics and Screening Center (NRSC) was established in early 2005 with the goal of developing technology platforms for the discovery of gene function, the unraveling of molecular pathways, the identification of novel drug targets and to support small molecule screening. In addition, the NRSC is a resource center that provides robotic technologies for medium to high throughput applications, provides support and expertise for automated cell and biochemical assays and is used for the development, production and maintenance of large functional genomic screening reagent collections.

A strong focus of the NRSC is on the development and application of large-scale functional genomic screening technologies. Since the generation of the first NKI human shRNA library in 2002, we have extended our RNAi platform with several large (genome-wide) collections for human and mouse. These collections are available as individual reagents and can be used to generate smaller sub-collections for specific screening projects. We have generated sub-collections for the human kinome, the PI3K/MAPK signaling network, a DNA damage collection, a hypoxia response collection and an epigenetic modifier collection. Besides our RNAi platforms we have also invested in the CRISPR/CAS9 technology. We have acquired different genome-wide sgRNA libraries for human and mouse and we have set-up a pipeline for the production of custom libraries for subsets of genes or specific applications using custom vector designs. In addition, we have incorporated technologies that allow for the (inducible) inhibition (CRISPRi) or activation (CRISPRa) of gene expression in mammalian cells.

Most screens are performed as pooled screens, a technology pioneered by us in 2002. We have continued to improve this technology and have developed an analysis pipeline for screening results. We assist individual researchers with setting up pooled screens and provide reagents, protocols and analysis tools to research groups within and outside of the NKI.

In addition to the generation and application of genomic tools we have the ability to perform automated small molecule screens. The NRSC provides a state-of-the-art infrastructure for medium to high-throughput screening projects including automated liquid handling, plate handling and sealing, well dispensers and plate readers. We provide access to several collections of small molecules including the SPECS collection (23,225 diverse compounds), the LOPAC collection (1,250 pharmacological active compounds), the NCI diversity and oncology sets, the John Hopkins FDA and foreign approved drugs and bioactive compounds (1,450 compounds) and several enzyme specific collections from SelleckChem including kinase inhibitors, the apoptosis library, the Epigenetic collection and the protease inhibitor library. These collections are used in both cell-based and biochemical assays to identify compounds that can be used as biological tools or possibly as starting points for chemical optimization and lead development.

BioImaging Facility

Lenny Brocks

Facility Manager

Marjolijn Mertz

Facility Manager

The BioImaging Facility provides scientific and technical support in basic and advanced light microscopy and image processing and analysis. We manage a diverse collection of light microscopes systems for brightfield and fluorescence applications, including widefield, confocal, and superresolution systems. We provide dedicated application trainings to microscope users of the institute and offer courses in light microscopy and image analysis. The BioImaging Facility participates in LCAM (van Leeuwenhoek Centre for Advanced Microscopy, Amsterdam), a formal collaboration between three innovative microscopy centres, located at the University of Amsterdam (UvA), the Academic Medical Centre (AMC) and the Netherlands Cancer Institute (NKI). The BioImaging Facility, together with the Jalink lab and Van Rheenen lab, constitutes the NKI part of LCAM.

The BioImaging staff provide the following services:

- Setup daily maintenance and regular quality checks of the microscopes
- Expert advice on experimental design and sample preparation
- Microscopy and image analysis training (introductions, workshops, courses)
- Custom solutions for image processing and quantification
- Data storage and backup on a central server
- Minor repairs of microscopes in other departments
- Technical advice for grant applications and microscopy purchases
- Access to and assistance with functional and/or advanced imaging techniques (FRET, FLIM, FCS, SuperResolution, Multiphoton, Intravital Imaging)

Training/Courses

- Introduction to microscopy
- In the footsteps of Antoni van Leeuwenhoek (5-day graduate school basic microscopy course)
- ImageJ/Fiji (image processing & analyses course)
- We regularly (-annually) participate in FEBS- and EMBO-sponsored advanced imaging courses (organized via LCAM)

Equipment list

- Spinning Disk Confocal (Andor Dragonfly)
- Four Confocal Microscopes (Leica SP5)
- TIRF microscope (Leica)
- Three (live imaging) widefield microscopes (Zeiss Z Observer Z1)
- Color widefield microscope (Zeiss AxioVert 200M)
- Macroscope (Zeiss AxioZoom V16 Stereo microscope)
- Three high-end workstations with image processing & analysis software (Huygens, Imaris, Matlab, Leica en Zeiss Zen)

Lenny Brocks PhD Facility Manager
Marjolijn Mertz MSc Facility Manager
Bram van den Broek PhD Post-doc
Amalie Dick PhD Microscopy manager

Publications

Halim VA, García-Santisteban I, Warmerdam DO, van den Broek B, Heck AJR, Mohammed S, Medema RH. Doxorubicin-induced DNA damage causes extensive ubiquitination of ribosomal proteins associated with a decrease in protein translation. Mol Cell Proteomics. 2018

Gogola E, Duarte AA, de Ruiter JR, Wiegant WW, Schmid JA, de Bruijn R, James DI, Guerrero Llobet S, Vis DJ, Annunziato S, van den Broek B, Barazas M, Kersbergen A, van de Ven M, Tarsounas M, Ogilvie DJ, van Vugt M, Wessels LFA, Bartkova J, Gromova I, Andújar-Sánchez M, Bartek J, Lopes M, van Attikum H, Borst P, Jonkers J, Rottenberg S. Selective Loss of PARG Restores PARylation and Counteracts PARP Inhibitor-Mediated Synthetic Lethality. Cancer Cell. 2018;33(6):1078-1093.e12

Annegien Broeks

Head Core Facility Molecular Pathology & Biobanking

Annegien Broeks PhD Head
Ingrid Hofland Technical staff
Dennis Peters Technical staff
Linde Braaf Technical staff
Sten Cornelissen Technical staff
Sanne Broersen Technical staff
Maartje Alkemade Technical staff
Charlotte van Rooijen Technical staff
Rianne van der Wiel Technical staff
Rianne van de Linden Technical staff
Donne Majoor Technical staff
Wouter Kievit IT staff
Yush Lam IT staff

Selected publications

Blank CU, [...], Schumacher TN. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med. 2018;24:1655-1661

Sobral-Leite M, [...], Schmidt MK. Assessment of PD-L1 expression across breast cancer molecular subtypes, in relation to mutation rate, BRCA1-like status, tumor-infiltrating immune cells and survival. Oncoimmunology. 2018;11

Visser LL, [...], Wesseling J. Clinicopathological Risk Factors for an Invasive Breast Cancer Recurrence after Ductal Carcinoma In Situ-A Nested Case-Control Study. Clin Cancer Res. 2018;24:3593-3601

Core Facility Molecular Pathology & Biobanking

Activities

The Core facility Molecular Pathology & Biobanking (CFMPB) was established in 2010 to ensure that human material is used properly and efficiently, especially in the case of scarce, valuable samples. The CFMPB registers, evaluates, coordinates, assists and facilitates research involving human related biospecimens (serum, blood, circulating DNA, FFPE and fresh frozen biopsies, DNA, RNA etc.). The facility provides professional expertise and support regarding medical-ethical issues in translational research with human biospecimen. All CFMPB activities are supported by an in house developed web application Application and Request Tool (ART). ART-CFMPB and ART-Biobank are the online tools for e.g. study registration, Institutional Review Board (IRB) review, lab logistics, track and trace of biospecimens and cost recovery. All the user activities are stored in the ART database and by doing so, information about the applications, biospecimen identifiers, succeeding actions and derivatives accumulates and this enriches the data already available.

The CFMPB has fully equipped and dedicated Molecular and Histology/Immunohistochemistry (IHC) labs. All routine IHC and newly developed IHC protocols (single & multiplex, brightfield and fluorescent), RNA scope and FISH are performed using the BenchMark & Discovery (Ventana) automated stainers (269 protocols up and running; 116 in research setting only), all in close collaboration with the Pathology department and pathologists. The Aperio & Vectra-3 scanners in combination with slidescore and HALO software tools enable digital pathology and multi-spectral image analysis. Next year we will explore and implement new multi-spectral image analysis techniques as the Nanostring Digital Spatial Profiling (DSP) and Codex (Akoya). To guarantee standard high quality, all DNA and RNA isolations from human (Biobank) samples (FFPE, FF, serum, blood etc.) are performed by, or under supervision of, the CFMPB technicians. All DNA and RNA isolations from human biospecimens are performed using the Qiacube or Qiasymphony, according to standard protocols and QC. Molecular analysis techniques like (RT)-PCR, MLPA and nCounter Nanostring are offered. In 2018 we have registered 97 new studies (431 studies up and running) and handled 844 lab requests (including e.g. 21.399 FFPE& 872 FF samples, 6949 DNA/RNA isolations and 10.521 IHC & 5604 HE stains).

Protein Facility

Patrick Celie

Head Protein Facility

Patrick Celie PhD Head
Alexander Fish PhD Post-doc
Magda Stadnik-Spiewak MSc Technical staff
John de Widt Technical staff

Selected publications

Stolt-Bergner P, Benda C, Bergbrede T, Besir H, Celie PHN, Chang C, Drechsel D, Fischer A, Geerlof A, Giabbai B, van den Heuvel J, Huber G, Knecht W, Lehner A, Lemaitre R, Nordén K, Pardee G, Racke I, Remans K, Sander A, Scholz J, Stadnik M, Storici P, Weinbruch D, Zaror I, Lua LHL, Suppmann S. Baculovirus-driven protein expression in insect cells: A benchmarking study. J Struct Biol. 2018;203:71-80

Uckelmann M, Densham RM, Baas R, Winterwerp HHK, Fish A, Sixma TK, Morris JR. USP48 restrains resection by site-specific cleavage of the BRCA1 ubiquitin mark from H2A. Nat Commun. 2018;9:229

Van Beusekom B, Heidebrecht T, Adamopoulos A, Fish A, Pardon E, Steyaert J, Joosten RP, Perrakis A. Characterization and structure determination of a llama-derived nanobody targeting the J-base binding protein 1. Acta Crystallogr F Struct Biol Commun. 2018;74:690-695

The genes within the DNA encode all the proteins that a cell requires to stay vital and function properly within a living organism. Proteins are essential molecules involved in almost all biological processes. DNA damage – as occurs in cancer – may cause mutations within genes and hence can lead to generation of dysfunctional proteins. These mutated proteins could become inactive or even hyper-active and cause deregulation of cellular function and -growth. To understand the (dys)function of proteins, e.g. in the context of cancer development, recombinant proteins can be designed, produced, purified and subsequently be characterized by a variety of functional and structural methods *in vitro*. The Protein Facility provides dedicated equipment, knowledge and experienced personnel to support all these experiments. Access is offered to both internal and external academic researchers.

Internal projects

Within the past year, the facility has provided support to multiple projects requested by 12 research groups within the NKI. A significant number of the projects involved the expression and purification of recombinant proteins. These were subsequently used by researchers as reagent for their own experiments, e.g. as reagent within biochemical assays, as tool in microscopy studies, for raising antibodies, etc. In a number of projects, biophysical characterization follow-up was requested to analyze protein oligomerization, stability and interaction with other molecules. A subset of proteins were specifically produced for structural studies (NMR and X-ray crystal diffraction). In addition to customized support to each individual project, the facility also maintains a repository of reagents that are of common use to many researchers. These include generally used proteins (enzymes, proteases, antibodies), cloning utilities (expression vectors, cloning reagents) and stock cell cultures.

External access

The facility is open to external academic researchers. Access is provided through direct contact, but also via European projects and infrastructures: the facility is part of Instruct-ERIC (https://instruct-eric.eu/), a European infrastructure in structural biology which provides access to high-end technology, and also participates in iNEXT (Infrastructure for NMR, EM and X-rays for Translational Research; www.inext-eu.org/), funded by the Horizon2020 program. About 20 % of the total capacity of the facility was dedicated to projects that were delivered through these infrastructures. A substantial part of this time was allocated to the access of our biophysical platform and to the so-called Structural Audit (which is part of iNEXT), a protein-quality control service to select proteins that are amenable for follow-up structural studies.

Networks

Implementation of new methods and technologies is essential to keep up-to-date with the latest developments in protein research. A useful source has been provided by two EU networks in which the facility participates as an active member: P4EU, which consist of various protein expression facilities and the biophysical network ARBRE MOBIEU. Both networks organize courses, meetings, benchmarking experiments, sharing of reagents/protocols and discussion of new methods. An example of the collaboration within the P4EU network is the publication of a benchmarking study on protein expression methods in Sf9 insect cells.

Biostatistics Center

Michael Hauptmann

Head Biostatistics Center

Michael Hauptmann PhD Group leader
Katarzyna Jozwiak PhD Academic staff
Sander Roberti MSc PhD student
John Zavrakidis MSc Junior researcher

Selected publications

Groot HJ, Gietema JA, Aleman BMP, Incrocci L, de Wit R, Witjes AJ, Groenewegen G, de Brouwer P, Meijer OWM, Hulshof MCCM, van den Berg HA, Smilde TJ, Vanneste BGL, Aarts MJ, van den Bergh ACM, Kerst JM, van den Belt-Dusebout AW, Lubberts S, Jozwiak K, Horenblas S, van Leeuwen FE, Schaapveld M. Risk of diabetes after para-aortic radiation for testicular cancer. Br J Cancer 2018;119:901-907

Halldorsson MO, Hauptmann M, Snaebjornsson P, Haraldsdóttir KH, Aspelund T, Gudmundsson EF, Gudnason V, Jonasson JG, Haraldsdottir S. The risk of developing a mismatch repair deficient colorectal cancer after undergoing cholecystectomy. Scand J Gastroenterol 2018;53(8):972-975

Krul IMK, Opstal-Van Winden AWJ, Janus CPM, Daniels LA, Appelman Y, Maas AHEM, de Vries S, Jozwiak K, Aleman BMP, van Leeuwen F. Cardiovascular disease risk after treatment-induced premature ovarian insufficiency in female survivors of Hodgkin lymphoma. J Am Coll Cardiol, 2018;72(25):3374-3375

The Biostatistics Center provides statistical expertise to researchers and doctors on diverse topics from all areas of observational and experimental biomedical cancer research. This involves developing and implementing statistical approaches to cover a wide range of topics including the design and analysis of epidemiologic studies and clinical trials, the identification of prognostic and predictive biomarkers, sample size calculations, risk prediction, missing data imputation, as well as animal and in vitro experiments. In 2018, the Biostatistics Center has been involved in, for instance, studies of late effects of cancer treatment. Using a case-cohort design within a multicenter cohort comprising survivors treated for testicular cancer before 50 years of age between 1976 and 2007 in 13 Dutch hospitals, risk of subsequent malignant neoplasms and risk of diabetes mellitus were investigated (Groot et al, 2018). Among Dutch women who were treated for Hodgkin lymphoma before 41 years of age between 1965 and 2000, risk of cardiovascular disease in relation to early artificial menopause was evaluated (Krul et al, 2018). Multiple imputation and linear excess relative risk modelling were employed. Conditional polytomous logistic regression was used for a case-control study nested in a cohort of all subjects diagnosed with colorectal cancer in Iceland in the period 2000-2009. There was no evidence of an increased risk of developing a mismatch repair deficient colorectal cancer among subjects who had undergone a prior cholecystectomy (Halldorsson et al, 2018).

Moreover, the group offers annual statistical training for NKI-AVL employees and graduate students from the Amsterdam University Medical Centre and elsewhere. A one-week course on Basic Medical Statistics covers explanation of standard statistical techniques for the evaluation of biomedical data. It provides an introduction into design aspects, methods of summarizing and presenting data, estimation, confidence intervals and hypothesis testing, and multivariable regression methods for the assessment of association. Additionally, several half-day workshops on specific methodological challenges such as sample size calculation, interaction analysis or missing data are also organized by the group.

Currently, the group has developed a web-based infrastructure for choosing an optimal design and innovative statistical analysis of animal studies conducted at the NKI. Researchers can use the website http://statsinvivo.nki.nl/ for explanations of basic statistical concepts and for online sample size calculations needed for planning and conducting informative, efficient and ethically acceptable mice experiments.

MCCA transgenic facility / animal facility T2

Ivo Huijbers

Head MCCA transgenic facility / animal facility T2

Ivo Huijbers PhD Head
Rahmen Bin Ali BSc Technical staff
Tanya Vermeeren-Braumuller BSc Technical staff
Fina van de Ahé Technical staff
Jan Paul Lambooij BSc Technical staff
Colin Pritchard MSc Technical staff
Linda Henneman PhD Technical staff
Lona Kroese MSc Technical staff
Leo Ennen BSc Team leader T2
12 Animal care takers

Selected publication

Maia ARR, Linder S, Song JY, Vaarting C, Boon U, Pritchard CEJ, Velds A, Huijbers IJ, van Tellingen O, Jonkers J, Medema RH. Mps1 inhibitors synergise with low doses of taxanes in promoting tumour cell death by enhancement of errors in cell division. 2018;118:1586-1595

Activities

In 2018 the organizational structure of the animal facility has been adjusted. The animal facility has been divided in three units, T1, T2 and T3, each with their own specialty, focus and head of facility. T2 is a combined experimental and breeding unit where mice are kept under specific pathogen free conditions (SPF). T2 houses the MCCA transgenic facility that creates custom-made genetically engineered mouse strains for researchers and performs the cryopreservation of mouse strains by freezing sperm or embryos.

In 2018, T2 has seen an increase in cages of 9%. Most mice at T2 have a defined genetic alteration or are mouse models of cancer. The latter are mice with the similar genetic alterations as seen in cancer patients. These mice develop cancer over time and are studied for basic cancer biology or to test new anti-cancer treatments. The 12 animal caretakers and their team leader look after the day-to-day care of animals. They also provide specialized biotechnical support making sure the best treatment is provided. In 2018, an optimized pain relief protocol has been implemented providing optimal pain relief with minimal discomfort to the mice. Also in 2018, a new revitalization pipeline was successfully implemented allowing the introduction of new strains in the facility by performing *in vitro fertilization* (IVF) using cryopreserved sperm.

In 2018, the MCCA transgenic facility created ~30 new genetically modified mouse strains for 20 unique customers. About half of the customers are group leaders at the NKI, the other half is divided equally between customers from national and international academia. Almost all mouse strains were made under full-service conditions covering all steps from vector design to screening of the founder mice and their respective offspring. The main innovations from 2018 are the creation of knock-in alleles in endogenous loci using CRISPR/Cas9 with long-single strand DNA (lssDNA) templates and the implementation of the goGermline technology. The latter technology is acquired from Ozgene and ensures 100% embryonic stem (ES) cell derived mice. This technology greatly improves the success rate of creating genetically engineered mice from ES cells and is a clear 3R improvement.

Robbie Joosten

Manager Research High-Performance Computing facility

Research High-Performance Computing facility

Our facility deploys, maintains, and secures High-Performance Computing solutions for eighteen research groups in the NKI and one research facility. The facility takes care of the backbone infrastructure and the group-owned computing platforms, so the research groups have the freedom to focus on the science of their computational work. This covers almost the entire spectrum of the research at the NKI as is exemplified by the publications that involved the facility's setup.

2018 was our first full year of operations. The facility has grown to 160 users of 17 machines with in total 850 CPUs, 3 TB of RAM, and 530 TB of storage. The growing user base has broad IT needs. Next to the compute nodes, the facility features 3 high-end GPU-computing workstations, two code repositories, a large scientific databank, several scientific webservers and services, and a lab equipment booking system.

Scientific computing requires a great deal of connectivity to the outside world. At the same time patient privacy is an important concern. Therefore, the network of RHPC is separate from the regular NKI-AVL network. This improves the safety of patient data, but makes data transfer to the facility from within the institute less convenient. Together with the Genomics Core Facility, a user-friendly data transfer system was implemented in the fall of 2018. Data transfer with external collaborators is increasing and many case-specific solutions were set up. The security of the facility was found to be very good in a third-party penetration test early 2018. Nevertheless, together with our users (notably the Molecular Carcinogenesis division) the security for interactive computing was further increased.

Robbie Joosten PhD Facility manager
Ismail Koraichi BSc Technical staff
Torben Wriedt MSc Technical staff

Selected publications

Kaaij LJT, Van der Weide RH, Ketting RF, De Wit E. Systemic Loss and Gain of Chromatin Architecture throughout Zebrafish Development. Cell Rep. 2018;24(1):1-10.e4

Kluin R, Kemper K, Kuilman T, Iyer V, Forment JV, de Ruiter J, ter Brugge P, Jonkers J, Velds A, Adams DJ, Peeper DS and Krijgsman O. XenofilteR: computational deconvolution of mouse and human reads in tumor xenograft sequence data. BMC Bioinformatics 2018;19:366

Van Beusekom B, Joosten K, Hekkelman ML, Joosten RP, Perrakis A. Homology-based loop modeling yields more complete crystallographic protein structures. IUCrJ, 2018;5:585-94

Genomics core facility

Ron Kerkhoven

Head Genomics core facility

Ron Kerkhoven PhD Head
Marja Nieuwland MSc Wet-lab team leader
Arno Velds MSc Bioinformatic team leader
Roel Kluin MSc Bioinformatic staff
Iris de Rink MSc Bioinformatic staff
Shan Baban MSc Technical staff
Wim Brugman MSc Technical staff
Charlaine van Steenis MSc Technical staff
Stéphanie van Zoelen MSc Technical staff
Samanta Zweers MSc Technical staff

Selected publications

Kluin RJC, [....], Krijgsman O. XenofilteR: computational deconvolution of mouse and human reads in tumor xenograft sequence data. BMC Bioinformatics. 2018;19(1):366

Scheper W, [....], Schumacher TN. Low and variable tumor reactivity of the intratumoral TCR repertoire in human cancers. Nat Med. 2019;25(1):89-94

Verhagen CVM, [....], Vens C. Fanconi anemia and homologous recombination gene variants are associated with functional DNA repair defects *in vitro* and poor outcome in patients with advanced head and neck squamous cell carcinoma. Oncotarget. 2018;9(26):18198-18213

The Genomics Core Facility (GCF) supports users in all aspects of Next Generation Sequencing experiments in their research projects. The facility provides advice, performs library preparation at consumable cost prize, runs the sequencing machines, manages the data storage and performs data analysis. The facility is involved in many research projects and reports on these subjects in lectures, scientific publications with NKI investigators and conference presentations. The facility also has an interest in making available new technologies and innovative sequencing applications and welcomes collaborations that enable this. Education of students and post-docs is supported by the core.

Equipment

The facility is equipped for deep sequencing with two Illumina HiSeq2500 and an Illumina MiSeq machine. In 2018 we renewed a set of PCR machines and acquired a qPCR setup for better library quantification. A new cleanroom with flow-cabinet was established for SmartSeq2 applications and a 10X Chromium controller was installed for droplet based Single Cell applications. This year the Covaris machine (fragmentation of nucleic acids) was replaced by a newly developed 8 tube version of the machine. Several instruments (BioAnalyzer, Qubit, Covaris and E-gel) were setup to be used hands-on by customers on request. Via collaborations with the NKI Oncode Institute research groups we acquired funding for a dedicated NextSeq500 machine for single cell applications.

Workflows

Standard routine is that users register new samples from their own PC in the sample tracking database GCFdb using a web based portal. Sample tracking, sequencing monitoring, billing administration, reporting and data maintenance are the main features of this in-house designed software package. In 2018, features for data sharing and for easy data transport to in house network systems were added. During the actual sample delivery to the core, sequencing setup, settings and expected results are discussed with the user. Projects are assigned to lab technicians keeping users informed of subsequent steps like sample preparation, pooling, sequencing and analysis. Data generated by the sequencing machines is stored centrally and secured at the NKI-IT department. Users receive links to primary data files (FASTQ) and have the choice to perform data analysis on their own or to collaborate with the facility for more in-depth analysis. Upon finalization of the work, the system calculates the costs for the work done, and a money transfer order is sent out.

Experiment types

The facility aims to be very flexible regarding the types of samples that can be delivered as well as the workflows that are available. A user can hand in tissue, cells, extracted nucleic acids or libraries ready for sequencing. The facility has acquired a lot of expertise in library preparation both from fresh samples as well as from formalin fixed (FFPE) samples. Common experiment types are RNAseq, miRNAseq, ChIPseq, CNVseq, PCRseq, Methyl-seq and Target Enrichment strategies. The latter comprise Exomes, Kinomes, as well as custom designed panels which can be ordered in collaboration with the facility. Besides preparing sequence libraries, the facility also performs sequencing on custom prepared libraries. Examples are the TRC (Mission) short hairpin screens, functional screens in haploid cells, CRISPR/Cas9 screens and screens for nuclear organization and epigenetics (DamID, TRIP).

New developments

The facility is involved in Low Input Sample preparation (Smart-seq2, Cell-seq2) and in Single Cell sequencing. After an educational visit to Harvard Medical School we started out using DropSeq single cell sequencing. Later this year this was repaced by the 10X-Genomics “Chromium” machine. By tagging cell populations with labeled antibodies, pooling strategies can be applied reducing the experimental costs of library preparation. Even combined analyses work in single cells: while counting mRNA molecules in thousands of indivual T-cells, the T-cell receptor sequence, was determined simultaneously in over 6,000 human T-cells.

Sjoerd Klarenbeek

Head Experimental Animal Pathology

Experimental Animal Pathology

Activities

The Experimental Animal Pathology facility provides broad pathology support for research projects involving the use of animals. Our activities include consultancy and collaboration with scientists in all phases of a project, from study design to publication. We help with the dissection of animals and tissue sampling, our technicians process and embed tissues, cut slides and perform a wide range of histochemistry and immunohistochemistry stains. We often develop and optimise staining protocols such as new immunohistochemistry procedures for epitopes of interest. Occasionally we process other types of samples, such as organoids or cells, or provide support for other institutes. Our pathologists partner with researchers in their projects, train and educate personnel, help to perform dissections, and provide detailed microscopic analysis of pathologic changes and content for scientific presentations and publications. The pathologists also perform diagnostic pathology analysis of sick animals, for the benefit of the health and welfare of animals in the institute.

It is important to identify the abnormalities that are induced by the experiment, but also to distinguish these findings from spontaneous or background pathology. The correct interpretation and reporting of findings by a comparative pathologist contributes to better and more effective research, avoiding the pitfalls of do-it-yourself pathology. Mammals are complex organisms with many interacting organ systems, and the effects of experiments or genetic events can be difficult to predict. Phenotypes may occur in any tissue, experimental procedures may lead to many local or systemic changes, and administered substances may have unexpected effects or toxicities. To add to the complexity, all these changes are often dynamic over time. This is why we offer a thorough and complete analysis of the pathology of animals when researchers are developing a new animal model or experimental setup. We aim to offer accessible specialised pathology support and a personal approach, with our doors open for all researchers.

Sjoerd Klarenbeek Pathologist
Ji-Ying Song Pathologist
Jelrik van der Meer Technical staff
Joost van Ooij Technical staff
Ellen Riem Technical staff
Lex de Vrije Technical staff
Valerie Wirokromo Technical staff

Selected publications

Boshuizen J, Koopman LA, Krijgsman O, Shahrabi A, van den Heuvel EG, Ligtenberg MA, Vredevoogd DW, Kemper K, Kuilman T, Song JY, Pencheva N, Mortensen JT, Foppen MG, Rozeman EA, Blank CU, Janmaat ML, Satijn D, Breij ECW, Peeper DS, Parren PWHI. Cooperative targeting of melanoma heterogeneity with an AXL antibody-drug conjugate and BRAF/MEK inhibitors. Nat Med. 2018;24(2):203-212

Kas SM, de Ruiter JR, Schipper K, Schut E, Bombardelli L, Wientjens E, Drenth AP, de Korte-Grimmerink R, Mahakena S, Phillips C, Smith PD, Klarenbeek S, van de Wetering K, Berns A, Wessels LFA, Jonkers J. Transcriptomics and Transposon Mutagenesis Identify Multiple Mechanisms of Resistance to the FGFR Inhibitor AZD4547. Cancer Res. 2018;78(19):5668-5679

Maia ARR, Linder S, Song JY, Vaarting C, Boon U, Pritchard CEJ, Velds A, Huijbers IJ, van Tellingen O, Jonkers J, Medema RH. Mps1 inhibitors synergise with low doses of taxanes in promoting tumour cell death by enhancement of errors in cell division. Br J Cancer. 2018;118(12):1586-1595

Flow Cytometry Facility

Martijn van Baalen

Head Flow Cytometry Facility

The Flow Cytometry Facility provides access to high-end flow cytometric analytical and state-of-the-art cell sorting equipment. We actively support NKI investigators with tailored advice and practical assistance in all phases of their experiments with regard to analytical flow cytometry and cell sorting.

The Flow Cytometry Facility maintains seven analytical flow cytometers for basic and high-parameter interrogation of experimental samples on a single cell level (up to 30 fluorescent labels), and five high-end cell sorters (up to 18 fluorescent labels) for isolation of the cells of interest with high purity. Quality Assurance and Quality Control is performed routinely to ensure consistent and robust performance, and timely scheduled preventative maintenance and repairs. All instruments are housed in BSL 2 lab environment to allow for safe handling of samples with known and unknown infectious pathogens. The available equipment provides flexibility and allows for tailored approaches to address a wide range of scientific problems and biological questions.

Our full cell sorting service by expert sort operators allows for bulk isolation and (indexed) single cell sorting of specific cell subsets from heterogeneous samples, based on scatter parameters up to complex immunological panels with 18 fluorescent labels, for a wide range of post-isolation applications. Some examples of post bulk sorting applications are: in vitro expansion and functional assays, *in vivo* transplantation, protein, DNA and RNA extraction for applications like mass spectrometry, and sequencing for genetic screens or gene expression. Common post-sort single cell applications include: cloning, DamID assays, qPCR, and sequencing.

We strive to meet the investigators' specific needs by providing tailored assistance with experimental design, sample preparation, data acquisition, and analysis, enabling the highest possible resolution, data quality and reproducibility. We provide introductory courses to allow independent use of the available analytical instruments and to ensure a high level of theoretical knowledge, optimal instrument use, and data quality. Additionally, we provide introductory and advanced training sessions on theoretical and technical topics related to flow cytometry, and independent operation of cell sorting instruments. We also organize specialized workshops and seminars on topics such as tumor dissociation and other sample preparation methods, optimizing protocols for staining of intracellular targets, and data analysis methods.

Finally, we are actively involved in (inter)national and virtual cytometry networks and instrument user groups to exchange knowledge with colleagues from the wider community, and allow investigators of the NKI to benefit from the latest developments and insights in the field of cytometry.

Martijn van Baalen Head
Debajit Bhowmick Operator
Frank van Diepen Operator
Anita Pfauth Operator

Selected publications

Boshuizen J, Koopman LA, Krijgsman O, Shahrabi A, van den Heuvel EG, Ligtenberg MA, Vredevoogd DW, Kemper K, Kuilman T, Song JY, Pencheva N, Mortensen JT, Foppen MG, Rozeman EA, Blank CU, Janmaat ML, Satijn D, Breij ECW, Peeper DS, Parren PWHI. Cooperative targeting of melanoma heterogeneity with an AXL antibody-drug conjugate and BRAF/MEK inhibitors. Nat Med. 2018;24(2):203-212

Dijkstra KK, Cattaneo CM, Weeber F, Chalabi M, van de Haar J, Fanchi LF, Slagter M, van der Velden DL, Kaing S, Kelderman S, van Rooij N, van Leerdam ME, Depla A, Smit EF, Hartemink KJ, de Groot R, Wolkers MC, Sachs N, Snaebjornsson P, Monkhorst K, Haanen J, Clevers H, Schumacher TN, Voest EE. Generation of Tumor-Reactive T Cells by Co-culture of Peripheral Blood Lymphocytes and Tumor Organoids. Cell 2018;174(6):1586-1598.e12

Scheper W, Kelderman S, Fanchi LF, Linnemann C, Bendle G, de Rooij MAJ, Hirt C, Mezzadra R, Slagter M, Dijkstra K, Kluin RJC, Snaebjornsson P, Milne K, Nelson BH, Zijlmans H, Kenter G, Voest EE, Haanen JBAG, Schumacher TN. Low and variable tumor reactivity of the intratumoral TCR repertoire in human cancers. Nat Med. 2019;25(1):89-94

Mouse Cancer Clinic / animal facility T1

Marieke van de Ven

Head Mouse Cancer Clinic / animal facility T1

Marieke van de Ven PhD Head T1
Charlotte Baak BSc Technical staff
Renske de Korte-Grimmerink BSc Technical staff
Natalie Proost BSc Technical staff
Bjørn Siteur Technical staff
Rebecca Theeuwsen BSc Technical staff
Niels de Wit BSc Head Imaging facility
Olaf van Tellingen Head Pharmacology facility
Artur Burylo Technical staff
Ben van de Graaff Team leader T1
7 animal caretakers

Selected publications

Buoninfante OA, Pilzecker B, Aslam MA, Zavrakidis I, van der Wiel R, van de Ven M, van den Berk PCM, Jacobs H. Precision cancer therapy: profiting from tumor specific defects in the DNA damage tolerance system. Oncotarget. 2018;9(27):18832-18843

Duarte AA, Gogola E, Sachs N, Barazas M, Annunziato S, R de Ruiter J, Velds A, Blatter S, Houthuijzen JM, van de Ven M, Clevers H, Borst P, Jonkers J, Rottenberg S. BRCA-deficient mouse mammary tumor organoids to study cancer-drug resistance. Nat Methods. 2018;15(2):134-140

Gogola E, Duarte AA, de Ruiter JR, Wiegant WW, Schmid JA, de Bruijn R, James DI, Guerrero Llobet S, Vis DJ, Annunziato S, van den Broek B, Barazas M, Kersbergen A, van de Ven M, Tarsounas M, Ogilvie DJ, van Vugt M, Wessels LFA, Bartkova J, Gromova I, Andújar-Sánchez M, Bartek J, Lopes M, van Attikum H, Borst P, Jonkers J, Rottenberg S. Selective loss of PARG restores PARylation and counteracs PARP inhibitor-mediated synthetic lethality. Cancer Cell. 2018;11;33(6):1078-1093

Activities

The Mouse Cancer Clinic / T1 is a facility where advanced mouse models are used as surrogate for cancer patients to identify and validate targets that can be exploited by anti-cancer therapy. The Mouse Cancer Clinic is composed of an intervention unit, a preclinical imaging facility and a bio-pharmacy unit working together in close collaboration with research groups at the NKI, other academic partners and pharmaceutical companies. The main objective is to find and test novel anti-cancer treatments, using the advanced cancer models, such as transgenic (spontaneous) mouse models, orthotopic transplantation models, human xenograft models that have been developed/ established at the NKI.

The knowledge of the molecular pathology of cancer cells is rapidly expanding and this now helps to design interventions that specifically interfere in the critical steps that drive cancer cells. This holds the promise of generating more efficacious therapies with fewer side effects. In order to more accurately translate preclinical studies to clinical outcome, it is essential to use cancer models that faithfully recapitulate the human disease. Moreover, when the treatment involves testing of new agents, it is necessary to consider the pharmacokinetic behavior of the experimental drugs in relation to their pharmacodynamics effects (target inhibition), especially since species-differences in pharmacokinetics of drugs is a potentially confounding factor. Obviously, it is not very useful when a drug demonstrates pre-clinical efficacy only at a dose level that results in plasma concentrations that cannot be achieved in patients. Therefore, we include the collection of data on plasma exposure (C_{max} and AUC, half-life) of test compounds in these intervention studies.

With the knowledge on pharmacokinetic behavior being established, an intervention study using one of our advanced mouse models can be designed guided by novel insights from basic research and clinical demands. Various approaches to treat cancer with classical chemotherapy, molecularly targeted agents, immuno-modulators, radiotherapy or combinations thereof are currently ongoing. In addition to systemically administered agents, we are also investigating loco-regional applications of drugs, surgery and radiation. The pre-clinical intervention unit can take care of the whole trajectory of preclinical trial design and execution, including support in the design/setup of the study, design suitable drug formulations, planning and execution of treatments, follow-up of tumor growth and/or metastasis formation, assessment of therapy response, collection of tissues and reporting of data. The longitudinal follow-up of tumors is greatly facilitated by dedicated state-of-the-art small animal imaging systems, including SPECT/CT, PET/CT and 7T MRI. Local and precise radiation beams can be delivered using the image-guided radiation therapy system for small animals. The lab of the bio-pharmacy unit is equipped with analytical instruments (LC-MS/MS, LC-UV/PDA, LC-FD and GFAAS) to execute bioanalytical assays.
In 2018 the Mouse Cancer Clinic carried out more than 120 projects for more than 12 research groups inside the NKI. 31 of the projects were for external academic customers and 4 for small pharmaceutical companies.

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 University of Amsterdam (AMC) and the VU University (VUmc), now merged into the Amsterdam University Medical Centers. 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 2018, 52 Dutch university Master students completed a placement of 6 to 10 months at the biomedical research divisions. The students came primarily from the University of Amsterdam (UvA) (23) and the VU University Amsterdam (VU) (17), but also from the universities of Utrecht (3), Leiden (7) and Rotterdam (3). 8 master students from universities outside the Netherlands completed an internship at NKI. 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 master course is a compulsory course for UvA Master students in Biomedicine, track Oncology. It is also offered as an elective to master students who do an internship at the NKI in a biomedical discipline. Other interested parties such as PhD students are welcome to attend the lectures as listener upon enrollment as attendee. The master course has a interactive program consisting of tutorials, student presentations and discussion and assignments. In addition, the students have to pass four exams in order to get study points. The course evolved around four main themes for which assignments and exams were organized, in addition to lectures covering the latest developments in the respective fields.

TABLE 1

COURSE IN EXPERIMENTAL ONCOLOGY

LECTURES	
Explore your options	M van den Boom
Cancer epidemiology	FI van Leeuwen
Next generation sequencing	R Kerkhoven
Early diagnostics	B Carvallo, R Fijneman
Medical imaging	E Vegt
Epigenetics in cancer	B van Steensel, Fr van Leeuwen
Radiotherapy	R Haas
Conventional chemotherapy	F Opdam
Telomeres and cancer	J Jacobs
Chromosome morphogenesis	B Rowland
Mouse models of cancer	I Huijbers
Non-coding landscape and cancer	R Agami
RNA translation and the ribosome	W Faller
Functional genomics	T Brummelkamp
Cancer genomics	L Wessels
Targeted therapy in melanoma	D Peeper
(Immunogenic) cell death	J Borst
Tumor microenvironment	K de Visser
Radioimmunotherapy	I Verbrugge
Macrophages in the microenvironment	L Akkari
THEMATIC BLOCKS	
INTRODUCTORY LECTURE, STATE-OF-THE ART LECTURES, STUDENT PRESENTATIONS + QUESTIONS, RESEARCH PROPOSALS AND EXAMS	
Hormone regulated cancers	W Zwart, H Horlings
DNA damage and genomic instability	C Vens, H Jacobs, M Tijsterman (guest)
Targeted therapy and resistance	R Beijersbergen, R Bernards
Immunology and immunotherapy	J Borst, P Kvistborg

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 Amsterdam University Medical Centers. The number of PhD students has been rising rapidly in the past years. In 2018, the institute had 249 PhD students registered at the OOA. 34 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 such as 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 of the research in the OOA at an early stage of the student's career, but also training in

TABLE 2

OOA PHD STUDENT COURSES AND EVENTS 2018

DATE	COURSE	ECTS	ORGANIZERS	# STUDENTS	RATING
FEB 7, 14, 21	**Introduction to clinical and translational oncology**	1.0	CTO Utrecht	7	ND
MARCH 12-16	**Knowledge gaps in breast cancer**	1.5	J Wesseling, M Kok, W Zwart (NKI-AVL)	36	4.1
MARCH 15	**Meet the expert Pandey**	0.3	E Ruhé (VUmc)	14	5.0
MARCH 26	**How to become a successful grant applicant**	0.05		39	3.7
APRIL 9-13	**Mouse morphology, genetics and function**	1.5	J Seppen, E Reits (AMC)	16	3.9
APRIL 16-20	**In the footsteps of Antoni van Leeuwenhoek – Basic microscopy**	1.5	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	4.5
APRIL 18 & 24	**Getting your manuscript out for review**	1.5	Y Duijker, E Ruhé (VUmc)	32	3.2
MAY 25	**OOA PhD day**	0.2	PhD council NKI-AVL	111	4.0
SEPTEMBER 14	**Theatre skills for presenters at the retreat**	-	P Lagerweij	25	4.6
SEPT 20 & 21	**Histopathology of human tumors**	0.6		38	3.7
OCTOBER 10-12	**Annual Graduate Student Retreat**	2.0	P Lagerweij, K van der Heijden, H te Riele (NKI-AVL)	230	4.2
OCTOBER 15-19	**In the footsteps of Antoni van Leeuwenhoek – Basic microscopy**	1.5	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)	15	4.2
OCT 29 – NOV 9	**BioBusiness**	3.0	A Griffioen, E Huijber, J van Beijnum (VUmc)	5	4.4
NOVEMBER 13-17	**Basic Medical Statistics / SPSS**	1.5	M Hauptmann, K Jozwiak, J Zavrakidis, S Roberti, A Morra, D Giardiello (NKI)	90	4.2
NOVEMBER 22	**Masterclas prof Piccart**	0.3	E Ruhé (VUmc)	13	4.8
NOVEMBER 23	**Ethics and Integrity in Science**	0.15	P Borst, B van Steensel (NKI)	30	4.1
NOV 30 & DEC 6	**ImageJ/Fiji**	0.6	M Mertz, L Brocks (NKI)	21	ND
DECEMBER 6-14	**O2Flow Cytometry**	1.5	J Garcia Vallejo (VUmc)	14	4.1
THROUGHOUT THE YEAR	**Lunch meetings with NKI-AVL seminar speakers**	-	NKI seminar committee	150	ND

PhD student retreat 2018

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 Amsterdam oncology centers.

Senior graduate students can participate in a joint retreat with other cancer institutes in Europe. In 2018, this event was held in London, United Kingdom, organized by the students from the the Francis Crick Institute, 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, 7 participants)
- 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 addition, an OOA PhD council has been installed consisting of representatives of the participating Amsterdam oncology centers, which organizes events specifically focused on career development of graduate students.

POSTDOCS

In 2018 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 (alumni) career development seminars and workshops about intellectual property 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 NKI Postdoc Career Development Program that is offered by the NKI to all its postdocs. This program has been developed together with AVL Academy and the postdoc dean. 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 2018, 53 postdocs started in the basic program.

Basic Postdoc Career Development Program 2018

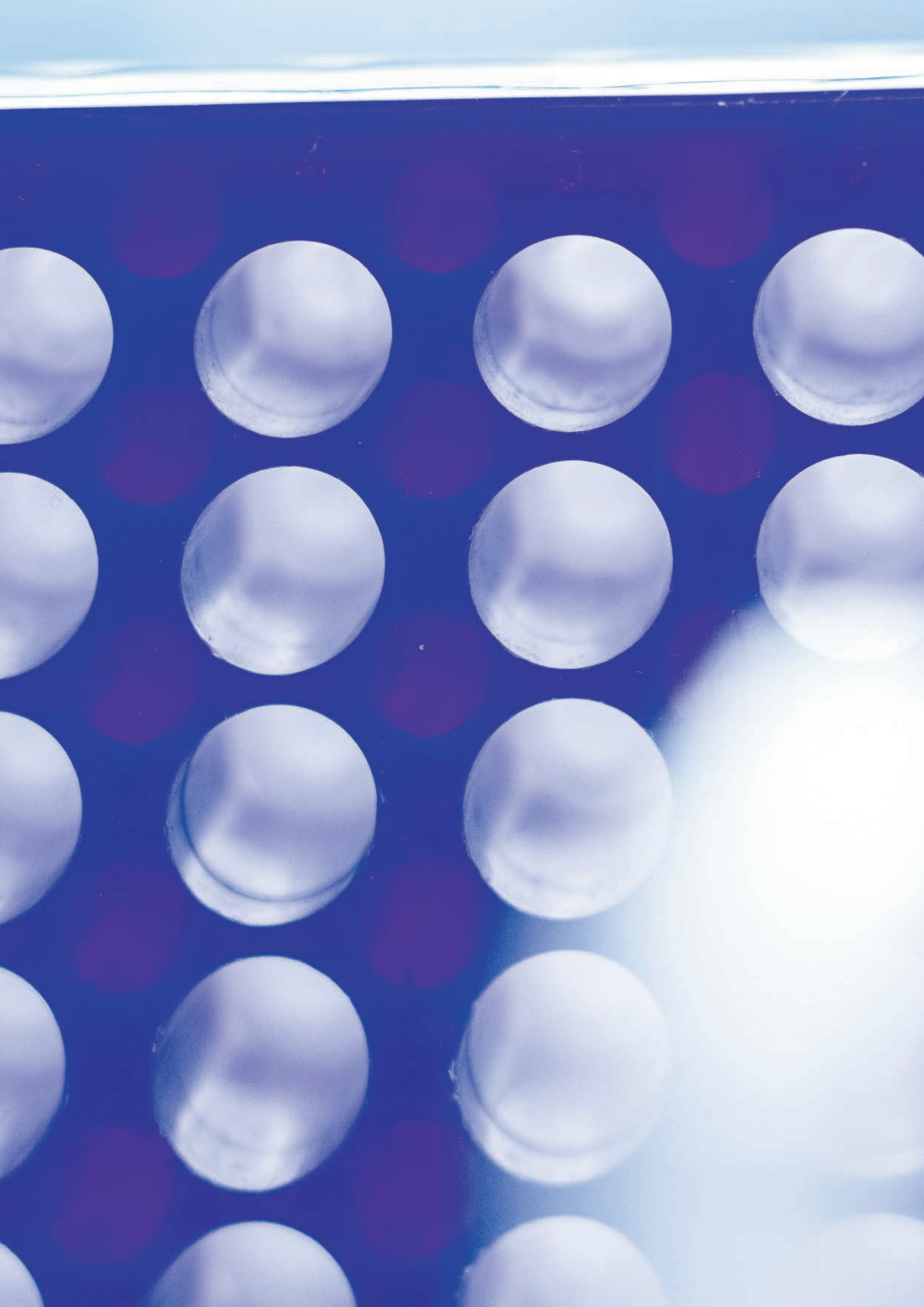
Day 1. Personal effectiveness: time and project management
Day 2. Communication & cooperation
Day 3. Creating your future, take ownership

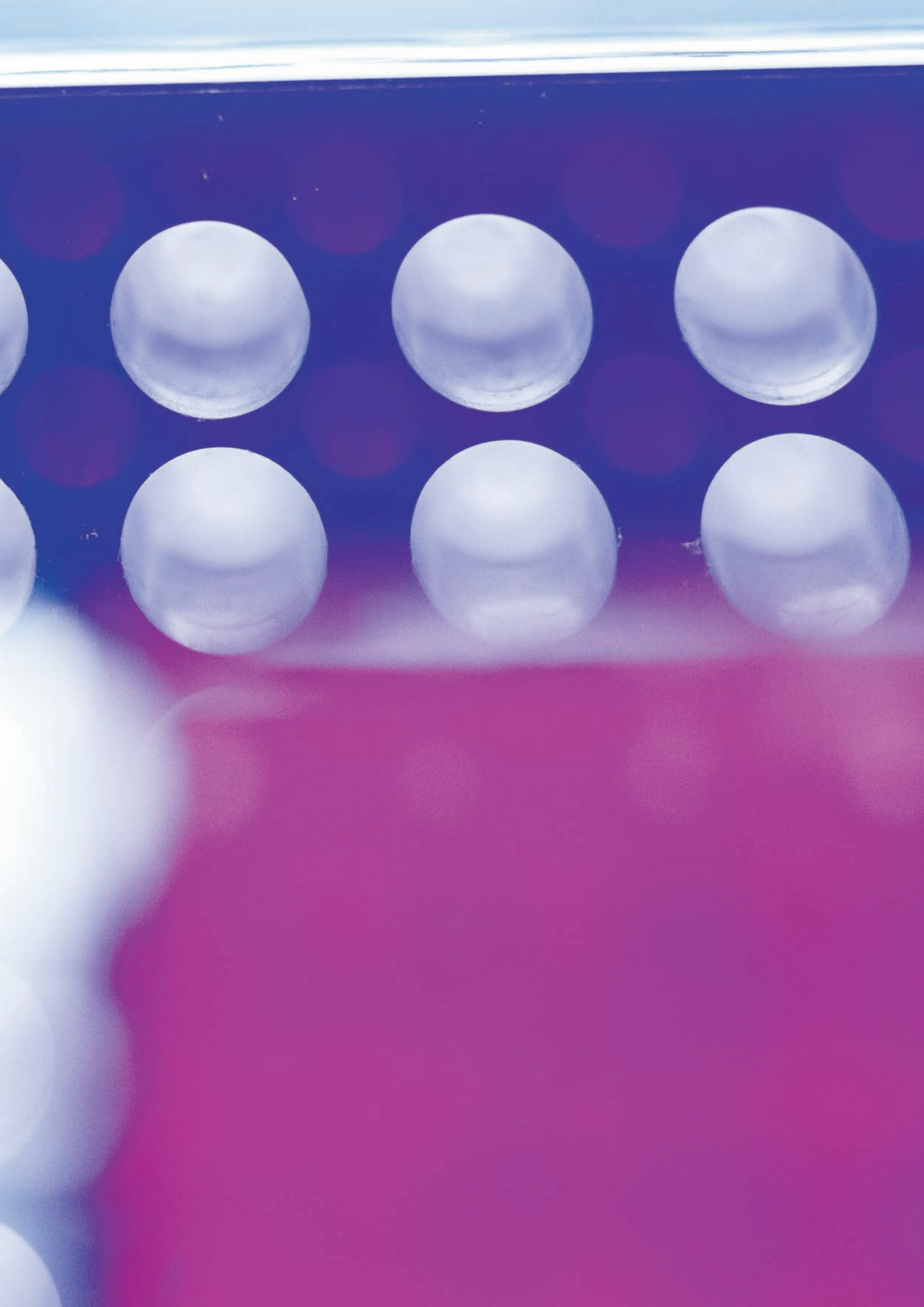
All postdocs that have completed the basic program are invited in subsequent years to follow one of the one-day workshops as part of the Advanced Postdoc Career Development Program. In 2018, 59 postdocs registered for a workshop of the advanced program.

Advanced Postdoc Career Development Program 2018

1. Influence and impact
2. Shaping your Career
3. Influencing group dynamics
4. Scientific Project Management
5. Grant Writing

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 adjusted every year based on the evaluations of the workshops and suggestions from the postdocs.





Clinical trials

ALL SITES

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
C14EMB	Prospective study on the treatment of unsuspected pulmonary embolism in cancer patients	Joke Baars	other	07/01/2014 (29/11/2018)
M09NIB	The NIB-Cohort study, therapeutic drug monitoring of tyrosine kinase inhibitors	Neeltje Steeghs	other	09/06/09
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 biopsy protocol)	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	Neeltje Steeghs	other	13/09/12
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 (BP29392)	Neeltje Steeghs	I	23/01/2015 (7/12/2018)
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	Serena Marchetti	other	31/03/2015 (09/07/2018)
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 (roar)	Neeltje Steeghs	II	13/11/2014 (30/06/2018)
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	Neeltje Steeghs	I	18/12/2014 (01/06/2018)
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	Frans Opdam	I/II	11/03/15
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 (BP29435)	Neeltje Steeghs	I/II	21/04/2015 (13/07/2018)
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 (BP29541)	Neeltje Steeghs	I	14/01/2015 (23/08/2018)
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	I	25/07/16

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
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 (BP29842)	Neeltje Steeghs	I	18/12/15
M15KEY	A clinical trial of Pembrolizumab (MK-3475) evaluating predictive biomarkers in subjects with advanced solid tumors (KEYNOTE 158)	Marloes van Dongen	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	Sofie Wilgenhof	I/II	28/07/17
M15MPA	An open-label, multicohort, phase II study of MPDL3280A in advanced solid tumors (Basket)	Cecile Grootscholten	II	03/07/2015 (16/5/2018)
M15MSR	An Open Label, Phase Trial of the DNA-PK Inhibitor MSC2490484A in Combination with Radiotherapy in Patients with Advanced Solid Tumors	Baukelien van Triest	I	17/07/15
M15PDR	Open label multicenter Phase I/II study of the safety and efficacy of PDR001 administered to patients with advanced malignancies	Neeltje Steeghs	I/II	29/09/2015 (30/04/2018)
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)	Frans Opdam	I	04/05/16
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)	Frans Opdam	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)	Neeltje Steeghs	I	26/02/2016 (23/08/2018)
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)	Neeltje Steeghs	I	26/02/16
M15SRB	Postoperative local stereotactic radiotherapy versus observation following complete resection of a single brain metastasis	Dieta Brandsma	III	09/09/2015 (31/10/2018)
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	Frans Opdam	I	01/06/2016 (30/03/2018)
M15TRE	A Phase II, multi-center, open-Label study of Tremelimumab monotherapy in patients with advanced solid tumors (TremeBasket)	Neeltje Steeghs	II	18/12/2015 (29/10/2018)
M16AOX	A Phase 1/2a Study of BMS-986178 Administered Alone and in Combination with Nivolumab or Ipilimumab in Advanced Solid Tumors	Michiel van der Heijden	I/II	20/10/2016 (31/10/2018)
M16APF	Analysis of pleural fluid and ascites to improve diagnostics for patients with cancer	Serena Marchetti	other	24/03/2016 (17/07/2018)
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	24/06/2016 (16/10/2018)

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M16GAC	A Phase I Open Label study of GSK3359609 administered alone and in combination with anticancer agents in subjects with selected advanced solid tumors	Frans Opdam	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	Sofie Wilgenhof	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	15/09/2016 (07/11/2018)
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	08/08/2016 (07/06/2018)
M16MOL	A phase I/II study of MEDI4736 (anti-PD-L1 Antibody) in combination with Olaparib (PARP inhibitor) in patients with advanced solid tumors (MEDIOLA)	Neeltje Steeghs	I/II	01/09/16
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
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	07/11/2016 (24/01/2018)
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	Frans Opdam	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	Frans Opdam	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)	Neeltje Steeghs	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	Neeltje Steeghs	I	06/10/17
M17LET	An open-label, multi-center, roll-over study to assess long term safety of lenvatinib monotherapy or lenvatinib combination regimen or comparator treatment arm to cancer patients in Eisai sponsored lenvatinib trials	Marloes van Dongen	II	15/08/18
M17MIW	A Phase Ib, open label, multicenter study of the safety and efficacy of MIW815 (ADU-S100) administered by intratumoral injection with PDR001 to patients with advanced/metastatic solid tumors or lymphomas	Neeltje Steeghs	I	02/02/18
M17MPE	A Phase 1 Study of MK-5890 as Monotherapy and in Combination with Pembrolizumab in Participants with Advanced Solid Tumors	Marloes van Dongen	I	15/05/18

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M17PCV	A phase Ia/Ib open-label, dose-escalation study of the safety and pharmacokinetics of RO7198457 as a single agent and in Ccombination with Atezolizumab in patients with locally advanced or metastatic tumors	Neeltje Steeghs	I	04/10/18
M17QLQ	Validation of the EORTC computerized adaptive testing (CAT) instrument – Feasibilty and field study	Neil Aaronson	other	28/11/17
M17QOL	Phase III development of an EORTC QoL cancer survivorship questionnaire	Lonneke van de Poll - Franse	III	12/06/18
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	Neeltje Steeghs	I/II	23/05/17
M17TDM	Therapeutic drug monitoring for oral anti-cancer drugs	Neeltje Steeghs	other	09/08/17
M18COM	Communication in Second Opinions - the SO-COM study	Gemma de Kenter	other	29/03/18
M18COP	Prospective, multi-centre trial to evaluate effectiveness of 45-min and 20-min postinfusion cooling time for patients treated with scalp cooling to prevent Paclitaxel-induced alopecia (COP)	Carolien Smorenburg	other	19/06/18
M18TLO	A Phase I, Open-Label Study of GSK1795091 Administered in Combination with Immunotherapies in Participants with Advanced Solid Tumors	Neeltje Steeghs	I	25/09/18
N10CRC	Proof of principle and pharmacological phase 0 crossover study with controlled release capecitabine (ModraCape001)	Serena Marchetti	I	17/11/2011 (13/11/2018)
N10MOP	Development and clinical activity of low dose metronomic chemotherapy with oral paclitaxel	Serena Marchetti	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	Serena Marchetti	other	11/04/13
N14CCT	Phase I pharmacological study of continuous and intermittent chronomodulated capecitabine therapy	Serena Marchetti	I	18/06/14
N15FED	Food-effect study of weekly administration of (bi-) daily Oral Docetaxel (ModraDoc006) in combination with ritonavir	Serena Marchetti	I	03/05/2017 (03/07/2018)
N15LDC	The effect of prehydration on the pharmacokinetics of low-dose Cisplatin	Wouter Vogel	other	06/11/15
N15SGI	A phase I trial to assess the mass balance and pharmacokinetics of 14cguadecitabine in subjects with AML, MDS, or solid tumors	Marloes van Dongen	I	29/08/2016 (21/08/2018)
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	other	23/05/16
N16CRY	The effect of Cryotherapy in preventing oral mucositis associated with doxorubicin treatment	Carolien Smorenburg	other	09/05/16
N16GEM	Phase 0 proof of concept study: a clinical pharmacokinetic microdosing trial with gemcitabine	Serena Marchetti	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

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N16LUR	Mass Balance Study of PM01183 (lurbinectedin) Administered as a 1- hour Intravenous Infusion to Patients with Advanced Cancer	Frans Opdam	I	19/04/2017 (01/03/2018)
N16NVG	The effectiveness of patient navigation in cancer care (navigatie)	Eveline Bleiker	other	27/12/2016 (06/11/2018)
N16PDA	Validation of Pharmacokinetic Assays for determination of Nivolumab and Pembrolizumab concentrations in serum	Serena Marchetti	other	16/01/17
N16PZN	Proof of principle and pharmacological phase 0 study with improved solubility Pazopanib (PazSol001)	Neeltje Steeghs	other	15/09/2016 (31/10/2018)
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	04/05/2017 (03/08/2018)
N17MRB	Monitoring MRI changes before and during Radiotherapy Treatment of Brain Tumors	Gerben Borst	other	31/08/17
N17ROW	Reiniging van gecontamineerde postoperatieve oncologische wonden met kraanwater of antiseptische spoelvloeistof - een gerandomiseerde klinische studie	Rob Kuin	other	05/02/18
N18BREL	The MR-Linac Technical feasibility protocol for development of MR-guided adaptive radiation therapy (UMBRELLA-2)	Marlies Nowee	other	26/09/18
N18MRC	Development of MRCAT: electron density maps for radiotherapy dose calculations from MR images as alternative for planning CT scans	Abrahim Al-Mamgani	other	21/03/18
N18ULN	Ultrasound-based navigation during liver surgery	Theo Ruers	other	10/08/18

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 study)	Johanna van Sandick	biobank	17/06/15
B15PON	Paired healthy & tumor organoid Biobank (carcinomas)	Emile Voest	biobank	09/09/2015 (28/11/2018)
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
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

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
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
B17CON	CONventional TReatment Or Leave DCIS	Jelle Wesseling	biobank	27/12/17
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
B18UBC	Longitudinal tumor, urine and blood sampling in patients with urinary tract cancer treated with chemotherapy	Michiel van der Heijden	biobank	15/10/18
BRAIN / CNS				
E1709	A phase III trial of Marizomib in combination with standard Temozolomide-based radiochemotherapy versus standard Temozolomide-based radiochemotherapy alone in patients with newly daignosed glioblastoma	Dieta Brandsma	III	30/10/18
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	27/10/2015 (31/10/2018)
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
N17ICO	Position stability during radiosurgery of brain tumours	Gerben Borst	other	18/01/18
N17MRB	Monitoring MRI changes before and during Radiotherapy Treatment of Brain Tumors	Gerben Borst	other	31/08/17
N18POB	Dose and Volume Escalation of Preoperative Brain Irradiation in GBM Patients (POBIG trial)	Gerben Borst	I/II	19/06/18
BREAST				
M05BRI	Long term risk of breast cancer following treatment of Hodgkin's disease (BRIGHT)	Nicola Russell	other	05/01/06
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	30/11/2011 (31/10/2018)
M12DEN	Early detection of breast cancer in women with dense breasts (DENSE study)	Claudette Loo	other	19/09/12

Type of cancer study (nick name)	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	14/03/2014 (30/03/2018)
M13MBC	Male Breast Cancer: prospective into perspective	Nicola Russell	other	10/04/2014 (07/12/2017)
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	14/10/2013 (19/11/2018)
M14ABC	A feasibility study of niraparib for advanced, BRCA1-like, HER2-negative breast cancer patients (ABC)	Sabine Linn	II	15/01/18
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	24/07/2014 (06/02/2018)
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
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)	Sabine Linn	I/II	21/04/2015 (31/10/2018)
M15INF	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
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
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)	Neeltje Steeghs	I	01/11/16
M17GEL	AssessinG Efficacy of carboplatin and ATezOlizumab in metastatic Lobular breast cancer (GELATO)	Marleen Kok	I/II	06/10/17

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M17PAB	Effect of a physical activity promotion program offered online or via blended care on physical activity level in breast and prostate cancer survivors (PABLO)	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 (PRECiSE Project)	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)	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
M17TOP	Tailored treatment in Older Patients (TOP-1): Omission of radiotherapy in elderly patients with low risk breast cancer	Marie Jeanne Vrancken Peeters	other	28/02/18
M18HAR	Favorable and unfavorable effects of risk-reducing salpingo-oophorectomy (RRSO) in women with a high genetic risk of ovarian cancer (HARMOny)	Floor van Leeuwen	other	12/09/18
M18LBC	Tailoring Neoadjuvant therapy in hormone receptor positive, HER2 negative, luminal breast cancer (NEOLBC)	Sabine Linn	II	15/11/18
M18LORD	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
N07BOS	Genetic determinants of survival and second breast cancer development in premenopausal breast cancer patients (BOSOM)	Marjanka Schmidt	other	12/12/2007 (29/01/2018)
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
N12OLG	High-dose alkylating chemotherapy in oligo-metastatic breast cancer harboring homologous recombination deficiency (OLIGO)	Gabe Sonke	III	03/07/12
N13ORB	Olaparib dose escalation combined with radiotherapy in patients with inoperable breast cancer	Gabe Sonke	I	23/08/13
N14MLS	Pilot for high-resolution SPECT imaging of breast cancer lumpectomy specimens for 3D identification and quantification of resection margins	Wouter Vogel	pilot	24/07/2014 (31/10/2018)
N15CGC	A comparison of a hybrid compact gamma camera with planar lymphoscintigraphy to simplify the SN procedure (Xstrahl)	Marcel Stokkel	other	14/04/2015 (31/10/2018)
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-trial	Marleen Kok	II	10/09/15
N16MIC	Minimally Invasive Complete Response Assessment of the breast after neoadjuvant chemotherapy (MICRA)	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	other	02/02/2017 (31/10/2018)
N16PRB	Pre-operative Breast Irradiation (PROBI)	Astrid Scholten	I/II	18/04/17

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N16SEN	Simplifying the sentinel node procedure in breast cancer using a portable gamma camera in order to replace conventional preoperative lymphatic mapping (SENTIMAP)	Marcel Stokkel	other	06/07/17
N18CPB	Ervaren beperkingen ten gevolge chronische pijn na borstkanker: een kwalitatieve studie naar het perspectief van de patiënt	Kisten Nienhuys	other	25/04/18

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	07/01/2016 (31/10/2018)
E1409	A Prospective Colorectal Liver Metastasis Database with an Integrated Quality Assurance Program	Theo Ruers	other	13/01/2016 (31/10/2018)
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	A randomized trial of dose escalation in definitive chemoradiotherapy for patients with oesophageal cancer	Berthe Aleman	III	12/02/13
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
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 (DCCG)	Cecile Grootscholten	III	09/06/15
M14NEC	Phase II Study of cisplatin and everolimus in patients with metastatic or unresectable neuroendocrine carcinomas (NEC) of extrapulmonary origin	Margot Tesselaar	II	10/02/16
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	30/04/2015 (02/01/2018)
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
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 (BMS-936558)	Jan Paul de Boer	I/II	27/10/2015 (06/11/2018)
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

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
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		26/06/2015 (08/05/2018)
M16BAC	A phase II open-label study with the anti-PDL1 Atezolizumab monoclonal antibody in combination with Bevacizumab in patients with advanced chemotherapy resistant colorectal cancer and MSIlike molecular signature	Neeltje Steeghs	II	19/12/17
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)	Neeltje Steeghs	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
M16EPS	The European Polyp Surveillance study (EPoS) Two randomized controlled trials and an observational cohort study (EPoS I/II/III)	Monique van Leerdam	other	29/03/17
M16INC	Intensive therapy for esophageal anastomotic strictures (INCA)	Jolanda van Dieren	II	12/04/17
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)	Neeltje Steeghs	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	20/04/2017 (04/12/2018)
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	Neeltje Steeghs	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
M16TGA	Phase I/II study with galunisertib combined with chemotherapy regimens in patients with advanced chemotherapy resistant colorectal cancer and a TGFbeta signature (MoTriColor1) (EORTC1615)	Neeltje Steeghs	I/II	16/05/18
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
M16VIB	A phase II study of vinorelbine in advanced BRAF-like colon cancer (EORTC1616) (MoTriColor2)	Neeltje Steeghs	II	02/02/18
M16WAS	Multicentre evaluation of the "wait-and-see" policy for complete responders after chemoradiotherapy for rectal cancer	Geerard Beets	other	24/02/17

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N17BNI	An Open-label Phase 1b/2 Study of Binimetinib Administered in Combination with Nivolumab or Nivolumab Plus Ipilimumab in Patients with Previously Treated Microsatellite-stable (MSS) Metastatic Colorectal Cancer with RAS Mutation	Neeltje Steeghs	I/II	17/08/18
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 - a prospective obeservational cohort study (PLCRC)	Geerard Beets	IV	22/08/17
M17HCR	Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases- a feasibility study (pump)	Koert Kuhlmann	pilot	13/02/18
M17OFP	A Multicentre Phase II Study of AZD1775 plus Chemotherapy in Patients with Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Frans Opdam	II	02/01/2018 (21/06/2018)
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	19/01/2006 (29/11/2017)
M18PIE	Preoperative Image-guided Identification of Response to neoadjuvant chemoradiotherapy in Esophageal cancer (PRIDE trial)	Marcel Verheij		31/05/18
M18SAN	Surgery As Needed for Oesophageal cancer: Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer (SANO)	Johanna van Sandick	III	25/06/18
M18SPO	The (ir)relevance of WHO criterion 2 for the diagnosis of Serrated Polyposis Syndrome	Monique van Leerdam	other	29/11/18
N12INT	Pilot study to evaluate the tumor-reactiviity of infiltrating T cells in human malignancies	Wouter Scheper	pilot	05/09/12
N13NAV	IImage-guided navigation during abdominal surgery (NAVIGATION 1)	Theo Ruers	pilot	17/10/13
N13OME	Organ motion and early tumor response measurement during chemoradiotherapy for esophageal cancer	Francine Voncken	other	17/01/2014 (07/09/2018)
N14ITO	Immunogenicity of Tumor Organoids, a feasibility study	Emile Voest	other	22/07/14
N14RCS	In vivo identification of rectum and coloncarcinoma during surgery using optical spectroscopy techniques (ColoSpect)	Theo Ruers	other	31/07/14
N14SNS	Selecting cancer patients for treatment using Tumor Organoids (SENSOR)	Emile Voest	other	16/08/16
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	23/05/2016 (04/12/2018)
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 (NICHE trial)	Myriam Chalabi	other	20/01/17

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
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
N17PND	Neoadjuvant capecitabine, oxaliplatin, docetaxel and atezolizumab in non-metastatic, resectable gastric and GE-junction cancer (PANDA trial)	Myriam Chalabi	II	27/02/18
N18ULN	Ultrasound-based navigation during liver surgery	Theo Ruers	other	10/08/18

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 (ENGOT-EN2-DGCG)	Hans Trum	III	24/08/16
M05PPO	Proteomic patterns in blood and tissue of ovarian cancer patients	Willemien van Driel	other	12/01/2006 (02/01/2018)
M07RCV	Phase II study of definitive radiochemotherapy for locally advanced squamous cell cancer of the vulva: an efficacy study	Baukelien van Triest	II	26/06/2007 (14/11/2018)
M10MKO	Phase II and pharmacological study with WEE-1 inhibitor MK-1775 combined with carboplatin in patients with p53 mutated epithelial ovarian cancer	Frans Opdam	II	08/07/10
M11CIR	Charting of immune reactivity against HPV in patients with HPV-induced (pre-) malignant lesions (Circle 2)	Gemma Kenter	other	05/04/2012 (9/04/2018)
M14BBB	The Blood-Belly Barrier (tripleB)	Christianne Lok	nvt	03/05/16
M14SCM	Subcellular components and multi-drug resistance in epithelial ovarian carcinoma	Juliette van Baal	other	28/04/2016 (06/11/2018)
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	20/10/2015 (18/07/2018)
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	27/10/2015 (06/11/2018)
M15PAG	Topical 5% imiquimod cream for vulvar Paget's Disease: clinical efficacy, safety and immunological response (PAGET)	Marc van Beurden	other	20/11/2015 (31/10/2018)
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 an ovarian mass (HE4 prediction)	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	30/06/2016 (08/10/2018)
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

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
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
M17CPF	Neo-Adjuvant Chemotherapy and Conservative Surgery in Cervical Cancer to Preserve Fertility (NEOCON-F)	Nienke van Trommel	II	04/12/18
M17EBR	Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive Brachytherapy in locally advanced Cervical cancer (EMBRACE-II)	Monique Bloemers	other	04/06/18
M17GINC	The state of the (sentinel) lymph node microenvironment in patients with cancer of the cervix (GINA-Cervix)	Henry Zijlmans	other	28/02/18
M17GINV	The state of the (sentinel) lymph node microenvironment in patients with HPV-positive and HPV-negative cancer of the vulva (GINA-Vulva)	Henry Zijlmans	other	28/02/18
M17GSC	GERiatric Screening in the treatment of elderly patients with Ovarian Carcinoma (GERSOC)	Hans Trum	other	07/06/18
M17MRO	Clinical impact of dedicated MR staging of ovarian cancer	Max Lahaye	other	17/04/18
M17PDV	Physical Activity and Dietary intervention in OVArian cancer (PADOVA): a RCT evaluating effects on body composition, physical function, and fatigue	Willemien van Driel	other	01/05/18
M17SNX	A prospective observational trial on sentinel lymph node biopsy in patients with early stage cervical cancer (Sentix)	Hans Trum	other	22/10/18
M18CRA	Cancer risk assessment in women with vulvar intraepithelial neoplasia. Historic cohort study (part I) + Prospective study (part 2)	Marc van Beurden	other	06/11/18
M18KZH	Ontwikkeling option grid/keuzehulp t.b.v. behandeling gevorderd ovariumcarcinoom	Willemien van Driel	other	31/07/18
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
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 (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
HEAD AND NECK				
M11ART	Adaptive and innovative radiation treatment for improving cancer treatment outcome (ARTFORCE)	Olga Hamming-Vrieze	II	20/12/11
M14PAR	TachoSil patch application as replacement of closed suction wound drainage by parotid gland surgery: a prospective study	Fons Balm	other	22/01/15
M15CRH	Dutch randomized multicenter trial COmparing twO PalliativE RAdiaTION schemes for incurable head and neck cancer (COOPERATION)	Abrahim Al-Mamgani	III	12/11/2015 (01/06/2018)
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	27/10/2015 (06/11/2018)
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)	Sofie Wilgenhof	I	09/09/2015 (08/11/2018)
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	29/09/2017 (27/02/2018)
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) (CheckMate 714)	Margot Tesselaar	II	19/04/2017 (12/03/2018)
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
M17MOV	Optimising physical fitness in patients receiving chemo radiotherapy for head and neck cancer: a feasibility study (Move-FIT)	Martijn Stuiver	other	01/03/18
M18TUN	Validation of TUNE criteria in patients treated with chemoradiotherapy using cisplatin for head and neck squamous cell carcinoma (TUNE)	Lotje Zuur	other	15/05/18
N05HME	De korte termijn invloed van een Heat and Moisture Exchanger op de endotracheale temperatuur en luchtvochtigheid bij gelaryngectomeerden	Michiel van den Brekel	other	01/09/2005 (24/10/2018)
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
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 (IMRAD)	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
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

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
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 (SHAFE study)	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	02/12/2016 (14/08/2018)
N16EMS	The effectiveness of device-driven Expiratory Muscle Strength Training (EMST) in total laryngectomy patients; a pilot study	Michiel van den Brekel	pilot	19/04/2017 (01/03/2018)
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	04/10/2017 (29/10/2018)
N16QPS	Quality check of PSMA PET for imaging salivary gland toxicity	Wouter Vogel	pilot	02/09/2016 (31/10/2018)
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
N17LFO	Effectiveness of lipofilling in patients with oropharyngeal dysfunction (speech and/ or swallowing) after treatment for head and neck cancer	Ludi Smeele	other	19/12/17
N17SDC	Salivary duct carcinoma: treatment outcomes of 14 patients in the Netherlands Cancer Institute	Martin Klop	other	10/11/2017 (01/11/2018)
N17SPE	The timed Swallowing Performance EATing and drinking (SPEAT) test to objectify dysphagia in head and neck cancer patients	Ludi Smeele	other	24/04/18
N17SSF	Prospective assessment of swallowing and speech function 10 years after preventive swallowing rehabilitation and chemoradiotherapy for head and neck cancer	Ludi Smeele	other	09/03/18
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
N18EMT	Active and passive elasticity measurements of the tongue using in vivo measurement techniques	Ludi Smeele	other	10/08/18
N18HSP	Are circulating hematopoietic stem and progenitor cells a potential biomarker for therapy response and disease progression in patients with squamous cell carcinoma of the head and neck?	Lotje Zuur	other	06/07/18

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N18PCN	Prospective study Evaluating CtDNA as a biomarker for treatment failure in head and Neck squamous cell carcinoma (PECAN)	Abrahim Al-Mamgani	other	15/05/18
N18VOQ	Voice quality and voice related quality of life in patients treated with totallaryngectomy; A prospective data collection.	Klaske van Sluis	other	20/02/18

LUNG

C15MET	Compassionate use programma crizotinib voor patienten met een MET mutatie	Michel van den Heuvel	other	28/01/2015 (15/11/2018)
C15RET	Compassionate use programma sunitinib voor patienten met een RET mutatie (RET003)	Michel van den Heuvel	other	27/01/2015 (28/11/2018)
C15ROC	Compassionate use Rociletinib	Egbert Smit	other	09/12/2015 (31/10/2018)
C17LOR	Compassionate use programma lorlatinib	Michel van den Heuvel	other	08/03/17
E1205	EORTC randomized phase II study of pleurectomy/ decortication (P/D) preceded or followed by chemotherapy in patients with early stage malignant pleural mesothelioma	Paul Baas	II	15/03/18
M11LUN	A project of European Thoracic Oncology Platform (lungscape)	Paul Baas	other	29/12/2011 (06/11/2018)
M12PHA	Prophylactic Cranial Irradiation with or without hippocampal avoidance in SCLC: a randomized phase III study	José Belderbos	III	27/03/2013 (19/03/2018)
M13DAP	Combination of dacomitinib and PD-0325901 in advanced KRAS mutation positive colorectal, non-small cell lung and pancreatic cancer	Frans Opdam	I	15/01/2014 (21/08/2018)
M13N19	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 (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	Frans Opdam	I/II	19/05/15
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 Theelen	II	09/06/15
M14LTK	Phase I/II study with lapatinib plus trametinib in patients with metastatic KRAS mutant colorectal, non-small cell lung and pancreatic cancer	Frans Opdam	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	12/09/2014 (01/11/2018)
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 (PEMBRO-RT)	Paul Baas	II	03/07/2015 (03/04/2018)
M14TUM	Tumor organoids: feasibility to predict sensitivity to treatment in cancer patients (TUMOROID trial).	Emile Voest	pilot	22/07/14

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
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 (CINC280A2201)	Egbert Smit	II	15/09/15
M15LEM	Lung cancer Early Molecular Assessment trial (LEMA)	Sjaak Burgers	other	29/06/16
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
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	12/11/2015 (31/10/2018)
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	22/05/2017 (31/07/2018)
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
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	07/07/2017 (15/02/2018)
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)	Neeltje Steeghs	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, ROSI 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
M17DNM	A randomized, open-label phase II/III study with dendritic cells loaded with allogenic tumor cell lysate (PheraLys) in subjects with mesothelioma as maintenance treatment (MesoPher) after chemotherapy. (DENIM)	Paul Baas	II	15/11/18
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) (caspian)	Egbert Smit	III	10/05/2017 (04/06/2018)
M17FNN	[18]F-PD-L1 PET/CT to predict response to Nivolumab in patients with NSCLC	Joop de Langen	other	26/10/18
M17IMG	[89]Zr-pembrolizumab-PET imaging in patients with locally advanced or metastatic melanoma or nonsmall cell lung cancer	John Haanen	pilot	23/07/18
M17IPL	Repeatability of 18F FDG/CT and immunological profiling of lymph nodes in NSCLC	Joop de Langen	pilot	23/01/18
M17PPD	PDR001 in combination with platinum-doublet chemotherapy in PD-L1 unselected metastatic NSCLC patients	Sjaak Burgers	I	02/11/17
M17RLC	Reirradiation for recurrent lung cancer in the thorax: overall survival, local control, and toxicity: a phase 2 trial	Joost Knegjens	II	07/11/18
M17ZML	Companion biomarker development for MEDI4736 treated non-small-cell lung cancer patients using [89]Zirconium-labeled MEDI4736 -a feasibility study	Joop de Langen	pilot	13/06/18

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
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	14/08/2017 (26/06/2018)
M18ACX	Phase II study of afatinib in combination with cetuximab in EGFR exon 20 insertion positive non-small-cell lung cancer	Joop de Langen	II	11/12/18
M18BNI	An Exploratory Study of the Biologic Effects and biomarkers of Nivolumab Combined With Ipilimumab in Subjects With Treatment-Naive Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) (CheckMate 592)	Joop de Langen	II	23/10/18
M18DSN	A phase 2, multicenter, open-label, 2-cohort study of trastuzumab deruxtecan (DS-8201a), an anti-HER2 antibody drug conjugate (ADC), for HER2-overexpressing or-mutated, unresectable and/or metastatic non-small cell lung cancer	Egbert Smit	II	14/11/18
M18SRP	Combining SBRT and immunotherapy in early stage NSCLC patients planned for surgery: exploring safety and immunological proof of principle	Joop de Langen	other	25/05/18
N11ORL	Olaparib dose escalating trial in patients treated with radiotherapy with or without daily dose cisplatin for locally advanced non-small lung cancer	Baukelien van Triest	I	21/02/2012 (01/02/2018)
N12LON	Longitudinal analysis of lung cancer-specific immunity in stage III and IV lung cancer patients	Michel van den Heuvel	other	18/01/2013 (15/11/2018)
N12PRO	Pharmacogenomic profiling of short-term cultures of malignant pleural mesothelioma	Josine Quispel	other	21/09/2012 (19/12/2017)
N13FPB	Fluid phase biopsy (circulating tumour DNA and serum tumour markers) in patients with non-small cell lung cancer	Sjaak Burgers	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
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/16
N17DTL	A Phase Ib, Open-label, Single-center study to assess the safety of cancer-immunotherapy induction with Tremelimumab and Durvalumab prior to Chemoradiotherapy and/or Resection in the treatment of locally advanced NSCLC (Induction-1)	Willemijn Theelen	I	05/10/18
N18NUA	NUtritional Assessment in Non-small Cell lung cancer patients (NUANCE)	Martijn Stuiver	other	29/06/18

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	21/10/2014 (31/10/2018)
M17MIW	A Phase Ib, open label, multicenter study of the safety and efficacy of MIW815 (ADU-S100) administered by intratumoral injection with PDR001 to patients with advanced/metastatic solid tumors or lymphomas	Neeltje Steeghs	I	02/02/18
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

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
LYMPHOMA - NON-HODGKIN'S				
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)	Frans Opdam	I	27/10/16
M17MIW	A Phase Ib, open label, multicenter study of the safety and efficacy of MIW815 (ADU-S100) administered by intratumoral injection with PDR001 to patients with advanced/metastatic solid tumors or lymphomas	Neeltje Steeghs	I	02/02/18
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	12/05/2014 (31/10/2018)
C18CEM	NPP programma cemiplimab	John Haanen	other	09/11/18
E1208MG	Prospective registry of Sentinel Node (SN) positive melanoma patients with minimal SN tumor burden who undergo Completion Lymph Node Dissection (CLND) or Nodal Observation (Minitub)	Alexander van Akkooi	other	23/04/15
M11TCR	Feasibility study using T-cel receptor gene therapy in metastatic melanoma	John Haanen	II	17/04/2012 (30/10/2018)
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	27/10/2015 (06/11/2018)
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)	Sofie Wilgenhof	I	09/09/2015 (08/11/2018)
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
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
M17IMG	[89]Zr-pembrolizumab-PET imaging in patients with locally advanced or metastatic melanoma or nonsmall cell lung cancer	John Haanen	pilot	23/07/18
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
M17PTS	Towards patient-tailored cancer immunotherapy supported by a multifaceted predictive signature composed of integrative omics and molecular imaging (POINTING)	John Haanen	other	12/11/18

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
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	21/08/2017 (03/04/2018)
M18CAP	A Phase III, Open-Label, Multicenter, Two Arm, Randomized Study to Investigate the Efficacy and Safety of Cobimetinib Plus Atezolizumab Versus Pembrolizumab in Patients With Previously Untreated Advanced BRAF V600 Wild-Type Melanoma (imspire)	Christian Blank	III	12/03/2018 (08/11/2018)
M18IDO	A Phase 3, Randomized, Double-blind Study of BMS-986205 Combined with Nivolumab versus Nivolumab in Participants with Metastatic or Unresectable Melanoma that is Previously Untreated	Christian Blank	III	15/03/2018 (20/4/2018)
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	29/08/2006 (19/12/2017)
N13GEN	Regulation of skin tumorgenesis by integrin alpha3beta1	Arnoud Sonnenberg	other	27/11/13
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	31/03/2016 (23/08/2018)
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	Sofie Wilgenhof	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 (BCC-COMI)	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)	Marianne Crijns	other	19/04/17

MISCELLANEOUS

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	27/06/2016 (31/10/2018)
M15GRA	Prospective registration study on growth behavior of aggressive fibromatosis without therapeutic intervention (GRAFITI)	Frits van Coevorden	other	15/09/2015 (12/12/2018)
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)	Sofie Wilgenhof	I	09/09/2015 (08/11/2018)
M15TLP	A multicenter, long-term extension study to further evaluate the safety and tolerability of Telotristat Etiprate (LX1606). TELEPATH	Margot Tesselaar	III	16/10/2015 (01/07/2018)

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
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	21/04/2017 (31/10/2018)
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
M17CLE	CLE in diagnosing Pleural Malignancies, a comparison with pathology	Paul Baas	other	16/08/17
M17CMT	A Randomized, Double-blind Study to Evaluate the Efficacy and Safety of Cabozantinib (XL184) at 60 mg/Day Compared to 140 mg/Day in Progressive, Metastatic Medullary Thyroid Cancer Patients (EXAMINER)	Jan Paul de Boer	IV	15/05/18
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
N14SRO	Somatostatin receptor expression and occupancy during lanreotide therapy	Marcel Stokkel	other	12/09/2014 (2/02/2018)
N15HNT	Hepatic NET metastasis embolization biomarker evaluation (HEP-NET)	Margot Tesselaar	other	13/01/16
N17ICO	Position stability during radiosurgery of brain tumours	Gerben Borst	other	18/01/18
N17MRD	Healthy volunteer imaging techniques development for motion management in MR-guided adaptive radiotherapy	Gabe Sonke	other	09/11/17
M18ORG	Modeling neuroendocrine tumors using adult stem cellderived organoids (NET organoids)	Margot Tesselaar	other	23/11/18

SOFT TISSUE / OSTEOSARCOMA

E1202	Phase II trial of cabazitaxel in metastatic or inoperable locally advanced dedifferentiated liposarcoma	Neeltje Steeghs	II	07/11/18
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	20/07/2016 (19/12/2017)
E1402	International randomised controlled trial for the treatment of newly diagnosed Ewing's sarcoma family of tumours (Euro Ewing 2012)	Martijn Kerst	other	18/01/18
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
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 (nick name)	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: (GIST-TDM)	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 (SSG XXII)	Neeltje Steeghs	III	04/07/17
M18QUE	The impact of the diagnostic trajectory in sarcoma patients on stage at diagnosis, primary treatment, clinical outcome and quality of life (Quest)	Rick Haas	other	05/06/18
N10DMY	Dose reduction of preoperative radiotherapy in Myxoid liposarcomas (DOREMY)	Rick Haas	II	15/12/10
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	18/08/2011 (29/10/2018)
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
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	18/11/2016 (07/05/2018)
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)	Sofie Wilgenhof	I	09/09/2015 (8/11/2018)
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). WMO-protocol	André Bergman	other	30/10/15
M15VPM	A phase I/II open label clinical trial assessing safety and efficacy of intravesical instillation of VPM1002BC in patients with recurrent non-muscle inasive bladder cancer after standard BCG therapy	Kees Hendricksen	II	18/01/18

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
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
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) (arches)	Henk van der Poel	III	23/12/2016 (13/12/2017)
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 (Fingerprint)	Martijn Kerst	other	07/10/16
M16HFL	Hypofractionated Focal Lesion Ablative Microboost in prostatE cancer (Hypo-FLAME)	Floris Pos	other	13/07/2016 (16/08/2018)
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	14/03/2017 (12/10/2018)
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 trial)	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	19/04/2017 (22/03/2018)
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
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
M17EPC	A Phase 3 Randomized, Double-Blind Clinical Study of Pembrolizumab + Epacadostat vs Pembrolizumab + Placebo as a Treatment for Recurrent or Progressive Metastatic Urothelial Carcinoma in Patients who have Failed a First-Line Platinumcontaining Chemotherapy Regimen for Advanced/Metastatic Disease (KEYNOTE-698/ECHO-303)	Michiel van der Heijden	III	12/04/18
M17EPP	A Phase 3 Randomized, Double-Blind Trial of Pembrolizumab (MK-3475) in Combination with Epacadostat (INCB024360) or Placebo in Participants with Cisplatin-ineligible Urothelial Carcinoma (KEYNOTE-672/ECHO-307)	Michiel van der Heijden	III	02/02/18
M17LUC	A randomized international clinical trial on lymphadenectomy in urothelial carcinoma in the renal pelvis and ureter (DaBlaCa)	Kees Hendricksen	other	15/01/18
M17MDN	A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) in Combination with Durvalumab versus Nivolumab Monotherapy in Subjects with Select Advanced Malignancies	Hans van Thienen	I/II	13/02/18

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M17MRP	Risk assessment and MR imaging in prostate cancer diagnosis: an impact analysis (MR PROPER)	Henk van der Poel	other	23/01/18
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 (CheckMate 90)	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 (PABLO)	Wim Groen	other	19/10/17
M17PRO	Prostate cancer follow-up care in secondary and primary health care (PROSPEC study)	Lonneke van de Poll - Franse	other	12/04/18
M17RCU	A randomized, open label, multicenter Phase 3 study to evaluate the efficacy and safety of Rogaratinib (BAY 1163877) compared to chemotherapy in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy (Fort-1)	Michiel van der Heijden	III	25/04/18
M17REB	REduce BIAdder CAncer REcurrence in patients treated for upper urinary tract urothelial carcinoma (REBACARE Trial)	Kees Hendricksen	other	24/11/17
M18CLR	A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma (CLEAR)	Hans van Thienen	III	23/10/18
M18ERC	European Active Surveillance of Renal Cell Carcinoma study (EASE RCC study)	Axel Bex	other	07/08/18
M18IMB	An open label, multicenter extension study in patients previously enrolled in a Genentech- and/or F. Hoffmann-La Roche LTD-sponsored Atezolizumab study (IMBrella)	Michiel van der Heijden	other	03/10/18
M18JNJ	An Open-label, Multicenter, Phase 1b Study of JNJ-63723283, a PD-1 inhibitor, administered in combination with apalutamide in subjects with metastatic castration-resistant prostate cancer	André Bergman	I/II	29/11/18
M18NBB	A Phase 2, Randomized, Open-label Study of Nivolumab or Nivolumab/BMS-986205 Alone or Combined with Intravesical BCG in Participants with BCG-Unresponsive, High-Risk, Non-Muscle Invasive Bladder Cancer	Michiel van der Heijden	II	16/11/18
M18RAP	Cost-Effectiveness of Robot-Assisted Prostatectomy versus laparoscopic prostatectomy a 5 year multi-institutional study of PROMs from a Dutch perspective (CERA-PRO)	Henk van der Poel	other	12/04/18
M18TGC	Sentinel Lymph Node Procedure in Testicular Germ Cell Tumour (SENATOR)	Simon Horenblas	other	31/08/18
N08SNR	Site and distribution of sentinel lymph nodes in renal cell carcinoma, a phase II study	Axel Bex	II	19/03/2009 (1/02/2018)
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	08/05/2013 (31/10/2018)
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	18/12/2013 (31/10/2018)
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

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
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	20/04/2015 (06/09/2018)
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
N15PEN	Chemoradiation in the treatment of loco-regionally advanced Penile Cancer	Floris Pos	other	31/08/15
N16DIP	Clinical evaluation of a prototype drop-in gamma probe for (robot-assisted) laparoscopic sentinel node biopsy	Henk van der Poel	other	18/12/17
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/16
N17DIP	Clinical pharmacokinetics of intravenous docetaxel in patients with castration-resistant prostate cancer and non-castration-resistant prostate cancer	André Bergman	other	27/12/17
N17JAV	Neoadjuvant AXITINIB plus AVELUMAB for patients with localized RCC and a moderate to high risk of recurrence. A phase II study (NEOJAVALIN)	Axel Bex	II	16/05/18
N17NAB	Phase 1B Study to assess safety and efficacy of Neo-Adjuvant Bladder Urothelial Carcinoma COmbination-immunotherapy (NABUCCO/CA209-9Y4)	Michiel van der Heijden	I	04/12/17
N17PSI	Increasing pazopanib exposure by splitting intake moments	Neeltje Steeghs	IV	22/05/17
N18ISG	Inhibition of salivary gland function to reduce uptake and toxicity of PSMA-ligands	Wouter Vogel	pilot	28/05/18
N18PER	PEnile cancer Radio- and Immunotherapy Clinical Exploration Study – a Phase 1B study of atezolizumab with or without radiotherapy in penile cancer.(PERICLES)	Michiel van der Heijden	I	21/09/18

Invited speakers

Samuel Aparicio, Vancouver, Canada
Decoding cancer evolution at single cell resolution

Ulrich auf dem Keller, Lyngby, Denmark
Protease network degradomics – deciphering protease signaling pathways in normal and diseased skin

Maria Barna, Stanford, United States
Ribosome diversity: Implications for translation of the genetic code & organismal life

René Bernards, Amsterdam, The Netherlands
Bringing scientific discoveries to the clinic quickly

Amy Berrington, Bethesda, United States
Second breast cancers in the US Childhood Cancer Survivors Study: radiotherapy, chemotherapy and breast cancer sub-type

Eveline Bleiker, Amsterdam, The Netherlands
DNA testing for hereditary cancer: psychosocial issues to consider

Jef Boeke, New York, United States
Engineering genomes, karyotypes, and the dark matter of the human genome

Jannie Borst, Amsterdam, The Netherlands
Enticing T cells to attack cancer: the importance of CD4+ T cell help

Boudewijn Burgering, Utrecht, The Netherlands
Metabolic interplay of normal and cancer stem cells with their niche

Jeffrey Chao, Basel, Switzerland
Imaging the lives of mRNAs in space and time

Caroline Dean, Norwich, United Kingdom
Epigenetic switching and antisense transcription

Anne Dejean, Paris, France
Chromatin roles for SUMO

Nynke Dekker, Delft, The Netherlands
Chromatin dynamics and eukaryotic replication studied at the single-molecule level

Daniel Durocher, Toronto, Canada
Charting the genetic architecture of the DNA damage response

Daniel Gerlich, Vienna, Austria
Mitotic chromosome mechanics

Michiel van der Heijden, Amsterdam, The Netherlands
Rapidly evolving treatment landscape in urothelial cancer: let's make it more personal

Mathias Heikenwälder, Heidelberg, Germany
On the role of immune cells in liver cancer

Steven Henikoff, Seattle, United States
Structural epigenomics: Precision mapping of the chromatin landscape

Ping-Chih Ho, Lausanne, Switzerland
Cold tumors, you are fired up!

Ben Lehner, Barcelona, Spain
Mutations and their interactions in individuals

Christian Ottensmeier, Southampton, United Kingdom
Genomic assessment of cancer infiltrating immune cells to guide treatment decisions

Caetanos Reis e Sousa, London, United Kingdom
Dendritic cells in immunity to infection and cancer

Alfred Schinkel, Amsterdam, The Netherlands
Of mice and drugs

David Solit, New York, United States
Defining the actionable genome

Laura van 't Veer, San Francisco, United States
Molecular heterogeneity guides adaptive treatment for breast cancer

Stephen West, London, United Kingdom
A Life on Holliday

Jing Yang, San Diego, United States
Epithelial-mesenchymal plasticity in carcinoma metastasis

Jonathan Yewdell, Bethesda, United States
T cell immunodominance

Omer Yilmaz, Cambridge, United States
Dietary control of intestinal stem cells in physiology and disease

Research projects supported by the Dutch Cancer Society

Principal investigator	Number of projects	Title	Started	Ended / Ends
Aaronson, N.K.	NKI 2014-6788	A randomized controlled trial of internet-based cognitive behavioral therapy for breast cancer patients with climacteric symptoms	01/02/15	31/01/19
Agami, R.	11574	Exploring the role of serine metabolism adaptations in platinum resistant high grade serous ovarian cancer	01/09/18	31/08/22
Agami, R.	10315	Diricore, a platform for the discovery of novel amino acid vulnerabilities in agg ressive cancer	01/01/17	31/12/20
Agami, R.	11037	Exploiting proline vulnerability for cancer therapy	01/11/17	31/10/21
Akkari, L.	10658	Improving the effects of standard of care therapy in glioma by modulating tumor-associated macrophages and microglia functions	01/06/17	31/05/22
Al-Mamgani, A.	NKI 2015-8054 C	Dutch randomized multicenter trial COmparing twO PalliativE RAdiaTION schemes for incurable head and neck cancer	18/12/15	18/12/19
Amant, F.C.H.	10094	Cancer tReAtment During pregnancy: from fetaL safety to maternal Efficacy	01/05/17	30/04/21
Amant, F.C.H.	11132	Postpartum breast cancer diagnosed during involution: a distinct entity with unique clinicopathological, molecular and immunological features?	01/01/18	31/12/21
Baas, P.	NKI 2015-7823	Defining new and personalized treatment options for patients with malignant mesothelioma	01/01/16	31/12/19
Beets-Tan, R.G.H.	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	30/09/21
Beets-Tan, R.G.H.	10611	Radiomics for the prediction of response to neoadjuvant treatment on rectal carcinoma	01/10/17	30/09/19
Beets, G.L.	UM 2015-7738	Multicentre evaluation of the wait-and-see" policy for complete responders after chemoradiotherapy for rectal cancer	01/10/15	30/09/21
Beets, G.L.	10513	Datamanagement for project Multicenterevaluation of the wait-and-see policy for complete responders after chemoradiotherapy for rectal cancer	01/09/17	31/08/21
Belderbos-Candiff, J.S.A.	2013-6096	Prophylactic Cranial Irradiation with or without hippocampal avoidance in SCLC: a randomized phase III study	01/03/14	30/06/18
Bernards, R.	NKI 2012-5401	Finding genetic dependencies in cancer: the missing link in personalized medicine	01/01/13	31/12/18
Bernards, R.	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	31/10/19
Bernards, R.	2013-5859	Engineering a liver cancer model on a chip	01/09/17	31/08/19
Bleiker, E.M.A.	2014-6944	Het informeren van familieleden met een hoog risico op kanker: ondersteuning van erfelijkheidsadviesvragers bij familiecommunicatie door middel van een digitaal stamboomportaal	01/01/15	31/01/18
Bleiker, E.M.A.	NKI 2014-7031	Choices in breast surgery and reconstruction: implementation and testing of a web-based psycho-educational intervention to facilitate decision making	01/11/15	31/10/20
Bleiker, E.M.A.	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	31/07/20
Borst, G.R.	10902	New era of radiosensitization by modulating radiosensitizing agents during RT	01/02/18	31/01/23

Principal investigator	Number of projects	Title	Started	Ended / Ends
Borst, J.G.	NKI 2013-5951	Enhancing the anti-tumour effecacy of immunotherapy by localized radiotherapy	01/05/14	30/04/20
Borst, J.G.	11079	CytotoxicTcell programming atthe dendritic cell interface	01/09/17	31/08/21
Borst, J.G.	10894	Achieving synergy between radiotherapy and immunotherapy to increase control of metastatic cancer	01/02/18	31/01/23
Borst, J.G.	10764	Inducing and sustaining anti-tumor immunity by chemo-radiotherapy	01/01/18	31/12/19
Boven, van H.H.	2013-5869	Fellowship Hugo Horlings	01/08/14	31/07/18
Boven, van H.H.	10510	Genetic properties of breast carcinomas associated with cancer-immune interactions	01/11/17	31/10/21
Brummelkamp, T.R.	11352	Identification and validation of genetic factors that determine sensitivity to Weel inhibition in high-grade ovarian cancer and related cancers	01/10/18	30/09/23
Brummelkamp, T.R.	NKI 2015-7609	A mutation-based approach to examine the principles of synthetic lethality in human cells	01/04/16	31/03/20
Driel, van W.J.	11540	Primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for stage III ovarian cancer: a randomized phase III trial	01/10/18	30/09/25
Driel, van W.J.	2011-5149	Dutch Gynaecological Oncology Group	01/02/12	31/12/18
Driel, van W.J.	2006-4176 CT	Phase III randomised clinical trial for stage III ovarian carcinoma randomising between secondary debulking surgery with or without hyperthermic intraperiotoneal chemotherapy	14/03/07	01/11/18
Faller, W.J.	10535	The role of translation elongation in models of intestinal cancer	01/07/17	30/06/22
Haanen, J.B.A.G.	2013-5924	Feasibility study using T-cel receptor gene therapy in metastatic melanoma	05/02/13	05/02/19
Haanen, J.B.A.G.	10034	Towards patient-tailored cancer immunotherapy supported by a multifaceted predictive signature composed of integrative omics and molecular imaging	01/09/17	31/08/21
Haas, R.L.M.	NKI 2015-8069	Dose Reduction of preoperative radiotherapy in Myxoid liposarcomas	01/01/16	31/12/19
Harten, van W.H.	NKI 2014-6078	Advanced Logistics Optimization of the Radiotherapy Treatment	01/02/15	31/01/20
Harten, van W.H.	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	31/08/20
Harten, van W.H.	10325	Does physical exercise during adjuvant cardiotoxic chemotherapy protect against cardiac injury among women with breast cancer?	01/09/17	31/08/20
Hauptmann, M.	10004	Statistical assessment of cancer risks from therapeutic radiation exposure incorporating the spatial distribution of radiation dose in the target organ	01/12/17	30/11/21
Hauptmann, M.		Novel statistical methods for efficient identification of biomarkers for personalized cancer treatment	01/09/17	31/08/21
Heide, van der U.A.	NKI 2013-5937	Quantitative multi-parametric MR imaging for tumor delineation in focal radiotherapy of prostate cancer	01/05/14	30/04/18
Heide, van der U.A.	2013-6311	Brachytherapy for rectal cancer: a better balance between tumor control and side effects	01/11/14	31/10/20
Heide, van der U.A.	10088	Focal escalation of the radiation dose to the tumor in prostate cancer	01/04/17	31/03/21

Principal investigator	Number of projects	Title	Started	Ended / Ends
Heijden, van der M.S.	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	31/05/20
Huijbers, I.J.G.	2017-8231	A facility for production and distribution of engineered mouse models for cancer research	01/01/18	31/12/20
Jacobs, H.B.	NKI 2012-5713	Exploring DNA-Damage Tolerance as a Drug-Target for Chemosensitization and a Mechanism of Chemoresistance	01/06/13	31/05/19
Jacobs, H.B.	10032	Precision CancerTherapy: Profiting from Tumor Specific Defects and Synthetic Lethality in the DNA Damage Tolerance System	01/03/17	28/02/21
Jacobs, H.B.	10796	Role of DNA Damage Tolerance Pathways in Genome Maintenance, Tissue Homeostasis, and Cancer Suppression	01/10/17	30/09/21
Jacobs, J.J.L.	10999	Mechanisms of DNA repair pathway control at DNA double-strand breaks and telomeres	01/10/17	30/09/21
Jonkers, J.M.M.	NKI 2014-6532	Tumor escape from radiotherapy: identification and targeting of the underlying mechanisms	01/08/14	31/07/18
Jonkers, J.M.M.	2014-7048	Ex vivo assays for selection of breast and ovarian cancer patients for PARP inhibitor tratment	01/09/15	31/08/20
Jonkers, J.M.M.	NKI 2015-7589	Cancer-associated fibroblasts as therapeutic targets in invasive lobular breast carcinoma	01/01/16	30/06/20
Jonkers, J.M.M.	NKI 2015-7877	Functional analysis of BRCA1 variants and domains to improve genetic counselling and treatment strategies	01/01/16	31/12/19
Jonkers, J.M.M.	2015-7835	Combatting therapy resistance by integrating genomic, transcriptomic and proteomic data from mouse models of invasive lobular breast carcinoma	01/01/17	31/12/20
Kok, M.	NKI 2015-7542	KWF fellowship	01/06/15	31/05/19
Kok, M.	10653	Mapping immunosuppressive cascades in breast cancer patients treated with immunotherapy	01/09/17	31/08/19
Kvistborg, P.	NKI 2015-7978	How checkpoint blockade alters the quality of tumor specific T cells	01/09/16	31/08/21
Leerdam, van M.E.	10274	Evaluation of optimal intervals for colonoscopy surveillance: a randomized trial	01/02/17	31/01/29
Leeuwen, van F.	11490	DOT1L as a druggable epigenetic writer in T cell programming and immunotherapy	01/12/18	31/05/19
Leeuwen, van F.	NKI 2014-7232	Epigenetic Pathways in Cancer Development and Treatment: Crosstalk between Conserved Histone Modifiers in T-cell Lymphoma	01/11/15	31/10/19
Leeuwen, van F.E.	NKI 2011-5270 A	A nationwide survivorship care program for adult (non-)Hodgkin lymphoma survivors	01/06/12	31/07/18
Leeuwen, van F.E.	10164	Favorable and unfavorable effects of risk-reducing salpingo-oophorectomy (RRSO) in women at high genetic risk of ovarian cancer	01/07/17	30/06/21
Leeuwen, van F.E.	10424	Cardiotoxicity and second cancer risk after treatment of aggressive B-cell Non-Hodgkin lymphoma	01/01/18	31/12/21
Leeuwen, van F.E.	NKI 2017-8237	The BETER-REFLECT biobank: A REsource For studies on Late Effects of CancerTreatment	01/02/18	31/01/22
Leeuwen, van F.E.	10933	A risk prediction tool for cardiovascular disease in breast cancer patients	01/12/17	31/08/21

Principal investigator	Number of projects	Title	Started	Ended / Ends
Leeuwen, van F.E.	VU 2017-8288	Psychosocial factors and cancer incidence: a pre-planned meta-analysis of the pSychosocial	01/12/17	30/11/21
Lenstra, T.L.	BUIT 2012-5349	Single cellanalysis of the sense-antisense transcriptional balance	01/12/16	30/11/18
Linn, S.C.	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	31/01/20
Linn, S.C.	2015-7808	Clinical Impact of Intratumor heterogeneity in metastatic breast cancer	01/04/16	31/03/19
Lohuizen, van M.M.S.	11700	Identifying and testing new intervention therapies for mesotheliomas	01/09/18	31/08/22
Lohuizen, van M.M.S.	NKI 2014-7208	Testing therapeutic responses to Polycomb inhibition in preclinical mouse models of Kras mutant lung cancer	01/07/15	30/06/19
Marchetti, S.	NKI 2013-6249	Safety, feasibility and cost-effectiveness of genotype- and phenotype-directed individualized dosing of fluoropyrimidines	01/09/14	31/08/20
Medema, R.H.	NKI 2014-6787	Determinants of cell fate after DNA damage	01/04/15	31/03/19
Medema, R.H.	NKI 2015-7742	Enhancing chromosome segregation errors in cancer therapy	01/07/15	30/06/19
Medema, R.H.	NKI 2015-7832	Exploring the vulnerabilities of chromosome unstable tumor cells	01/05/16	30/04/20
Meijer, G.A.	KWF 2013-6338	Molecular Stool test for postpolypectomie surveillance	01/07/15	30/06/19
Meijer, G.A.	KWF 2013-6025	Tumor-specific protein biomarkers for early detection of colorectal cancer	01/04/15	31/08/18
Meijer, G.A.	KWF 2014-6813	Identifying signaling pathways	01/09/15	31/08/19
Meijer, G.A.	2013-5885	DCR1 and its role in response of colorectal cancer patients to irinotecan treatment	01/04/15	31/10/19
Meijer, G.A.	NKI 2014-6635	Deciphering diagnostic and companion therapies for mesenchymal colorectal cancer	01/04/15	31/03/19
Meijer, G.A.	8166	Translational research IT (TraIT) in transition Health RI - Sustaining FAIR data stewardship support for translational cancer research	01/02/17	31/01/20
Meijer, G.A.	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	30/09/21
Opdam, F.L.	11352	Identification and validation of genetic factors that determine sensitivity to Weel inhibition in high-grade ovarian cancer and related cancers	01/10/18	30/09/23
Peeper, D.S.	2014-7241	In vivo cancer drug target discovery screens exploiting T cell immunity	01/09/15	31/08/19
Peeper, D.S.	NKI 2015-7595	Function-based unbiased discovery of clinically exploitable metabolic vulnerabilities of cancer cells	01/10/16	30/09/20
Peeper, D.S.	10425	Targeting phenotype switching as a therapy for melanoma	01/09/17	31/08/21
Peeper, D.S.	10304	Increasing drug holiday impact on therapy-refractory cancers for more durable responses	01/01/17	31/12/20
Perrakis, A.	10215	Membrane glycerophosphodiesterases: novel players in cell differentiation and cancer biology	01/01/17	31/12/20
Poll, van de L.V.	2015-7527	Psychosocial and physical problems and needs of adolescents and young adults (AYAs) with cancer: Towards comprehensive patient-centered care	01/10/18	01/08/20

Principal investigator	Number of projects	Title	Started	Ended / Ends
Poll, van de L.V.	NKI 2015-7932	A randomized study, PROstate cancer follow-up care in secondary and Primary health care	01/09/17	31/08/22
Ramshorst, van G.H.	2015-7506	Surgical, functional and reconstructive treatment of pelvic tumours - a multidisciplinary approach	01/06/16	30/11/18
Rheenen, van J.E.	11491	Mechanistic insight in the role of cell competition in growth of colorectal cancer liver metastases	01/01/19	31/12/22
Rheenen, van J.E.	2015-7838	Understanding the role of SOX4 in educating the mammary tumor niche: the potential for personalized therapeutic targeting	01/10/17	31/12/19
Rheenen, van J.E.	2013-5847	How to win or loose:The role of cell competion in tumor growth	01/10/17	31/12/18
Rheenen, van J.E.	10123	The intermediate filament network in glioma invasion	01/05/17	30/04/21
Riele, te H.P.J.	NKI 2014-6702	Replication stress in cancer: mechanisms and consequences for therapy	01/10/14	30/09/18
Riele, te H.P.J.	NKI 2014-7176	Development of prevention strategies for intestinal cancer in lynch syndrome using novel mouse models	01/08/15	31/07/19
Riele, te H.P.J.	10645	Investigation of variants of uncertain clinical significance for use in clinical practice	01/02/18	31/01/22
Riele, te H.P.J.	11074	Targeting replication rescue pathways	01/03/18	28/02/23
Rookus, M.A.	CANCER12-054-Tr	Development of a Comprehensive Risk Prediction Model for BRCA1 and BRCA2 mutation carriers	01/04/14	31/03/18
Rookus, M.A.	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	31/01/20
Rowland, B.D.	11665	SWI/SNF-mediated cohesin loading: A dual role in tumorigenesis?	01/07/19	30/06/23
Rowland, B.D.	NKI 2015-7657	Locking Together the Sister Chromatids	01/11/15	31/10/19
Ruers, T.J.M.	NKI 2014-6596	Clinical implementation of image-guided surgery in rectal cancer	01/05/15	30/04/19
Ruers, T.J.M.	NKI 2016-8162	TomTom voor de OK (via Vriendenloterij)	01/01/17	31/12/19
Ruers, T.J.M.	10747	Improving the outcome of breast cancer surgery by real time assessment of resection margins using Hyperspectral Imaging	01/01/18	31/12/21
Schagen, S.B.	NKI 2015-7737	Trajectories of cognitive decline in survivors of non-CNS cancers: from precancer diagnosis to late life after cancer	01/09/16	31/08/20
Schagen, S.B.	NKI 2015-7937	Monitoring, understanding and managing cognitive problems in cancer patients without central nervous system disease: putting knowlegde into practice	01/01/17	31/12/22
Schagen, S.B.	UU 2015-7954	Effect of physical exercise on cognitive function after chemotherapy in patients with breast cancer	01/09/16	31/08/20
Schmidt, M.K.	10758	Risk prediction, screening and Therapy of breast cancer in women from CHEK2 c.1100delC families in the Netherlands	01/10/17	31/10/21
Schmidt, M.K.	11655	Balancing risks of under- and overtreatment in young breast cancer patients: a focus on the triple negative subtype	01/02/19	30/09/22
Schmidt, M.K.	2013-6253	Risk management of contralateral breast cancer: development and validation of an online decision aid for physicians and patients	01/10/14	30/09/19

Principal investigator	Number of projects	Title	Started	Ended / Ends
Schmidt, M.K.	2015-7632	Breast cancer prognosis: identification of hereditary genetic variants	01/03/16	29/02/20
Schumacher, A.N.M.	NKI 2013-6122	Linking cancer exomes to cancer immunotherapy	01/08/14	31/07/20
Schumacher, A.N.M.	NKI 2017-8244	Netherlands Facility for Cancer Immune Analysis	01/05/18	30/04/23
Sixma, T.K.	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	31/10/18
Sixma, T.K.	NKI 2015-8082	Elucidating regulation of tumor suppressor BAP1 in genome stability maintenance	01/12/16	30/11/20
Sonke, G.S.	NKI 2012-5685	High-dose alkylating chemotherapy in oligo-metastatic breast cancer harboring homologous recombination deficiency	01/07/12	30/09/19
Sonke, G.S.		Improving the outcome of ovarian cancer patients: whwn and why to use neoadjuvant chemotherapy or primary surgery in advanced ovarian cancer	01/10/15	30/09/19
Sonke, J.J.	11964 ALPE	Cardiac changes after radiotherapy with high fraction doses for early stage lung cancer	01/01/19	30/06/21
Sonnenberg, A.	NKI 2013-5971	Regulation of tumorgenesis by integrin alpha3	01/11/13	31/10/18
Tellingen, van O.	11165	Radiosensitization of glioma through induction of mitotic enrichment	01/01/18	30/06/20
Vens, C.	VU 2014-7072	A multiparameter radiogenomics-based decision support system for personalized treatment of advanced stage head and neck cancer patients	01/11/15	31/10/19
Verheij, M.	10327 2017-8287	Multicentre randomised phase II trial of neo-adjuvant chemotherapy vs. chemotherapy/chemoradiotherapy vs. chemoradiotherapy followed by surgery in resectable gastric cancer	01/12/17	30/11/21
Visser, de K.E.	10083	Enhancing the success of immunotherapy for metastatic breast cancer by overcoming tumorassociated immunosuppressive mechanisms	01/05/17	30/04/21
Visser, de K.E.	10623	Dissecting how tumor-associated myeloid cells counteract chemotherapy response of breast cancer	01/04/18	31/03/22
Voest, E.E.	2015-7732	Tumor organoids : feasibility to predict sensitivity to treatment in cancer patients	01/07/15	30/06/18
Voest, E.E.	HUBR 2014-7006	Exploring The Use Of Lung Cancer Organoids In Personalized Medicine	01/02/16	31/01/20
Voest, E.E.	10014	The Drug Rediscovery Protocol	01/06/17	31/05/20
Vogel, W.V.	10606	Comprehensive functional salivary gland management to avoid an iatrogenic dry mouth	01/11/17	31/10/21
Wesseling, J.	NKI 2014-6250	Management of low risk ductal carcinoma in situ: watchful waiting or not? A randomized, non-inferiority trial	01/02/15	31/01/21
Wesseling, J.	NKI 2014-7167	Secondary prevention of breast cancer: risk stratification for personalized management of screen-detected ductal carcinoma in situ	01/10/15	30/09/19
Wesseling, J.	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	30/06/19
Wesseling, J.	11105	Improving breast cancer screening among young high risk women by blood-based methods	01/02/18	31/01/22
Wessels, L.F.A.	11741 ALPE	From fixed to functional pathology: defining intermediate phenotypes that determine prognosis and therapy response	01/12/18	30/11/20

Principal investigator	Number of projects	Title	Started	Ended / Ends
Wessels, L.F.A.	NKI 2013-6007	Prediction of response to neoadjuvant chemotherapy in luminal (ER-positive/ HER2-negative)breast cancer	01/10/14	31/12/18
Wessels, L.F.A.	NKI 2015-7835	Combatting therapy resistance by integrating genomic, transcriptomic and proteomic data from mouse models of invasive lobular breast carcinoma	01/01/17	31/12/20
Wessels, L.F.A.	NKI 2014-7080 A	Genetic causes of resistance to new androgen receptor signaling inhibitors in circulating tumor DNA of metastasized castration resistant prostate cancer patients	01/06/15	31/05/20
Zwart, W.T.	NKI 2014-6711	Drugging steroid hormone receptors in novel tumor types; new apllications of existing drugs	01/09/14	31/08/18
Zwart, W.T.	NKI 2015-7733	Companion diagnostics for endocrine treatment selection in breast cancer	01/07/15	30/06/19
Zwart, W.T.	10084	Biomarker discovery for prognostication and treatment selection in prostate cancer through Androgen Receptor profiling	01/06/17	31/05/21

Research projects supported by other organisations

Principal investigator	Granting agency	Title	Started	Ended / Ends
Aaronson, N.K.	Pink Ribbon	Zorg op maat om fysieke fitheid en welzijn van vrouwen met gemetastaseerde borstkanker te bevorderen	01/09/15	01/02/19
Agami, R.	European Commission	enhReg, Exploring enhancers Achilles Heel	01/10/13	30/09/18
Agami, R.	Stichting Oncode Institute	Oncode Agami	01/09/17	31/08/22
Agami, R.	ZonMw	Uncovering cancerous enhancers of prostate and breast cancers	01/03/17	28/02/21
Akkari, L.	AVL Foundation	Immunologie & Kanker	01/01/18	31/12/19
Akkari, L.	NWO	Zwaartekracht programma 2012 Akkari	01/01/17	31/12/21
Akkari, L.	SFN	Startgeld Akkari	01/01/17	31/12/21
Akkooi, van A.C.J.	Amgen B.V.	The infra structure registry: prospective melanoma stadium III registry	01/07/17	31/12/19
Akkooi, van A.C.J.	EORTC	Transitional study moving towards logical and personal combination therapies in the treatment of melanoma in-transit metastases and improving understanding of underlying biology	01/05/18	30/04/19
Altelaar, M.	NWO	Proteins@Work; A large-scale proteomics research facility for the life sciences	01/05/13	30/06/19
Amant, F.C.H.	European Commission	CRADLE: Cancer tReAtment During pregnancy: from fetaL safety to maternal Efficacy	01/10/15	30/09/20
Baas-Vrancken Peeters, M.J.	Innovatiefonds	Towards omitting breast surgery in patients with pathologic complete response after neoadjuvant systemic therapy	01/03/18	31/12/20
Baas-Vrancken Peeters, M.J.	Pink Ribbon	Towards patient tailored locoregional treatment of breast cancer in patients treated with neoadjuvant systemic therapy	01/09/16	31/08/19
Baas, P.	BMS en AstraZeneca	Mesoscape	01/09/17	31/12/19
Baas, P.	European Commission	DC-based immunotherapy to treat Malignant Mesothelioma	01/01/16	31/12/19
Baas, P.	Synthon Bio-pharmaceuticals	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	30/09/18
Beets-Tan, R.G.H.	ZonMw	Clinical impact of dedicated MR staging of ovarian cancer patients	28/12/17	28/12/21
Beijersbergen, R.L.	AVL Foundation	Pixels tegen darmkanker	01/08/11	31/03/18
Beijersbergen, R.L.	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, J.H.	European Commission	Afri-KA-DIA: Towards an adapted, safe, effective combination treatment for African visceral leishmaniasis (Kala Azar) and improved diagnostic tools	18/12/17	18/12/20
Beijnen, J.H.	ZonMw	Optimizing drug development for the neglected tropical disease visceral leishmaniasis through a systems pharmacology model	01/12/16	30/11/19
Berg, van den J.H.	Ameco Adviesgroep	Risico-beoordeling gg-T-cellen	01/12/17	31/07/18

Principal investigator	Granting agency	Title	Started	Ended / Ends
Berg, van den J.H.	Bristol Myers Squibb Company	Urelumab to improve tumor reactivity of Tumor Infiltrating Lymphocytes (TIL) derived from ovarian cancer and NSCLC using urelumab	31/07/17	31/01/19
Berg, van den J.H.	MedImmune	Immunomagnetic selection of PD1 + Peripheral Blood Mononuclear Cells (PBMC's)	10/07/17	10/10/18
Berg, van den J.H.	UNSW Sydney	UNSW collaboration	01/09/18	31/12/19
Bergman, A.M.	Movember	Benchfee	01/07/13	31/03/18
Bernards, R.	Astex UK	ERN1 inhibition in KRAS mutant solid tumors and in BRAF mutant melanoma	01/09/14	30/06/19
Bernards, R.	Astex UK	SHP2 inhibition in KRAS mutant solid tumors	01/03/16	22/12/19
Bernards, R.	CGC	POC clinical trial voor melanoma patiënten	01/12/15	31/12/21
Bernards, R.	European Commission	SENCAN - Senescence therapy for cancer	01/10/18	30/09/23
Bernards, R.	European Commission	RATHER Rational Therapy for Breast Cancer: Individualized Treatment for Difficult-to-Treat Breast Cancer Subtypes	01/01/11	30/06/18
Bernards, R.	European Commission	Molecularly guided trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of colorectal cancer (MoTriColor)	01/10/15	30/09/19
Bernards, R.	Eli Lilly and Company Limited	Abemaciclib (LSN2813542) CDK4/6 mesylate salt synthetic lethal interactions in KRAS mutant colorectal cancer	12/01/16	12/01/19
Bernards, R.	KNAW	Award	01/10/13	30/09/18
Bernards, R.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21
Bernards, R.	NWO	3D colony quantification organoids	01/04/13	31/12/21
Bernards, R.	NWO	CRISPR library	01/04/15	31/12/21
Bernards, R.	NWO	Diamond Graduate Program J. Kahn	01/09/15	31/08/19
Bernards, R.	Overig	Therapie op maat door mutatieanalyse bij kanker	01/07/11	31/07/18
Bernards, R.	Stand up to cancer (SU2C)	Targeting SHP2 in pancreatic cancer	01/11/18	31/12/19
Bernards, R.	Stichting Oncode Institute	Oncode Bernards	01/09/17	31/08/22
Bernards, R.	University of California (UCLA)	Interrogation of Resistance Mechanisms to Checkpoint Inhibitors Using Functional Genomics	01/11/17	31/10/19
Berns, A.J.M.	European Commission	Combination therapies for personalized cancer medicine	01/05/13	30/04/19
Berns, A.J.M.	NWO	Mouse Clinic for Cancer and Aging research (MCCA)	01/10/12	31/12/18
Berns, A.J.M.	Stichting Oncode Institute	Oncode Berns	01/09/17	31/08/22
Beurden, van M.	AVL Foundation	Onderzoek naar vrouwen met LS, die kanker ontwikkelen	01/05/18	30/04/19
Blank-de Hoop, C.U.	AVL Foundation	Impulsplan Immuuntherapie	01/04/18	31/03/20
Blank-de Hoop, C.U.	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	31/05/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Blank-de Hoop, C.U.	Bristol Myers Squibb USA	Systematic analysis of Cutaneous and Uveal Melanoma	01/06/17	31/05/19
Blank-de Hoop, C.U.	Bristol Myers Squibb USA	Improve the understanding of systemic melanoma-mediated immune suppression by deep serum profiling	01/06/17	31/05/19
Blank-de Hoop, C.U.	Bristol Myers Squibb USA	Impact of NSAIDs on the response to checkpoint therapy	02/08/17	02/08/19
Bleiker, E.M.A.	Cancer Research UK	Precision	01/05/17	30/04/22
Bleiker, E.M.A.	EORTC	Kwaliteit van leven data	01/12/15	31/12/19
Bleiker, E.M.A.	Zorginstituut Nederland	Mannen met Borstkanker	15/02/18	14/11/19
Borst, J.G.	→1 Sub.gev	Molecular characterization of human dendritic cell subset(s) that can relay help for the cytotoxic T cell response	01/07/18	30/06/21
Borst, J.G.	Aduro Biotech, Europe B.V.	Identification and validation of novel T-cell modulators in Immune Oncology	01/07/17	30/06/19
Borst, J.G.	AVL Foundation	Dendritic Cell project	01/01/18	31/12/22
Borst, J.G.	Elekta Ltd	Radio-immunotherapy in cancer treatment	01/06/16	31/05/21
Borst, J.G.	Fonds Weten-schappelijk Onderzoek	Refining cancer cell death and danger signals for the improvement of immunotherapy	01/01/18	31/12/21
Borst, J.G.	LUMC	Mutation-bearing (G)MOPD Cells: Drivers of LCH Pathology?	01/03/18	28/02/19
Borst, J.G.	NWO	Mechanisms of action of the Ubiquitin-like modifier ISG15 in immune regulation	01/01/15	31/08/19
Borst, J.G.	NWO	Exploiting T cell metabolism as a target for therapeutic intervention	01/01/15	31/12/18
Borst, J.G.	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	31/07/19
Brekel, van den M.W.M.	>1 Sub.gev	Head and neck cancer research	01/10/10	31/12/19
Brekel, van den M.W.M.	>1 Sub.gev	Virtual Therapy - VTG project HHC. Prediction of functional loss	01/10/16	30/09/19
Brekel, van den M.W.M.	ATOS	Research and new product development	01/01/14	30/06/20
Brekel, van den M.W.M.	AVL Foundation	Hoofd-Hals Targeted therapy	01/01/15	31/12/20
Brekel, van den M.W.M.	Brunel	Sponsorgelden Brunel	01/01/14	31/07/19
Brekel, van den M.W.M.	European Commission	Training Network on Automatic Processing of PAthological Speech	01/11/17	31/10/21
Brekel, van den M.W.M.	Patienten-vereniging Hoofd-Hals	De ontwikkeling van een keuzehulp voor patiënten met een orofarynxcarcinoom waarvoor een chirurgisch curatieve behandeling mogelijk is	01/07/18	30/06/19
Broek, van den D.	Roche	AVENIO first evaluation and validation	01/09/18	01/09/19
Broek, van den D.	ZonMw	ctDNA on the way to implementation in the Netherlands	27/03/19	26/03/23

Principal investigator	Granting agency	Title	Started	Ended / Ends
Broeks, A.	BBMRI-NL	Art 2.0, a national application and request tool for studies using biobank material	01/11/16	31/03/18
Brummelkamp, T.R.	European Commission	A global alliance for Zika virus control and prevention ZIKAlliance	01/10/16	30/09/19
Brummelkamp, T.R.	EMBO	Long-Term Fellowship Dr. Abdelghani Mazouzi	01/07/18	30/06/20
Brummelkamp, T.R.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21
Brummelkamp, T.R.	NWO	Human Genes and Intracellular Phenotypes	01/03/17	28/02/22
Brummelkamp, T.R.	Stichting Ammodo	Ammodo Award 2015 voor Biomedical Sciences	04/03/16	04/03/19
Brummelkamp, T.R.	Stichting Oncode Institute	Oncode Brummelkamp	01/09/17	31/08/22
Burgers, J.A.	→1 Sub.gev	Switch maintenance treatment with gemcitabine for patients with malignant mesothelioma who do not progress after 1st line therapy with a pemetrexed-platinum combination	01/03/13	30/06/19
Chalabi, M.	Bristol-Myers Squibb Belgium	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	30/09/20
Driel, van W.J.	AVL Foundation	Onderzoek voor ovarium carcinoom	01/10/17	30/09/19
Faller, W.J.	EMBO	Long-Term Fellowship Dr. Joana Da Silva	01/07/18	30/06/19
Faller, W.J.	NWO	Mouse Clinic for Cancer and Aging research (MCCA)	01/11/16	31/12/18
Faller, W.J.	NWO	Zwaartekracht programma 2012	01/01/17	31/12/21
Faller, W.J.	SFN	Start-up package PI Faller	01/11/16	31/10/21
Haanen, J.B.A.G.	→1 Sub.gev	Leven met niet meer te genezen kanker	01/08/17	31/12/18
Haanen, J.B.A.G.	Bristol Myers Squibb Company	Analysis of PD-1T TILs as biomarker for response to anti-PD-1 therapy in non-small cell lung cancer	01/09/18	28/02/19
Haanen, J.B.A.G.	Bristol Myers Squibb Company	Analysis of PD-1 Blockade in Virus-Associated Cancers	01/12/14	31/05/18
Haanen, J.B.A.G.	Bristol Myers Squibb Company	REsPonses to noveL Immunotherapies in ex vivo Cultured tumor frAgments	14/02/18	14/02/19
Haanen, J.B.A.G.	Bristol Myers Squibb USA	Fresh TIL in Heme Malignancies	01/02/16	31/05/18
Haanen, J.B.A.G.	Merck (MSD)	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	31/08/19
Haanen, J.B.A.G.	Neon Therapeutics	T Cell Program, Stimulation of neo-antigen specific T cell responses from patient PBMC	01/02/16	31/12/19
Haanen, J.B.A.G.	ZonMw	Randomized controlled trial comparing TIL treatment to ipilimumab for the treatment of advanced stage melanoma	01/07/15	30/06/19
Haas, R.L.M.	→1 Sub.gev	Radiobiology of Sarcomas. Radiotherapy fractionation sensitivity of (myxoid lipo-) sarcomas in vitro and in vivo	01/06/16	30/11/19
Harten, van W.H.	Agendia B.V.	Kosten-effectiviteits-analyses op MINDACT data	01/07/17	31/12/18

Principal investigator	Granting agency	Title	Started	Ended / Ends
Harten, van W.H.	AVL Foundation	Monopolie met maatschappelijk rendement - Verantwoord omgaan met patenten in de oncologie	01/01/17	28/02/21
Harten, van W.H.	Cancer Research UK	Precision	01/05/17	30/04/22
Harten, van W.H.	ZonMw	Technology Assessrnent of Next Generation Sequencing in Personalized Oncology	31/12/16	31/12/19
Hauptmann, M.	AVL Foundation	Startgeld Hauptmann	17/07/17	01/08/20
Hauptmann, M.	European Commission	Implications of Medical Low Dose Radiation Exposure	01/06/17	31/05/21
Heide, van der U.A.	→1 Sub.gev	System Technologies for Adaptive Real-time Image-guided Therapies	01/10/17	30/09/20
Heide, van der U.A.	Philips	Feasibility of MR-only in Radiation Oncology	13/12/17	30/04/22
Heide, van der U.A.	ZonMw	Quantivision project - perfect cut	15/05/15	15/05/19
Heuvel, van den M.M.	Bristol Myers Squibb USA	Introducing an easily accessible biomarker based on an active immune expression array can optimize personalized immunotherapy	01/11/16	31/01/19
Hofland, L.	AVL Foundation	Hoofdhuidkoeling	01/11/18	30/06/19
Horenblas, S.	AVL Foundation	Immunological aspects of the microenvironment of primary tumors, tumor-positive and tumor-negative lymph nodes in HPV+ and HPV- penile cancer patients	01/01/17	31/12/20
Horenblas, S.	Stichting J.C. van Veen	Bijdrage onderzoek urologie	01/01/11	31/12/21
Huijbers, I.J.G.	European Commission	Towards enduring mouse resources and services advancing research into human health and disease	01/01/17	31/12/20
Huijbers, I.J.G.	NWO	Mouse Clinic for Cancer and Aging research	01/10/12	31/12/18
Huitema, A.D.R.	Merus B.V.	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, A.D.R.	Merus B.V.	Support of clinical development program of the Merus bispecific monoclonal antibody MCLA-117 with PK/PD modeling and simulation	01/09/16	01/01/19
Huitema, A.D.R.	ZonMw	Individualized PeMetRexed dOsing in lung cancER and mesothelioma patients to improVE treatment response and allow treatment of patients with impaired renal function	01/12/17	30/11/21
Jacobs, H.B.	SFN	DOT1L project	01/07/18	30/06/20
Jacobs, H.B.	ZonMw	The role of stable immunoglobulin transcripts in establishing allelic exclusion	01/04/14	31/03/19
Jacobs, J.J.L.	European Commission	Joint Training and Research Program on Chromatin Dynamics and the DNA Damage Response	01/03/19	28/02/23
Jacobs, J.J.L.	EMBO	Small Grant for funding of research materials	01/01/17	31/12/19
Jacobs, J.J.L.	NWO-ALW	EMBO Young Investigators	01/01/13	31/12/19
Jalink, C.	STW	New Film Camera for molecular microscopy	01/09/16	15/06/20
Jonkers, J.M.M.	Cancer Research UK	Precision	01/05/17	30/04/22

Principal investigator	Granting agency	Title	Started	Ended / Ends
Jonkers, J.M.M.	European Commission	Combination Therapies for personalized medicine	01/05/13	30/04/19
Jonkers, J.M.M.	European Commission	Generation of the CanPath prototype - a platform for predictive cancer pathway modeling	01/03/16	28/02/21
Jonkers, J.M.M.	European Commission	Targeting SYNthetic lethal interactions for new cancer treatments TRAINing network	01/09/16	31/08/20
Jonkers, J.M.M.	HeritX, Inc	Immunoprevention of BRCA1-associated mammary cancer	01/03/18	28/02/21
Jonkers, J.M.M.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21
Jonkers, J.M.M.	NWO	Finding novel Achilles 'heels to prevent and target BRCA1-associated breast cancer	01/02/14	31/01/20
Jonkers, J.M.M.	Stand up to cancer (SU2C)	Laura Ziskin Price Award, A high -risk, high-rewarded breast cancer research project	01/02/18	31/01/19
Jonkers, J.M.M.	Stichting Oncode Institute	Oncode Jonkers	01/09/17	31/08/22
Jonkers, J.M.M.	University of Copenhagen/ Graduate School	Material budget	01/08/15	31/08/18
Jonkers, J.M.M.	University of Copenhagen/ Graduate School	Unraveling the genetic background of familial breast cancer	01/01/18	31/12/22
Jonkers, J.M.M.	ZonMw	Deciphering the contribution of cancer-associated fibroblasts to invasive lobular carcinoma development, progression and tumor microenvironment	01/01/19	31/12/21
Karakullukcu, M.B.	AVL Foundation	3D Lab	01/04/17	31/12/19
Karakullukcu, M.B.	Biolitec	Treatment of head and neck cancer	01/09/15	31/08/18
Kerkhoven, R.M.	AVL Foundation	single cell RNA sequencing using droplet based microfluidics (DropSeq)	01/07/16	30/06/18
Kok, M.	AVL Foundation	TONIC-Trial	01/09/15	31/12/19
Kok, M.	Breast Cancer Research Foundation	Exploiting the Foreign Antigenic Space in Breast Cancer	01/10/17	15/06/19
Kok, M.	Pink Ribbon	Discovery of biomarkers to select metastatic breast cancer patients for immunotherapy using anti-PD1	01/09/16	31/08/19
Kok, M.	st. Hendrika Roet Fonds	Immunology and cancer	01/12/18	30/11/28
Kvistborg, P.	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, P.	Merck Sharp & Dohme Corp.	Feasibility study of neo-adjuvant treatment with carboplatin, paclitaxel and pembrolizumab in stage IV epithelial ovarian cancer	01/10/16	30/09/20
Kvistborg, P.	SFN	Startgeld PI Kvistborg	01/09/16	31/08/21
Leerdam, van M.E.	MAAG LEVER DARM Stichting	Diagnostic yield of screening colonoscopy in Hodgkin lymphoma survivors at increased risk of treatment-induced colorectal cancer	01/05/15	30/04/18
Leeuwen, van F.	NWO	Principles of epigenetic inheritance	23/07/13	23/07/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Leeuwen, van F.	NWO Chemische Wetenschappen	Development of antibodies targeted at site-specific protein ubiquitylation	01/09/16	31/08/19
Leeuwen, van F.	NWO Chemische Wetenschappen	Development of antibodies targeted at site-specific protein ubiquitylation	12/08/15	12/08/18
Leeuwen, van F.	SFN	DOT1L project	01/07/18	30/06/20
Leeuwen, van F.E.	AVL Foundation	Beter Project	01/06/18	31/05/19
Leeuwen, van F.E.	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	31/08/18
Leeuwen, van F.E.	DES	Onderzoek CCAC van DES-dochters ouder dan 50 jaar	01/10/17	31/03/19
Leeuwen, van F.E.	European Commission	Implications of Medical Low Dose Radiation Exposure	01/06/17	31/05/21
Leeuwen, van F.E.	Erasmus Medisch Centrum	Long-term risk of endometrial cancer after ovarian stimulation for in-vitro fertilization	01/01/11	30/11/18
Leeuwen, van F.E.	Pink Ribbon	Cardiovascular morbidity and mortality in breast cancer survivors: identifying high risk subgroups	01/10/13	31/12/18
Leeuwen, van F.E.	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	30/11/19
Leeuwen, van F.E.	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
Leeuwen, van F.E.	The General Hospital Corporation D b/a Massachusetts General Hospital	LIFT-OMEGA	01/09/17	31/05/22
Leeuwen, van F.E.	Vlissingen Lymfoomfonds	Evaluatie BETER poliklinieken	01/03/18	31/12/19
Lenstra, T.L.	European Commission	Single-molecule visualization of transcription dynamics to understand regulatory mechanisms of transcriptional bursting and its effects on cellular fitness	01/01/18	31/12/22
Lenstra, T.L.	NWO	Zwaartekracht programma 2012	01/01/17	31/12/21
Lenstra, T.L.	NWO Exacte en Natuurweten-schappen	Unravelling how DNA organization is linked to transcriptional dynamics	01/09/18	31/08/21
Lenstra, T.L.	SFN	Start-up package PI Lenstra	01/12/16	30/11/21
Linn, S.C.	A Sister's Hope	Estrogen Receptor interactome from biopsies to guide endocrine treatment	01/01/12	31/10/18
Linn, S.C.	A Sister's Hope	Toward personalized medicine by using the nationwide population-based breast cancer registry (1989-2009) couple with biobanking: NBCP	01/06/12	28/02/19
Linn, S.C.	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	31/08/20

Principal investigator	Granting agency	Title	Started	Ended / Ends
Linn, S.C.	A Sister's Hope	Mutational analysis and BRCA1-like classification in WSG-ADAPT TN-Trial	01/01/17	30/06/19
Linn, S.C.	AVL Foundation	Breast cancer research aimed at saving lives	01/11/17	01/11/21
Linn, S.C.	AVL Foundation	STARZ Foundation	01/01/14	30/06/19
Linn, S.C.	AVL Foundation	Learning from unexpected cures	01/04/14	31/08/20
Linn, S.C.	AVL Foundation	TONIC-Trial	01/09/15	31/12/19
Linn, S.C.	European Commission	Rational Therapy for Breast Cancer: Individualized Treatment for Difficult-to-Treat Breast Cancer Subtypes	01/11/14	30/06/18
Linn, S.C.	ZonMw	Substantiele verbetering van de overleving van stadium III, BRCA1-like borstkankerpatiënten met doelgerichte behandeling	01/01/17	31/12/22
Lohuizen, van M.M.S.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21
Lohuizen, van M.M.S.	Stichting Oncode Institute	Oncode van Lohuizen	01/09/17	31/08/22
Lok, C.A.R.	→1 Sub.gev	Onderzoek Eierstokkanker -E-learning over genetische screening bij ovariumcarcinoom	01/08/15	31/12/18
Lok, C.A.R.	AstraZeneca BV	GenOva 2.0	01/04/17	31/12/18
Loo, C.E.	CTMM	COmputer-aided predIction of breast Cancer therapy response by means of multimodality imaging	01/06/15	30/11/18
Luenen, van H.G.A.M.	European Commission	Libra, gender equality	01/10/15	31/03/19
Medema, R.H.	NWO	Zwaartekracht programma	01/01/13	31/12/21
Medema, R.H.	NWO-ALW	Spatial and temporal control of the microtubule by kinase activity	16/01/15	16/01/18
Medema, R.H.	Stichting Oncode Institute	Oncode Medema	01/09/17	31/08/22
Medema, R.H.	ZonMw	Impact of chromatin context on DNA double-strand break repair kinetics, fidelity and signaling	01/07/16	30/06/20
Meijer, G.A.	→1 Sub.gev	A multivariable prediction model for prognosis of early stage colorectal cancer: comparing clinicopathological characteristics and molecular markers	01/04/15	31/03/20
Meijer, G.A.	AACR	AACR GENIE Project	01/07/16	30/06/19
Meijer, G.A.	AVL Foundation	Darmkanker en biomarkers	01/03/17	28/02/19
Meijer, G.A.	BBMRI-NL	BBMRI 2.0	01/01/15	31/12/18
Meijer, G.A.	European Commission	Building Enduring Life-science services	01/11/16	31/08/19
Meijer, G.A.	Health-Holland	CRC Bioscreen 2.0	01/09/16	31/08/18
Meijer, G.A.	Health-Holland	Liquid biopsy-based molecular diagnostics to monitor therapy response in metastatic colorectal cancer: PLCRC-ORCA EXTended beyond RAS	01/01/17	31/12/20
Meijer, G.A.	MAAG LEVER DARM Stichting	Opslag Poep Samples, Logistiek en Analyse van Gegevens	15/10/15	30/09/18

Principal investigator	Granting agency	Title	Started	Ended / Ends
Meijer, G.A.	MAAG LEVER DARM Stichting	Detectie van hoog-risico adenomen	01/02/17	31/07/18
Meijer, G.A.	Stichting Sacha Swarttouw-Hijmans	Vrij circulerend tumor DNA (ctDNA) als biomarker voor monitoring van patiënten met rectumkanker	01/05/18	30/04/20
Meijer, G.A.	Stichting Sacha Swarttouw-Hijmans	Securing Blood from Colon Adenoma Patients in the CLIPPER Trial to Enable Development of Biomarkers for Early Detection of High-Risk Colon Adenomas and CRC	01/05/18	30/04/20
Nederlof, P.M.	Roche	CGH Array	01/10/12	30/11/19
Nuijen, B.	Modra Pharmaceuticals B.V.	For Chemistry, Manufacturing and Control of ModraDoc006 tablets	28/05/18	31/12/18
Nuijen, B.	Modra Pharmaceuticals B.V.	To provide clinical services for Study: Multicenter safety, feasibility and pharmacokinetic phase I-II trial of ModraDoc006/r in patients with metastatic castration-resistant prostate cancer	25/05/17	31/10/18
Nuijen, B.	Modra Pharmaceuticals B.V.	For Chemistry, Manufacturing and Control of ModraDoc006 tablets	07/04/17	31/10/18
Peeper, D.S.	AVL Foundation	Screening novel therapeutic targets for immuno oncology	01/12/17	30/11/19
Peeper, D.S.	Bristol Myers Squibb USA	Defining and tackling immunotherapy resistance in melonoma and lung cancer	01/08/17	31/07/21
Peeper, D.S.	European Commission	Combination Therapies for personalized medicine	01/05/13	30/04/19
Peeper, D.S.	Genmab	Research into cell signal pathways and oncogenic divers	01/05/15	30/09/20
Peeper, D.S.	Josephine Nefkens Stichting	Identificatie van nieuwe immuuntherapie met Itellicyt Screener PLUS	01/03/18	28/02/22
Peeper, D.S.	Merck Sharp & Dohme Corp.	Identify tumor-intrinsic factors that induce resistance to anti PD-1 antibody treatment in vivo (Keytruda resistome) in the D10 system	13/11/18	13/11/19
Peeper, D.S.	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
Peeper, D.S.	Stichting Oncode Institute	Oncode Peeper	01/09/17	31/08/22
Perrakis, A.	European Commission	World-wide E-infrastructure for structural biology	01/11/15	31/10/18
Perrakis, A.	European Commission	INEXT - Access - Infrastructure for NMR, EM and X-ray crystallography for translational research	01/09/15	31/08/19
Perrakis, A.	Janssen Research & Development	Enhancement of PDB_REDO algorithms and software	01/01/16	30/04/19
Perrakis, A.	NWO	The molecular interactions allowing Mps1 to safeguard cell division	01/10/15	30/09/18
Perrakis, A.	NWO Chemische Wetenschappen	Structural and chemical basis for the biosynthesis and propagation of base J	01/09/14	31/08/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Perrakis, A.	NWO Chemische Wetenschappen	Optimized protein knowledge through transfer of evolutionary conserved features and chemical knowledge	15/11/14	14/11/19
Perrakis, A.	Universiteit Utrecht	Releasing the full potential of Instruct to expand and consolidate infrastructure services for integrated structural life science research	01/01/17	31/12/20
Poel, van der H.G.	CTMM	Prostate Cancer Molecular Medicine	01/12/09	30/06/18
Poel, van der H.G.	Intuitive Surgical Operations Inc.	Robot-assisted radioguided surgery using a drop-in gamma probe	01/03/18	29/02/20
Poll, van de L.V.	EORTC	Incorporating the patient voice in sarcoma research: How can we assess health-related quality of life in this heterogeneous group of patients?	01/01/19	31/12/20
Poll, van de L.V.	EORTC	Phase II and III development of an EORTC QOL cancer survivorship questionnaire	01/02/17	31/07/19
Poll, van de L.V.	SFN	Start-up package PI	01/01/16	31/12/18
Poll, van de L.V.	Stichting Roparun Palliatieve zorg	Project CALM	01/10/18	30/09/20
Poll, van de L.V.	Stichting Vrienden Integrale Oncologische Zorg	Onderzoek naar het effect van de Match app, een online interventie om het menselijk contact en begrip tussen jongvolwassenen met kanker en hun omgeving te verbeteren	01/10/18	30/09/20
Rheenen, van J.E.	CGC	CGC IV	01/10/17	31/12/21
Rheenen, van J.E.	Dr. Josef Steiner Krebsstiftung	Dr. Josef Steiner Cancer Research Award 2017	01/10/17	30/09/21
Rheenen, van J.E.	European Commission	Tumor cell death supports recurrence of cancer	01/10/17	31/08/20
Rheenen, van J.E.	European Commission	Research Training Network on Integrated Component Cycling in Epithelial Cell Motility (InCeM)	01/10/17	31/12/18
Rheenen, van J.E.	EMBO	Long-Term Fellowship Dr. Miguel Vizoso Patino	01/09/18	31/12/19
Rheenen, van J.E.	EMBO	EMBO Fellowship Jessica Morgner	01/10/17	31/12/18
Rheenen, van J.E.	H.F.S.P.O.	HFSPO Fellowship Claire Vennin	01/06/18	31/05/21
Rheenen, van J.E.	NWO	Intravital stem cell imaging to reveal the cellular processes that drive colorectal tissue homeostasis and tumor initiation	01/10/17	31/12/18
Rheenen, van J.E.	NWO-ALW	Identifying the physiological relevance of RNA transfer by microvesicles	01/10/17	15/07/18
Rheenen, van J.E.	Stichting Oncode Institute	Oncode van Rheenen	01/09/17	31/08/22
Rhijn, van B.	Universitat Basel	material costs	01/01/15	30/11/18
Riele, te H.P.J.	STW	Phenotypic assessment of intra- and extra-exonic variants of disease-related genes present in the human population	01/01/17	31/12/20
Rookus, M.A.	→1 Sub.gev	HEBON Centers	15/11/13	31/12/20
Rookus, M.A.	→1 Sub.gev	HEBON verlenging Denise Jenner	01/04/18	30/06/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Rookus, M.A.	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	31/03/18
Rosing, H.	Neon Therapeutics	Qualification of an UPLC-MS method for the identity analysis of neo-antigen peptides drug products and the quality control of these products	01/03/18	31/12/18
Rowland, B.D.	European Commission	Cohesin-mediated chromosomal looping: from linear paths to 3D effects	01/04/18	31/03/23
Rowland, B.D.	NWO Chemische Wetenschappen	Echo subsidie. How does cohesin release DNA?	01/01/16	31/12/18
Rowland, B.D.	SFN	Startgeld Rowland	01/04/17	31/03/22
Ruers, T.J.M.	AVL Foundation	Optical guided surgery	01/11/14	31/05/20
Ruers, T.J.M.	AVL Foundation	Pixelanalyse voor (vroeg)detectie van dikkedarmkanker	01/01/17	31/12/19
Ruers, T.J.M.	European Commission	Advancing Smart Optical Imaging and Sensing for Health	01/06/16	31/05/19
Ruers, T.J.M.	Health-Holland	TomTom project	01/12/16	30/11/19
Ruers, T.J.M.	Holland High Tech	ECSEL project ASTONISH	01/06/16	31/05/19
Ruers, T.J.M.	Innovation Exchange Amsterdam	Magnetische Marker voor Chirurgische Lokalisatie	01/06/16	31/05/20
Ruers, T.J.M.	Nijbakker-Morra Stichting	Fiberprobe; steriliseerbare instrument voor in vivo spectroscopisch onderzoek van resectiemarges	01/02/18	31/03/19
Ruers, T.J.M.	Philips	Research collaboration Philips	01/04/10	30/06/19
Ruers, T.J.M.	STW	Combining Optics and Acoustics For Realtime Guidance during Cancer Surgery	01/09/17	31/08/20
Sandick, van J.W.	Vrolijk	Slokdarmkankeronderzoek	01/01/08	30/06/20
Sandick, van J.W.	ZonMw	Combinatiebehandeling van cytoreductieve chirurgie en hypertherme intraperitoneale chemotherapie (HIPEC) bij patiënten met een maagcarcinoom en synchrone buikvliesmefasfasen en/of tumorpositief buikvocht	01/10/17	30/09/22
Schmidt, M.K.	BBMRI-NL	Personalized medicine: servicedesk ethiek en recht	01/09/18	28/02/19
Schmidt, M.K.	Cancer Research UK	Precision via Cancer Research UK	01/05/17	30/04/22
Schmidt, M.K.	European Commission	Breast CAncer STratification: understanding the determinants of risk and prognosis of molecular subtypes	01/09/15	31/08/20
Schmidt, M.K.	ZonMw	Fostering the responsible use of residual biospecimens and data in medical	01/05/17	30/04/19
Schmidt, M.K.	ZonMw	Personalized medicine: servicedesk ethiek en recht	01/09/17	31/08/19
Schumacher, A.N.M.	→1 Sub.gev	Cell Therapy NKI	01/07/11	30/06/19
Schumacher, A.N.M.	Cancer Research Institute	Unraveling the biology of CMTM6: A novel regulator of PD-Li identified through genome-wide genetic screening	01/01/17	31/12/19
Schumacher, A.N.M.	European Commission	Advanced T-cell Cancer Gene-Therapy	01/12/13	30/11/18

Principal investigator	Granting agency	Title	Started	Ended / Ends
Schumacher, A.N.M.	European Commission	APERIM: Advanced bioinformatics platform for PERsonalised cancer IMmunotherapy	01/05/15	30/04/18
Schumacher, A.N.M.	European Commission	Sensitivity of human tumors to T cell attack	01/12/17	30/11/22
Schumacher, A.N.M.	Kristian Gerhard Jebsen foundation	Jebsen grant	01/06/13	31/12/19
Schumacher, A.N.M.	MD Anderson Cancer Center	Acceleration of the Clinical Testing of CTLA-4 and P1 Blockade for Melanoma	01/03/14	28/02/18
Schumacher, A.N.M.	Merck KGaA	Single cell analysis of the tumor-immune ecosystem in human cancer: Dissecting the dynamics of immune-tumor cross talk following checkpoint blockade	01/06/17	31/05/20
Schumacher, A.N.M.	NWO	Zwaartekracht Schumacher	01/10/14	30/09/19
Schumacher, A.N.M.	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	30/06/19
Schumacher, A.N.M.	Stichting Oncode Institute	Oncode Schumacher	01/09/17	31/08/22
Sixma, T.K.	European Commission	Regulated Assembly of Molecular Machines for DNA REPAIR: a Molecular Analysis training Network	01/01/17	31/12/20
Sixma, T.K.	NWO	Structure-function analysis of transcription-associated DNA repair	01/06/18	31/05/24
Sixma, T.K.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21
Sixma, T.K.	NWO	Investering Therpophoresis HPLC imager	01/04/13	31/12/21
Sixma, T.K.	NWO	The molecular mechanism of USP48, a BRCA1 antagonist during DNA damage response	01/09/18	31/08/23
Sixma, T.K.	NWO	A program to enable discovery of catalytic and/or inhibitors of the USP4/11/15 family of deubiquitinating enzymes	01/09/18	31/08/23
Sixma, T.K.	NWO Chemische Wetenschappen	A movie of DNA mismatch repair: how information is transmitted by conformational change	01/01/17	31/12/22
Sixma, T.K.	NWO-ALW	Cellular activation of the allosterically inhibited UCHL5/INO80G complex	01/12/16	30/11/19
Sixma, T.K.	Stichting Oncode Institute	Oncode Sixma	01/09/17	31/08/22
Sonke, G.S.	A Sister's Hope	Long-term Survival in Metastatic HER2+ Breast Cancer	01/04/17	31/03/18
Sonke, G.S.	AVL Foundation	Donatie Team Westland	07/12/17	07/12/20
Sonke, G.S.	Pink Ribbon	Learning from long-term survivors in metastatic breast cancer	01/11/16	31/10/19
Sonke, J.J.	→1 Sub.gev	Personalized Radiotherapy Collaboration Agreement	01/01/15	31/12/19
Sonke, J.J.	EOS	Framework Research Agreement between Elekta and NKI-AVL	10/08/10	10/08/20
Sonnenberg, A.	DEBRA AUSTRIA	'High-content screening for new therapies for Epidermolysis Bullosa Simplex associated with Muscular Dystrophy (EBS-MD)	01/04/17	31/03/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Sonnenberg, A.	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	31/12/18
Steeghs, N.	→1 Sub.gev	REGISTER - REgistratie GIST nEdeRland	01/01/14	31/12/23
Steeghs, N.	European Commission	Molecularly guided trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of colorectal cancer	01/10/15	30/09/19
Steensel, van B.	AIRC	Twisting the boundaries: Role of Topoisomerase1 at the nuclear lamina	01/01/19	31/12/21
Steensel, van B.	AVL Foundation	Ontwikkeling Chromatin Genomics	01/11/14	31/10/24
Steensel, van B.	European Commission	Genomics of Chromosome Architecture and Dynamics in Single Cells	01/03/17	28/02/22
Steensel, van B.	Stichting Oncode Institute	Oncode van Steensel	01/09/17	31/08/22
Steensel, van B.	University of Illinois	NIH 4DNucleome deel 1 Mapping and Technology Development	28/09/15	31/07/20
Steensel, van B.	ZonMw	Impact of chromatin context on DNA double-strand break repair kinetics, fidelity and signaling	28/01/16	28/01/20
Stokkel, M.P.M.	AVL Foundation	Tumor specific imaging of prostate cancer using PSMA-PET	01/07/16	30/06/19
Stokkel, M.P.M.	Interne financiering	Reposit studie DOD	01/09/15	31/12/19
Stokkel, M.P.M.	STW	A feasibility study on Cerenkov Luminescence Imaging during prostate cancer surgery using Gallium-68 PSMA	01/08/17	31/10/19
Stuiver, M.M.	European Commission	Project on Exercise for Fatigue Eradication in Advanced Breast cancer to improve quality of life	01/01/19	31/12/23
Stuiver, M.M.	Nutricia Nederland B.V.	Voedingsstatus en het beloop van de behandeling van stadium III longkanker	01/11/17	31/12/19
Tellingen, van O.	AVL Foundation	Improving chemoradiation therapy of GBM by inhibition of glioma invasion: A proof-of-concept study	01/12/17	30/11/19
Tellingen, van O.	AVL Foundation	Multi-Targeted Combination Therapy for treatment of glioblastoma: in vivo proof-of-concept study	01/06/18	31/05/20
Tellingen, van O.	CellProtect Australia PTY Ltd	Efficacy study of S-CP201 and radiotherapy against orthotopic intracranial tumor models	01/01/17	30/06/18
Tellingen, van O.	Reneuron Limited	Efficacy study of exosomes against orthotopic intracranial tumor models	01/06/16	31/05/19
Tesselaar, M.E.T.	Merck BV	Database of retrospectively and subsequent prospectively gathered data of all MCC patients treated in the Netherlands as platform for a national MCC database	01/09/18	31/12/22
Tinteren, van H.	IKNL	Overeenkomst zelfregisterend melanoomcentrum DMTR	01/05/16	31/12/18
Tinteren, van H.	Modra Pharmaceuticals B.V.	Work order 1 Multicenter safety, feasibility and pharmacokinetic phase II trial of ModraDoc006/r in patients with metastatic castration-resistant prostate	01/06/17	01/07/19
Tinteren, van H.	Modra Pharmaceuticals B.V.	Food effect of weekly administration of (bi) daily Oral Docetaxel(ModraDoc006) in combination with ritonavir	01/07/17	31/03/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Tinteren, van H.	Modra Pharmaceuticals B.V.	Safety of extended use of the weekly oral docetaxel formulation ModraDoc006/r in patients with advanced solid tumors	01/07/17	30/09/20
Tinteren, van H.	NVALT	A phase III prospective double blind placebo controlled randomized study of adjuvant MEDI4736 in completely resected non-small cell lung cancer	08/02/18	08/08/22
Trommel, van N.E.	AVL Foundation	Onderzoek ADP Ovariumcarcinoom	01/09/17	31/08/21
Trum, J.W.	ZonMw	GERiatric Screening in the treatment of elderly patients with Ovarian Carcinoma (GERSOC) van C. Smorenburg	15/08/17	15/08/21
Ven, van de H.W.M.	European Commission	EurOPDX Distributed Infrastructure for Research on patient-derived cancer Xenografts	01/02/18	31/01/22
Vens, C.	AstraZeneca BV	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	01/07/19
Verheij, M.	AbbVie	Utility of the combination of APG880 with radiotherapy	12/07/16	01/10/18
Verheij, M.	AVL Foundation	Image Guided Therapy	01/01/17	31/12/20
Verheij, M.	European Commission	Clinical proof of concept through a randomized phase II study: a combination of immunotherapy and stereotactic ablative radiotherapy as a curative treatment for limited metastatic lung cancer	01/01/17	31/12/22
Visser, de K.E.	European Commission	Mechanistic insights into the impact of tumor-associated neutrophils on metastatic breast cancer	01/03/14	28/02/20
Visser, de K.E.	NWO	OOA NWO Diamond K.Kos	01/10/16	30/09/20
Visser, de K.E.	Roche Diagnostics GMBH	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	31/08/19
Visser, de K.E.	Stichting Oncode Institute	Deciphering the Cancer-Immune Landscape; towards personalized immune intervention strategies	01/08/18	31/07/21
Visser, de K.E.	Stichting Oncode Institute	Oncode de Visser	01/09/17	31/08/22
Voest, E.E.	NWO	Zwaartekracht programma 2012	01/03/14	31/12/21
Voest, E.E.	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	31/08/18
Voest, E.E.	ZonMw	COLOSYS: A systems approach to preventing drug resistance in colon cancer	01/05/16	30/04/19
Wesseling, J.	Cancer Research UK	Prevent Ductal Carcinoma in Situ Invasive Overtreatment Now - PRECISION	01/06/18	30/11/18
Wesseling, J.	Cancer Research UK	Precision via Cancer Research UK	01/05/17	30/04/22
Wesseling, J.	HeritX, Inc	Immunoprevention of BRCA1-associated mammary cancer	01/03/18	28/02/20
Wesseling, J.	Pink Ribbon	Preventing overtreatment of microcalcification-associated in situ breast lesions by implementing more accurate prognostic biomarkers	01/04/14	31/03/19
Wesseling, J.	Pink Ribbon	Low Risk Ductal carcinoma In Situ - a Randomized, Non-inferiority trial	01/04/14	31/03/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Wessels, L.F.A.	Cancer Research UK	Precision via Cancer Research UK	01/05/17	30/04/22
Wessels, L.F.A.	CGC	Bioinformatica CGC	01/11/13	31/12/21
Wessels, L.F.A.	CPCT	Tumor Organoids: A new preclinical model for drug sensitivity analysis	01/05/14	30/04/19
Wessels, L.F.A.	European Commission	Identification and functional validation of drugable targets/pathways for triple negative breast cancer	01/04/13	31/03/18
Wessels, L.F.A.	European Commission	Combination Therapies for personalized medicine	01/05/13	30/04/19
Wessels, L.F.A.	Genmab	Identification of Biomarkers for HexaBodyR-DR5/DR5 therapy	01/09/17	31/08/19
Wessels, L.F.A.	GlaxoSmith Kline	Computational analyses to unravel the mechanism of action of BET and EZH2 inhibitors and define biomarkers	01/02/16	31/01/19
Wessels, L.F.A.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21
Wessels, L.F.A.	Stichting Oncode Institute	Oncode Wessels	01/09/17	31/08/22
Wessels, L.F.A.	STW	Computer-aided Risk Assessment of Breast Cancer using Gene-Correlated Dynamic Contrast-enhanced MRI	01/01/13	31/03/18
Wessels, L.F.A.	ZonMw	COLOSYS: A systems approach to preventing drug resistance in colon cancer	01/02/17	31/01/20
Wessels, L.F.A.	ZonMw	Targeting theHER2 receptor: finding biomarkers for optimal anti-HER2 treatment	01/02/18	31/01/19
Wit, de E.	European Commission	From haplotype to phenotype: a systems integration of allelic variation, chromatin state and 3D genome data	01/09/15	31/08/20
Wit, de E.	NWO	The role of transcription factors in 3D genome organization	01/10/16	30/09/21
Wit, de E.	NWO	Impact of sequential driver mutations on epigenetic regulation during intestinal carcinogenesis	01/09/17	31/08/20
Wit, de E.	SFN	Junior PI De Wit	01/09/15	31/08/20
Wit, de E.	Stichting Oncode Institute	Oncode de Wit	01/09/17	31/08/22
Zuur, C.L.	W.M. de Hoopstichting	Aanschaf en opzetten laboratoriummaterialen voor het onderzoeken van bloedaanmaak bij hoofd-hals kankerpatiënten voor en na behandeling	01/04/18	30/09/21
Zwart, W.T.	A Sister's Hope	Ex-vivo intervention of metastatic breast cancers for novel drug testing and development in endocrine therapy-resistance	01/12/17	30/06/19
Zwart, W.T.	AVL Foundation	Integrative Androgen Receptor genomics as a readout for recurrence risk and treatment resistance of prostate cancer	01/09/17	31/01/19
Zwart, W.T.	European Commission	Training network in drug discovery targeting TRIM Ubiquitin ligases in disease	01/01/19	31/12/22
Zwart, W.T.	SFN	Startgeld Zwart	01/10/11	30/09/20
Zwart, W.T.	Stichting LSH-TKI	Deubiquitinating enzyme inhibitors as novel drugs in Estrogen Receptor-positive breast cancer	01/03/14	28/02/18
Zwart, W.T.	Stichting Oncode Institute	Oncode - Validation of a novel 9-gene-classifier to guide adjuvant treatment for prostate cancer	01/09/18	31/08/20

Principal investigator	Granting agency	Title	Started	Ended / Ends
Zwart, W.T.	Stichting Oncode Institute	Oncode Zwart	01/09/17	31/08/22
Zwart, W.T.	The Mark Foundation for Cancer Research	Short-term 3D-printing-based cultures of metastatic breast cancer for tailored therapy selection	01/12/18	01/12/19
Zwart, W.T.	ZonMw	Proteomic and genomic evaluation of metastatic breast cancer to facilitate personalized treatment selection	01/12/16	30/11/21

Personnel index

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z

REDACTIE Suzanne Corsetto

DTP/LAYOUT Copper Design, Houten | copper-design.nl |
FOTOGRAFIE Martin Hogeboom, Epe | www.martinhogeboom.nl |
DRUKKER NPN drukkers, Breda | www.npndrukkers.nl |