Radboud Institute for Molecular Life Sciences

Annual Report 2016

Institute for Molecular Life Sciences

Radboudumc

Postal address
259 RIMLS
P.O. Box 9101
6500 HB Nijmegen
The Netherlands

Visiting address
Geert Grooteplein 28
6525 GA Nijmegen

T: +31 (0)24 361 07 07
E: rimls@radboudumc.nl
I: www.rimls.nl

Editing: Judith Ariëns, René Bindels, Adrian Cohen, Dagmar Eleveld

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Front cover: The cover image depicts a collage of molecular life sciences photos

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Foreword

Every year, like many of our readers, we look back at the highlights of the last year, and 2016 is no different. Nationally, we can really be proud that Prof. Ben Feringa, Groningen University, won the Nobel Prize for chemistry – a sign that Dutch science is internationally leading. Closer to RIMLS, Prof. Mihai Netea, medical doctor, scientist, novelist, and recently, member of an elite group of scientists who have won the Spinoza prize. This prize is the highest honour for any scientist working in The Netherlands, often likened to the Nobel prize. On page 15 we have devoted special attention to an incredible year for Mihai and his team. Translating molecular research to healthcare is at the core of our mission and in 2016 there has been no better evidence of this than the group of Jolanda de Vries who succeeded in obtaining more than € 20 M for a clinical trial of a new skin cancer vaccine. The funding comes from the Dutch medical health insurance, something that is truly unique, paving the way to offer this treatment in the standard health insurance package.

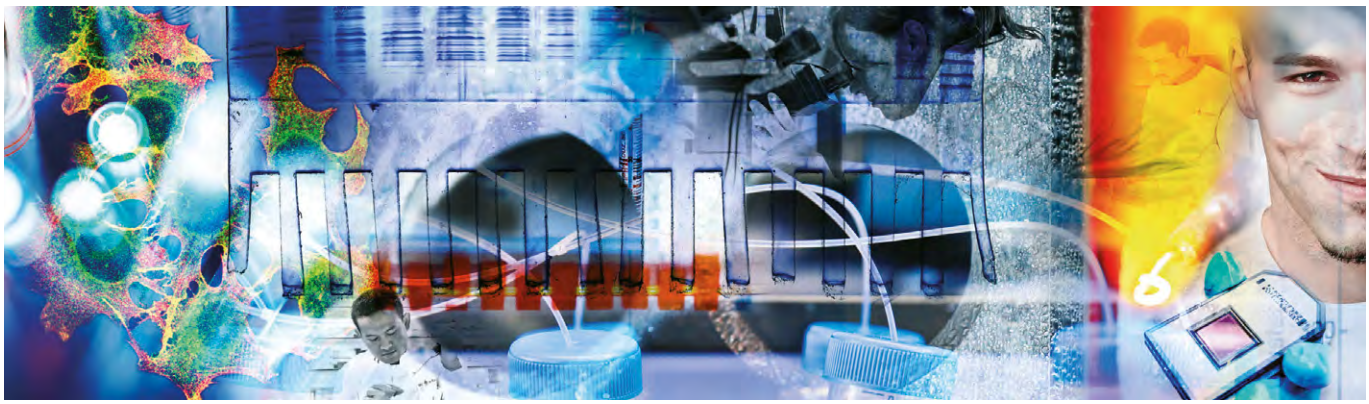
Being at the forefront of research is not an individual sport, it's a team 'game' fraught with challenges. Looking out for each other and inspiring your colleagues is essential to succeeding. The 2016 RIMLS annual report devotes attention to our young researchers hoping to follow in the footsteps of their role models. Many of our successful scientists are supported and coached by their supervisors and mentors who devote much of their free time to the next generation. For this, we're always very grateful. As an institute, we hope to play a part in the future of science by bringing researchers together to facilitate excellent research, education and ultimately to advance innovation in medicine. In 2016, we have organised many seminars, symposia and workshops, as well as a "RIMLSpeaks" debate for our principal investigators covering issues such as the value of science and publication pressure.

We wish all our colleagues an inspiring and healthy 2017. For now a look back to 2016.

Adrian Cohen
Scientific Manager

René Bindels
Scientific Director

Dagmar Eleveld
Scientific Manager



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Research

Mission

Researchers at the Radboud Institute for Molecular Life Sciences (RIMLS) seek to achieve greater insights into the molecular basis of disease. By integrating molecular and clinical research, the institute obtains multifaceted knowledge of normal and pathological processes. Within the general concept of personalized healthcare, findings are translated into clinical applications, into the development of diagnostics and into the treatment of patients. The institute offers a challenging and enriching learning environment, where researchers of all levels are exposed to societal-relevant medical research questions.

Education and Training

Our multi-disciplinary approach to research in molecular life science is reflected in an established RIMLS Graduate School with a dedicated 2-year research honours MSc degree in Molecular Mechanisms of Disease and a follow-up 3-4 year PhD program. In addition, the RIMLS actively participates in a post-doc platform and is committed to promoting career-track models, such as the Da Vinci, Galileo and Hypatia Tenure Track.

Research Themes and Innovation

The RIMLS accommodates research groups from the Radboud university medical center (Radboudumc) and the Radboud University's Faculty of Science. RIMLS aims to advance innovation in translational research, through high-end Technology Centers and by integrating diverse areas of scientific expertise within the molecular and medical sciences. In line with the Radboudumc strategic vision of having *a significant impact on healthcare,* research is clustered into clinically-orientated research themes from molecule to man plus a 'mechanism-based' theme, focusing on chemical biology and nanomedicine. RIMLS research comprises 12 themes, which are described briefly below:

- **Cancer development and immune defence**
  The primary goal here is to gain insight into the molecular, genetic and epigenetic processes that lead to the transformation of normal (stem) cells into malignant cancer cells. Insights into tumour microenvironments and interactions between the immune system and cancer are translated into specific forms of therapy, targeting the affected molecular pathways, and using (modified) immune cells to target tumour cells.

- **Rare cancers**
  Despite the rarity of each of the 186 rare cancers, they represent in total about a quarter of all cancer cases. Examples include head and neck cancer, sarcoma, thyroid cancer, neuroendocrine cancer, brain tumours, lymphoma, and paediatric cancer. The mission of this group is to improve diagnosis and prognosis for this patient group in an (inter)national collaborative setting.

- **Tumours of the digestive tract**
  Research focuses on improving the prognosis and treatment of patients with tumours of the digestive tract, in particular colorectal and pancreatic cancer. Key objectives are to develop diagnostic tools for staging and therapy response, and to innovate in surgical techniques and immunotherapy. Improving knowledge of the aetiology, epidemiology and genetics of these tumours will improve cancer therapy in high-risk patients.

- **Urological cancers**
  Research is designed to identify and evaluate the effectiveness of new biomarkers and imaging techniques for risk, diagnostic, prognostic and predictive assessment in prostate, bladder and kidney cancer. In addition, the intention is to evaluate new and existing prevention and treatment modalities for these types of cancer. Synergistic multidisciplinary research collaboration - from molecular life sciences to population sciences - is the tool to ensure that there is a strong focus on 'utility' for patients and public health.

Research

- **Women's cancers**
  Central to this theme is improving patient-centred quality of care in women's cancers (breast, ovarian, cervix, vulva, endometrium, and pregnancy-related) in partnership with patients. This includes prevention, early diagnosis or implementation of new management strategies, supported by a better understanding of carcinogenesis and tumour development, with special attention being paid to hereditary causes, preservation of fertility and personalized care after treatment.

- **Infectious diseases and global health**
  The mission within this theme is to achieve national and international leadership in research and research training in infectious diseases, immunity and global health. The main aim is to improve the diagnosis, treatment and prognosis of patients with infections through fundamental, translational and epidemiological-based investigative approaches to studying disease pathogenesis.

- **Inflammatory diseases**
  In the Western world, chronic inflammation is among the leading causes of morbidity and mortality. Central to this theme is understanding and controlling inflammatory disease for the benefit of patients by i) unravelling the (immune)pathogenesis of inflammatory disease processes; ii) elucidating the role of tissue specific factors in the regulation of local immunity and inflammation; iii) identifying druggable targets and biomarkers; iv) developing clinical grading tools; v) carrying out pharmacogenetic and epidemiological studies.

- **Mitochondrial diseases**
  The mission of researchers working on this theme is to understand the cellular bioenergetics in health and disease at all levels of complexity. The knowledge gained will make it possible to develop preventive measures and contribute substantially to the development of treatment strategies for mitochondrial diseases.

- **Reconstructive and regenerative medicine**
  This theme focuses on the development and clinical translation of innovative diagnoses and therapies – including regenerative medicine and nanomedicine – for personalized care and cure of patients needing reconstruction of lost or damaged tissues. This is achieved by transdisciplinary research involving leading research groups in medicine, dentistry, biochemistry, chemistry, biology and materials science.

- **Renal disorders**
  Current and future care of patients with renal and renal-related disorders can be improved considerably. To achieve this, the researchers aim to i) increase insight into the molecular and immunological basis of rare glomerular and tubular disorders; ii) develop biomarkers for optimal prediction of prognosis; and iii) apply strategies for the prevention and improvement of renal replacement therapy.

- **Vascular damage**
  Early detection of atherosclerosis, primary and secondary prevention of atherosclerosis, optimal treatment of atherosclerosis to preserve end-organ function, and implementation of effective diagnostics and therapies in practice are the key focus areas of this theme. The researchers probe the causes and consequences of vascular injury and translate this knowledge into improved personalized cardiovascular healthcare.

- **Nanomedicine**
  This mechanism-based theme focuses on the design, synthesis and characterization of molecules and molecular assemblies in order to elucidate structure and function of natural systems. Knowledge gained is applied to developing nanostructured devices for diagnostics, targeted delivery and tissue repair. Examples include artificial cells, molecular probes and tissue-mimetic materials.

Research

Collaboration

Present-day science tackles the most complex problems. These can't be solved by single researchers or even single institutions. Forming sustainable, interactive networks of scientists across international borders is indispensable for conceptual breakthroughs and the translation of fundamental findings into clinical practice. Building options for inter-institutional collaboration e.g. visiting professorships / lecturers, exchange possibilities for Masters students and PhD candidates, technology workshops, is a key ambition for the years ahead. The aim is to establish fully translational disease pipelines from 'molecule to man', and back again.

Locally, RIMLS is allied with the Institute for Molecules & Materials, the Radboud Institute for Health Sciences and the Donders Centre for Neuroscience, providing a solid platform for integrating chemical synthesis, nanomedicine and neuroscience with molecular life sciences and health sciences. Nationally, RIMLS has contacts with other UMCs and universities as well as with public and private partnerships. Internationally, RIMLS collaborates with many prestigious institutes, such as Broad Institute (Massachusetts, USA), University of California (California, USA), Tel Aviv University in Israel, University College London (London, UK) and The Wellcome Trust Sanger Institute (Cambridge, UK). Within Europe, there is increasing cooperation with the University of Duisberg-Essen, specifically the Graduate School of Biomedical Science (BIOME) and with the Institute for Research in Biomedicine (IRB, www.irbbarcelona.org) in Barcelona. On 3rd June 2015, Paul Smits, Dean of Radboudumc, signed an agreement with Joan Guinovart, Director of IRB, paving the way for researchers to participate in each other's research and education programmes. Early in 2016, this initiative was given a €0.5 M Euro boost with a Horizon2020 grant: European Academy for Biomedical Science (ENABLE, www.enablenetwork.eu), a consortium that will connect aspiring European researchers of tomorrow with prominent scientists of today. Involved in the consortium are two other partner institutions, namely Novo Nordisk Foundation Center for Protein Research (CPR) and the Italian-based European School of Molecular Medicine (SEMM).

Societal Impact

RIMLS's mission is in line with the Radboudumc's strategic vision to "have a significant impact on healthcare" and to advance "personalized medicine", one of the major societal themes at our medical center. The importance of molecular life sciences-related research in society is emphasized in education and research at RIMLS. Training researchers in life sciences is of great importance for society, since those currently studying at RIMLS will form a new generation of scientists and biotechnology entrepreneurs who will develop novel treatments and diagnostics.

RIMLS researchers contribute actively to the dissemination of research results via public conferences, teaching in schools and colleges as well as in the media. One shining example is that of Jolanda de Vries (Cancer development and immune defense) who appeared in national television and radio to inform the public of a new experimental vaccine treatment that reduces the risk of the recurrence of skin cancer. Jolanda de Vries and Mirjam Zegers (Woman's cancers) participated in a Radboud Institute for Health Sciences (RIHS) and Radboudumc Center for Oncology (RUCO) patient evening on the future of cancer. Similarly, Jan Smeitink (Mitochondrial medicine) organized a public information day for patients with mitochondrial disorders. On World Kidney Day a large multidisciplinary team of researchers working in the Renal disorders theme made a seminal public contribution raising awareness about kidney disease. Furthermore, RIMLS researchers including Mihai Netea (Infectious diseases and global health) and Irma Joosten (Inflammatory diseases) took part in the InScience Dutch International Science Film Festival, a joint initiative of Arthouse LUX and Radboud University. Mihai Netea also appeared regularly in the media to discuss his new discoveries on the workings of the immune system, scientific results that have lead to rewriting of the school biology text books. From the Infectious diseases and global health theme, Taco Kooij was in the news about the potential role of heavy metals in the fight against malaria, Ronald van Rij received media attention about a potential new drug target against Dengue virus and Patrick Zeeuwen was also in the spotlight regarding the bacteria that live in our skin. Also from this theme, Monique van der Voet and Ronald van Rij starred on an episode of the children's education television show 'Klokhuis' to explain how the fruit fly (Drosopila melanogaster) can be used as an experimental model organism.

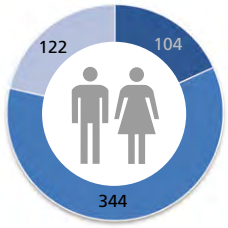
In 2015 Anna Simon (Inflammatory diseases) spent considerable time working in Sierra Leone, during the Ebola outbreak, a disease that killed a horrific number of people. Her personal experiences during this period, have been transformed into a book "Ebola – behind the mask", dedicated to the many victims (photo, inset Anna Simon in Sierra Leone).

Clinical groups interact with patients and their relatives at Radboudumc on a daily basis, have close ties with patient organizations, and are involved in public and strategic policy. From January 1, 2017 changes will be made in the national screening programme for cervical cancer. Many researchers from Radboudumc and RIMLS, together with other national centers, will be involved in the new screening based on human papillomavirus (HPV) instead of abnormal cells in a smear test. Finally, many RIMLS researchers efforts have been acknowledged in high-level personal awards. On page 14, examples from 2016 can be found.

Facts & Figures

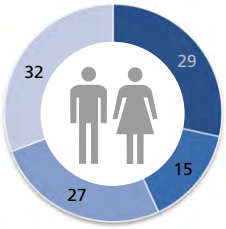
www.RIMLS.nl
75.000 page-views
400.000 unique page views
2 min average visit

Staff (fte) per appointment



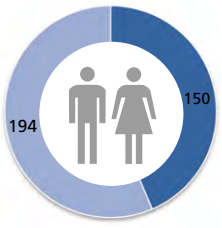
Tenured Non tenured Support

Tenured Staff (fte)



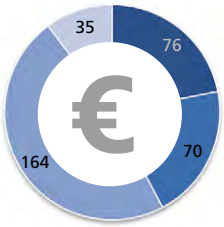
Professors Associate Professors
Assistant Professors Researchers

Non-Tenured Staff (fte)



Researchers Doctoral Candidates

Non-Scientific Staff Funding (fte)



1st Funding Stream 2nd Funding Stream
3rd Funding Stream 4th Funding Stream

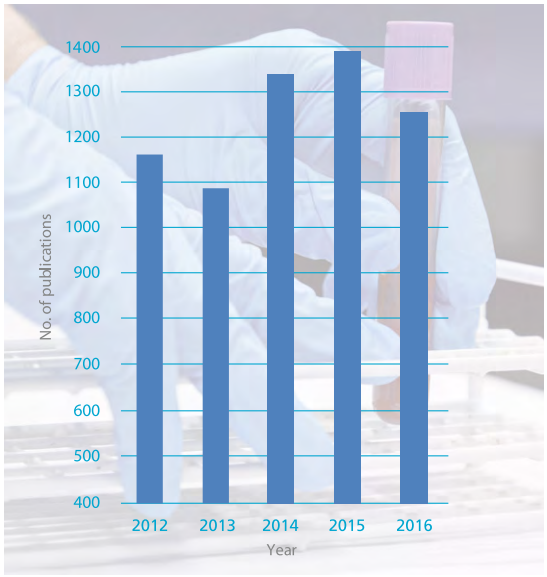
Scientific Staff Funding (fte)

1st Funding Stream 2nd Funding Stream
3rd Funding Stream 4th Funding Stream

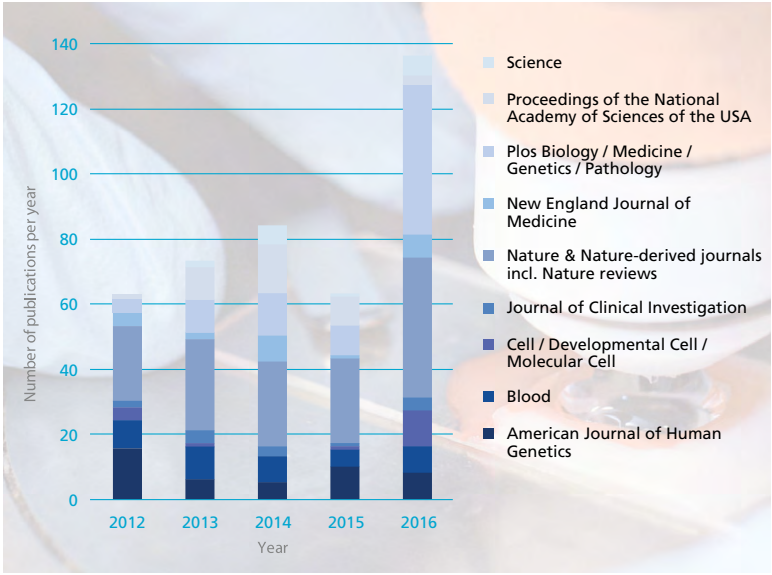
Number of graduations

75 Graduations & 3 Cum Laude

Total RIMLS publications



Number of publications in selected top-international journals

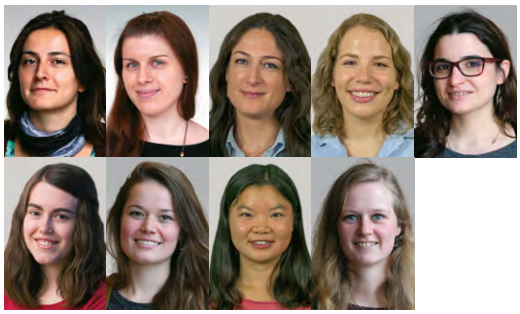


RIMLS & Selected Awards

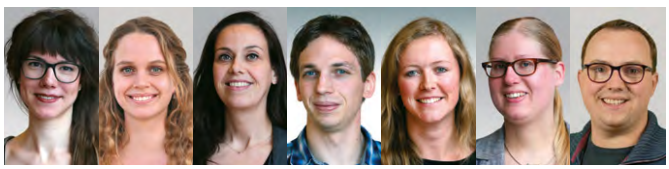
RIMLS Awards & Grants

Best Master thesis: Marilen Benner (Inflammatory diseases).
Best breakthrough paper: Lotte de Winde (Cancer development and immune defense).
Best PhD thesis: Kalijn Bol (Cancer development and immune defence).

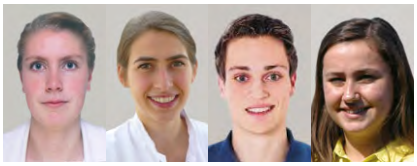
Best oral lecturers (PhD retreat): Jessie van Buggenum & Paul de Jonge (Urological cancers).
Best poster (PhD retreat): Jasmijn van Kampen (Cancer development and immune defense).



Winners of the RIMLS challenge (PhD retreat): Bilge San, Edyta Swider & Esther Willems (Cancer development and immune defense), Caroline Sieverink (Urological cancers), Irene Di Ceglie (Inflammatory diseases), Irene Lodoso Torrecilla (Reconstructive and regenerative medicine), Anique ter Braake (Renal disorders), Jiangyan Yu (Tumors of the digestive tract), & Cynthia de Bont (Nanomedicine).



Travel grant: Marilen Benner (Inflammatory diseases), Carlijn Bruggeling (Tumours of the digestive tract), Amelieke Cremers (Infectious diseases and global health), Andreas Kompatscher (Renal disorders), Svenja Mennens (Cancer development and immune defence), Nelleke Spruijt (Cancer development and immune defense), Laurens van de Wiel (Nanomedicine).



Best Master-PhD project proposals:

- Viola Klück (Infectious diseases and global health), Medicine: *"From bench to bedside: unravelling inflammatory mechanisms of hyperuricemia to prevent gout and associated diseases"*.
- Julia van Tuijl (Infectious diseases and global health), Medicine: *"The role of innate immunity in brain dysfunction in cardiac surgery patients"*.
- Laurens Verscheijden (Renal disorders), BMS: *"Building a virtual child to predict drug disposition in the pediatric brain"*.
- Cansu Yanginlar (Renal disorders), MMD: *"Trained autoimmunity as a driver in the pathogenesis of systemic lupus erythematosus"*.

Best PhD project proposals: In 2016, 8 PhD projects were awarded to RIMLS investigators:
Geert van den Bogaart (Cancer development and immune defense): *"Unraveling the role of autophagy in antigen cross-presentation"*; Harry Dolstra (Cancer development and immune defense): *"Deciphering immune checkpoint pathways crippling natural killer cell immunity against cancer"*; Erik Aarntzen (Tumours of the digestive tract): *"Multimodal imaging of distinct immune cell populations with optimized nanoparticles"*; Ronald van Rij (Infectious diseases and global health): *"Dissecting virus-host interactions in iPSC-based cell culture models for Zika and Dengue virus"*; Irma Joosten (Inflammatory diseases): *"Lessons learned in utero: born to be alive"*; Werner Koopman (Mitochondrial diseases): *"Targeting mitochondrial morphology to combat mitochondrial disease"*; Jeroen de Baaij (Renal disorders): *"CNNM2 as a new hotspot in blood pressure regulation"*; and Ronald Roepman (Renal disorders): *"Scrutinizing disassembly of the primary cilium and its role in cell cycle regulation and ciliopathy"*.

Best RIMLS-regional hospital PhD project proposals: In collaboration with Rijnstate and Canisius-Wilhelmina Ziekenhuis, respectively, two PhD positions were granted: Peter Pickkers (Infectious diseases and global health): *"Noradrenaline as a cause of sepsis?induced immunoparalysis: Time for a new vasopressor?"*; and Leon Massuger (Women's cancers): *"Implementing markers for the individualization of endometrial cancer treatment?"*

RIMLS & Selected Awards

Selected Consortium Grants

- The international PERISCOPE project received a €28 M European subsidy by the Innovative Medicine Initiative, of which €7 M from the Bill and Melinda Gates Foundation, to map the immune response to pertussis infection (whooping cough) and vaccination. Ronald de Groot (Infectious diseases and global health) is project coördinator.
- Jolanda de Vries (Cancer development and immune defense) will start a clinical trial with an experimental vaccine that reduces the risk of the recurrence of skin cancer. The study will last until 2021 and up to €20 M will be paid during that period by the Dutch government.
- The international research project, PERFORM, received €18 M grant from the Horizon 2020 Health Programme to develop a rapid test to reduce the use of unnecessary antibiotics and quickly identify deadly cases of meningitis, sepsis and other life-threatening bacterial infections. From the Radboudumc several groups are involve headed by Ronald de Groot and Marien de Jonge (Infectious diseases and global health). In total Radboudumc will receive €1.5 M.
- An international team coordinated by Prof. Aleksandra Trifunovic (University of Cologne) has been awarded a highly competitive €3.9 M Marie Sklodowska-Curie Innovation Training Network grant, REgulation of MItochondrial gene eXpression (REMIX), to train the next generation of scientists in mitochondrial gene expression regulation. From Radboudumc, Hans Spelbrink and Jan Smeitink, (Mitochondrial diseases) are involved.
- An STW perspective grant of €3 M has been awarded to Peter van der Kraan (Inflammatory diseases) and colleagues to develop a clinically-suitable method to stimulate cartilage repair.

- Jack Schalken and Gerald Verhaegh (Urological cancers) together with Guido Jenster (Erasmus MC) and Connie Jimenez (VUmc) received a €2 M Alpe D'HuZes/KWF grant to develop minimally invasive assays for the diagnosis and prognosis of prostate cancer.
- Nicole van de Kar (Renal disorders) and colleagues have been awarded €2.3 M from the Dutch Health Insurance Companies to optimize the duration & dose of the highly expensive drug, Eculizumab.
- A consortium consisting of CitiusBio BV, DKMS BV and Harry van Goor (Recontructive and regenerative medicine) was awarded a European Fund for Regional Development (EFRO) grant of €1,2 M to develop and validate the use of rapid measurement of hormones and biomarkers for heart disease as a compact point of care device.
- Mangala Srinivas (Nanomedicine) together with academic and industrial collaborators were awarded a €750,000 Dutch Technology Foundation (STW) grant to develop non-invasive cardiovascular imaging tools to monitor cardiac inflammation.

- A consortium consisting of Jan van Hest (Nanomedicine, RU), Harry van Goor and Sander Leeuwenburgh (Reconstructive and regenerative medicine) as well as industrial partners was awarded a €750,000 Dutch Technology Foundation (STW) grant to develop bone-adhesive membranes for advanced surgical treatment of tissue defects.
- The EU's Horizon 2020 Programme awarded €500,000 to the project "European Academy for Biomedical Science" (ENABLE) seeking to promote excellence in the biomedical sciences in Europe, strengthen scientific careers, and bring biomedicine closer to society. From the RIMLS, Adrian Cohen (RIMLS) is leading the Work Package on scientific symposia.

- A consortium of 7 EU partners, involving Toin van Kuppevelt (Reconstructive and regenerative medicine) has been awarded € 400,000 to study the diagnostic and therapeutic significance of specific alterations in heparan sulfate in Alzheimer's disease.
- Jan Smeitink, Frans Russel, Tom Schirris and Ria de Haas Mitochondrial diseases) have been awarded a Prinses Beatrix Spierfonds €250,000 grant to evaluate potential pharmacological interventions that stimulate the cellular cholesterol efflux.

- Jeroen van der Laak (Womens cancers), Bart Smeets, Eric Steenbergen and Luuk Hilbrands (Renal disorders), together with European partners were successful in acquiring a €250,000 ZonMW Joint Transnational grant (Sys-MIFTA) to elucidate pathological processes leading to renal transplant rejection.

RIMLS & Selected Awards

Veni, Vidi & ERC Awards

- Four RIMLS researchers were awarded NWO Veni grants, each worth €250,000 to develop innovative lines of research. Marije Doppenberg-Oosting (Rare cancers): *"Put the brake on Borrelia-induced joint inflammation"*, Sandra Heskamp (Rare cancers): *"Towards better patient selection for immune checkpoint inhibitor therapy for cancer: imaging of the PD-L1 and PD-1 pathway"*, Natalia Revelo Nuncira (Cancer development and immune defense): *"Turning on the alarms: how dendritic cells activate the immune attack"*, and Nelleke Spruijt (Cancer development and immune defense): *"NuRD regulates development"*.
- Michiel Schreuder (Renal disorders) was awarded a prestigious NWO-Vidi grant of €800,000, to develop his own innovative line of research: *"Why one kidney at birth is not enough ..."*.

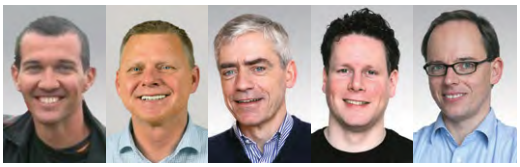
- Miriam Schmidts (Renal disorders) received a prestigious €1.5 M ERC starting grant for her research proposal: *"Novel Therapeutic Avenues for dynein-related Ciliopathies"*.
- Mangala Srinivas (Nanomedicine) was awarded an ERC Proof of Concept grant of € 150,000 to explore the innovation potential of her research: *"CONQUEST: Enabling advanced medical imaging"*.
- Annemiek van Spriel (Cancer development and immune defense) was awarded an ERC Consolidator Grant of €2 M for her project: "Secret surface" that aims to understand how cell surface receptors and membrane-proximal signalling proteins are organized by the tetraspanin web in tumour cells.

Selected Personal Grants & Awards

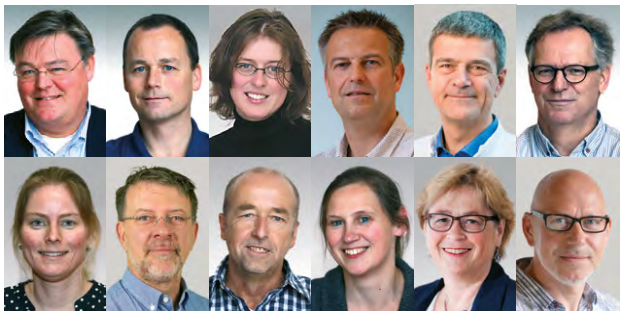
- Rick Wansink (Nanomedicine) has been awarded a €250,000 grant by the Prinses Beatrix Spierfonds to carry out the project *"Do anti-sense transcripts make pathobiological sense in myotonic dystrophy?"*.
- Three RIMLS researchers from the Inflammatory diseases theme were awarded Dutch Arthritis Foundation grants, each worth € 240,000, namely, Shahla Abdollahi: *"The functional relevance of the intestinal microbiome associated with new onset rheumatoid arthritis"*; Peter van Lent: *"Interplay of cholesterol and oxidative stress via LOX-1 fuels the flame of synovitis during joint destruction in osteoarthritis"* and Peter van der Kraan: *"Modification of the Smad lnker; missing link between inflammation and chondrocyte hypertrophy in osteoarthritis"*.
- Emmy Fleuren (Rare cancers): *"Synthetic lethal approaches for the treatment of 'AYA' sarcoma"* and Anneke Navis (Nanomedicine): *"Towards the root of the evil: Elucidation of the mechanism regulating neurodevelopmental factors essential for glioblastoma development and propagation"* have each been awarded a 2 year NWO Rubicon grant to conduct research at a foreign institute.

- Tom Schirris (Mitochondrial diseases): *"Elucidating the role of mitochondrial transport proteins in drug toxicity"* and Natalia Revelo Nuncira (Cancer development and immune defense): *"Polarized cytokine release at the dendritic cell immune synapse"* have each been awarded an EMBO Long-Term Fellowship to conduct research at a foreign institute.
- KWF awarded two Young Investigators grants of € 600.000 each to Sandra Heskamp (Rare cancers) for her project: *"Towards personalized use of immune checkpoint inhibitors by imaging of the PD-1/PD-L1 pathway"* and to Willemijn Hobo (Cancer development and Immune defense) for her project: *"Boosting graft-versus-leukemia immunity by combining hypomethylating angents and immunotherapy in patients with acute myeloid leukemia"*.
- Rachel van Swelm (Renal disorders) has received a Kolff Junior Postdoc grant of the Dutch Kidney Foundation (Nierstichting) of € 200,000 to execute her research project entitled *"Strike while the iron is hot: hepcidin-mediated protection against hemoglobin-induced acute kidney injury"*.
- Two researchers were each awarded a €100,000 ZonMW off-road subsidy to develop an innovative idea into a proof of concept. These 'high risk, high gain' projects were awarded to: Willemijn Hobo (Cancer development and immune defense): *"Aptamer technology for targeted siRNA delivery to dismantle the immunosuppressive tumor micro-environment"* and Patrick Jansen (Infectious diseases and global health): *"Antimalarials as a source of new anti-psoriatic drugs: adverse effects create opportunities"*.

RIMLS & Selected Awards



- Two groups of researchers obtained a Dutch Kidney Foundation Innovation Program grant, each €100,000:
  - Wilco Pulskens, Johan van der Vlag and Luuk Hilbrands (Renal disorders) will investigate whether functional reprogramming of renal tubular epithelial cells is involved in the progression from acute kidney injury towards chronic kidney disease.
  - Jürgen Dieker, Roland Brock (both Nanomedicine) and Johan van der Vlag (Renal disorders) will develop mRNA-based personalized therapies for inflammatory kidney diseases.



- This year, KWF awarded seven projects of RIMLS researchers:
  - Jack Schalken and Gerald Verhaegh (Urological cancers) together with colleagues from Erasmus MC and VUmc received a €2 M Alpe D'HuZes/KWF grant to develop *minimally invasive assays for the diagnosis and prognosis of prostate cancer.*
  - Iris Nagtegaal (Tumors of the digestive tract) together with colleagues from Academic Medical Center Amsterdam received € 1.1 M for the project: *"Evaluation of optimal intervals for colonoscopy surveillance: a randomized trial"*.
  - Harry Dolstra (Cancer development and Immune defense) and Leon Massuger (Women's cancers) received € 1M for the project: *"Intraperitoneal infusion of ex vivo-generated allogeneic natural killer cells in recurrent ovarian carcinoma patients: a phase I study"*.
  - Otto Boerman (Nanomedicine) and Sandra Heskamp (Rare cancers) received €600.000 for the project: *"Bimodal PSMA ligands for intra-operative tumor detection and photodynamic therapy of prostate cancer"*.
  - Paul Span (Women's Cancer) together with colleagues from Erasmus MC received €600.000 for the project: *"The role of APOBEC3B in breast cancer therapy resistance"*.
  - Frank van Leeuwen (Cancer development and Immune defense) received €500.000 for the project: *"Breaking therapy resistance in IKZF1 deleted Acute Lymphoblastic Leukemia"*.
  - Iris Nagtegaal, Marjolijn Ligtenberg, Nicoline Hoogerbrugge (all Tumors of the digestive tract) and Jeroen van der Laak (Women's cancers) received €450.000 for the project: *"Identify the patient and save the family - detecting hereditary pancreatic cancer"*.

- Alessandra Cambi (Nanomedicine) has been elected as MMD lecturer of the year.
- Ineke van der Zee and Rick Wansink (Nanomedicine) were both elected teacher of the year by the Medical Student's Association Nijmegen.

Selected awards & honours 2016

- Han van Krieken (Cancer development and immune defense) and Jan Smeitink (Mitochondrial diseases) were honoured with the highly prestigious Knight of the Order of the Dutch Lion in view of their services to medical research.
- Mihai Netea (Infectious diseases and global health) was elected to the Royal Netherlands Academy for Arts and Sciences (KNAW).
- Peter van der Kraan (Inflammatory diseases) was elected as board member Osteoarthritis Research Society International (OARSI).
- Peter Friedl (Cancer development and immune defense) received the European Society for Molecular Imaging (ESMI) 2016 Award for his work of preclinical imaging of cancer and immune cell function.
- Hans Jacobs (Cancer development and immune defense) received the Dutch Society of Clinical Chemistry (NVKC) Young Investigator Award 2016 for his contributions to medical immunology.

- Joost Drenth (Renal disorders) has been appointed Editorial Board member of European Radiology journal
- Niels Riksen (Vascular damage) has joined the ad hoc Medicalisation committee for the Health Council of the Netherlands, an independent scientific advisory body for government and parliament.

RIMLS & Selected Awards

- Bert van der Reijden (Cancer development and immune defense) became member of the scientific committee for KIKA, a charity for children with cancer.
- Jack Schalken (Urological cancers) became a member of the Global Scientific Council of the Movember foundation (Australia).
- Mangala Srinivas (Cancer development and immune defense) was elected to the board of the Young Academy of Europe.
- Annemiek van Spriel (Cancer development and immune defense) joined Scientific Board of the Dutch Cancer Society.
- Frans Russel (Renal disorders) has been elected to the Editorial Board of the journal Current Opinion in Toxicology and has been re-elected to the Dutch Health Council.

Innovation News

- Mercurna, a spinoff from Radboudumc, won the Venture Challenge 2016. Mercurna aims to develop precision medicine for chronic kidney disease. The members of the Mercurna team are Sander van Asbeck, Jürgen Dieker and Roland Brock (Nanomedicine).
- Khondrion (CEO Jan Smeitink), (Mitochondrial diseases) initiated the KHENERGY study, a phase 2 clinical trial of KH176 for mitochondrial diseases.
- Yannick Wouters (Infectious diseases and global health) won the Medical Inspirator Prize 2016 with his research project *"Rapid DNA-test for bloodstream infections in intestinal failure patients"*.
- Radboudumc's spin off Noviogendix was acquired by MDxHealth. The Nijmegen staff has doubled in 2016 to 16 employees. Jack Schalken (Urological cancers) is advisor to the board of MDxHealth.

Appointments

- Han van Krieken (Cancer development and immune defense) was elected as the new Radboud University Rector Magnificus.
- Carl Figdor (Cancer development and immune defense) was appointed as Extraordinary Professor on the TEFAF Oncology Chair in the Faculty of Health, Medicine and Life Sciences, Maastricht University.

Spinoza Prize

Annualy NWO awards the Spinoza Prize, the highest award in Dutch science, to three or four researchers working in the Netherlands who, according to international standards, belong to the absolute top of science. On 13th September, Mihai Netea received the NWO Spinoza Prize. The award ceremony was held at the Nieuwe Kerk in The Hague. During the awards ceremony Mihai Netea presented his plans for using the research prize worth €2.5 M, *"With my work I strive to have an impact on patients' lives"*. At the end of the award ceremony all laureates received the bronze statuette of the Dutch philosopher Baruch Spinoza.

Who was Spinoza?
Baruch Spinoza was born in Benedito de Espinosa, Portugal (1632 - 1677). Spinoza was a Dutch philosopher of Sephardi/ Portuguese origin. By laying the groundwork for the 18th century Enlightenment and modern biblical criticism, including modern conceptions of the self and the universe, he became to be considered one of the great rationalists of 17th-century philosophy.

Photographer: Sascha Schalkwijk

An incredible year
In 2016, Mihai Netea has published over 80 articles, 5 of which in a single issue of Cell. Mihai has also published in 2016 in prestigious journals such as Science, Nature genetics and Nature medicine. In 2016, Mihai was elected to the Royal Netherlands Academy for Arts and Sciences (KNAW). He currently has published over 600 articles with more than 24,000 citations.

Mihai was born and studied medicine in Cluj-Napoca, Romania. He completed his PhD at the Radboud University Nijmegen, investigating the cytokine network in sepsis. After working as a post-doc at the University of Colorado, he returned to Nijmegen where he finished his clinical training as an infectious diseases specialist, and where he currently heads the division of Experimental Medicine. His main research interests are sepsis and immunoparalysis, recognition of pathogens, primary immunodeficiences, and the study of immune system memory. He is also involved in several projects on ancient DNA and understanding the evolution of the immune system. In his spare time he enjoys reading history and science fiction, while occasionally writing about the future. For instance, he wrote a science-fiction novel entitled "North-West passage to the Moon". He lives with his wife and two children in Nijmegen.

Scientific Activities

PhD Retreat

The 22nd edition of the annual RIMLS PhD retreat was a great success! We welcomed about 200 participants, including 6 guests from the Institute for Research in Biomedicine (IRB) in Barcelona. Twenty final year PhD candidates discussed (elements of) their PhD projects during oral presentations. All other PhD candidates presented their research during four poster sessions.

This year we were grateful to Dick Swaab, a renowned neurobiologist from the Netherlands Institute for Neuroscience and member of the Royal Netherlands Academy of Arts and Sciences, who lectured on his research on sexual dimorphism and how it relates to brain anatomy. His address was followed by a lively discussion from the audience. After this inspiring lecture it was time to crack your own brains by playing interactive games, over a glass of beer, wine or juice. With the participation of the DJ from Skyfly, and the new addition of a photo booth (photo left), the party brought all the elements necessary for a fun and relaxing night. Once again "The RIMLS Challenge" was proof that science is evolving into a more cooperative environment where communication skills are pivotal. The creative minds of our PhD candidates and their artistic skills were put to test during the pitching session. Gijs Meeusen, founder of Artesc and author of the book "The Art of Presenting Science", gave a two-hour workshop in non-verbal communication. Gijs guided participants during the preparations for the challenge and joined the jury in judging the pitches. Entitled "The Secrets from the Lab" this year's challenge was the perfect way to end our retreat. Next year the retreat will be held on 20th & 21st April 2017.

Radboudumc Postdoc Initiative (RPI)

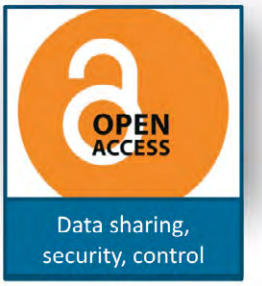
The RPI is a platform that represents Postdocs, research clinicians and final year PhD candidates. It's a diverse group of researchers with individualised career choices and career needs. In this respect, they voice concerns, share experiences and exchange knowledge. This year the RPI appointed a new chairman Sandra Heskamp (Rare cancers) and secretary Janet Vos (Tumours of the digestive tract). In addition to raising relevant issues for the Postdoc community, the RPI organizes a series of lunch seminars, which feature invited speakers on various topics important to a postdoctoral career. This year, two lunch seminars were organized with the topics: *"How to publish BIG"*. To get a glimpse of what it takes to have a high?quality paper, suitable for the top journals, Nael Nadif Kasri and Joost Drenth gave their insights from both the author and editor perspective. The second lunch meeting was entitled *"How to become an independent scientist"*. The invited speakers Maroeska Rovers and Dirk Lefeber shared their own experiences with building up a career in scientific research. The informal *"Pizza and beer"* event was extended in 2016 inviting special guests to discuss the emerging topics, such visiblity of postdocs via Art & Science initiative, the discussion on mentoring, the possibilities in the further career development (eg. Project YOU, career counselling, activities in RU and Radboudumc) and the grant possibilities. RPI continues to participate in the introduction day of the Radboudumc, which is offered to starting Postdocs. In addition, the RPI has been represented during major career development events at RU and Radboudumc, such as the *Radboud Career Week, RU Get inspired, and RU Get in Touch.* In 2016 RPI started with RPI Newsletter, appearing 3x a year, to announce and report on all above mentioned activities.

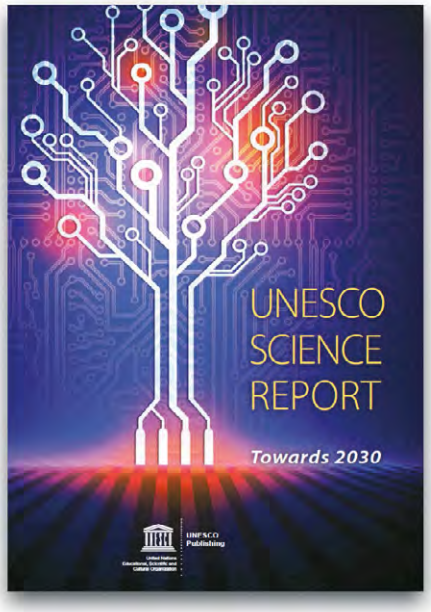
Scientific Activities

RIMLSpeaks

On 5th October 2016, the first RIMLSpeaks was organized for selected group leaders, "Our scientific system in need of change"? In recent years, our scientific landscape has changed dramatically. The number of published articles has increased significantly, the competition for grants is huge, the call for social responsibility and impact has risen sharply. During a thought-provoking debate Gerard Meijer (President, Radboud University) and Barend van der Meulen (Head Science System Assessement, Rathenau Institute) discussed these issues with our (junior) principal investigators. After the discussion there was a round table dinner to discuss some more in a social setting. The following topics were discussed by the panel and audience: a) Publication-numbers and rankings are an accurate measure of the quality of a researcher, b) There are too many researchers In the Netherlands, c) The Radboudumc needs to limit the number of research lines, d) Within 5 years 50% of the professors should be women, e) The quality requirements that the Radboudumc currently uses for our dissertations (preferably at least 3 accepted articles as first author) are too high and obstruct a PhD graduation within four years, f) PhD candidates should be trained for a career outside the science.

Emerging issues





The RIMLS as Graduate School

MSc Molecular Mechanisms of Disease

The RIMLS offers a high-quality Master's programme in Molecular Mechanisms of Disease (MMD), which is taught by our leading researchers and clinicians. MMD offers a challenging programme that meets the needs of talented students with the drive, motivation and ambition to push forward their scientific careers. Our master programme provides an excellent preparation for research in top institutions and for building an international research network. The small-scale and interactive nature of the MMD modules offer a challenging educational environment for both, students and lecturers at the crossroads between 'bench' and 'bedside' research activities.

The MMD Master's programme provides students with excellent qualifications to enter an international PhD programme. Our graduate students distinguish themselves through their high knowledge level and independent working attitude. Most of them enter a PhD programme in Nijmegen or elsewhere in the world. Students have found PhD positions at for example the Karolinska Institute (Sweden), Stanford University (USA), Institute for Research in Biomedicine Barcelona (Spain) and the RIMLS itself.

Awarded excellence
In 2016 the MMD programme was re-accredited by the Accreditation Organisation of the Netherlands and Flanders (NVAO) and obtained an impressive overall rating of "good" which is awarded to less than 10% of the master programmes in the Netherlands. The accreditation panel was impressed by the translational profile and approach of the MMD programme. Its focus and intended learning outcomes are regarded as an international example, and were assessed as "excellent".

Students' comments on MMD and RIMLS research:

Jeroen Slaats – MMD graduand 2016, PhD candidate RIMLS; winner of a Radboudumc PhD fellowship
"MMD offers a highly motivated and enthusiastic learning environment to prepare for a successful scientific career. The extensive grant writing exercises and numerous oral presentations provided me with excellent training for winning a Radboudumc PhD fellowship. The MMD programme not only taught me competences in scientific skills, but it also gave me the confidence and courage to pursue a research training internship in a world-leading research group abroad. I recently started my PhD studies at the department of Cell Biology, in which I focus on the intriguing mechanisms of tumor immune escape. I would love to continue my career in scientific research, and MMD provided an excellent foundation for that."

Marilen Benner – MMD graduand 2016, PhD candidate RIMLS; winner of the Radboud University Academic Award 2016
"After my bachelor, I knew that I wanted to focus more on research. I applied for the MMD Master with the expectation of getting a good preparation for a PhD. Looking back, I have gained a lot more from MMD than I had anticipated. We started with theoretical courses and an important part of them were the soft skills associated with them. We were encouraged to get in touch with and challenge international experts in lectures, masterclasses and meetings. I was able to build up a network in my field of interest. Due to this I got the opportunity to join the lab of Dr. Jack Strominger at Harvard University for my final master's internship. On a professional level, MMD has been a stepping stone for my scientific career."

Estel Collado Camps – MMD graduand 2016, PhD candidate RIMLS
"I graduated on MMD in September 2016 and started my PhD right after my graduation. Again at the Radboudumc, and in the beautiful city of Nijmegen, where I now feel at home. My PhD project is a complete new start for me: different topic, different techniques, different group. There's still so much to learn, and facing this challenge I've realised how important my previous experiences were. MMD is not only about learning concepts. Rather, MMD gave me the tools to understand and use academic literature, share ideas and communicate effectively, think critically and be able to envisage new scientific questions and ways to answer them. Once a colleague said that "we're not afraid to learn", and that's the key. This is why I look forward to new challenges and I am not afraid to get out of my comfort zone."

The RIMLS as Graduate School

Doctoral Research and Training

The RIMLS Graduate School constitutes a challenging, yet enriching learning environment where researchers are exposed to societal-relevant multidisciplinary research questions along the theme of understanding the molecular basis of disease. The academic medical setting provides the perfect mix of researchers for students to explore the length of the molecule-to-man pipeline. PhD candidates are offered an interdisciplinary training program that can tailored to meet individual interests. In particular, candidates are encouraged to develop and refine their research competencies and transferable skills necessary for a successful independent scientific career. PhD's who complete the research and training requirements within the agreed research period are eligible for a RIMLS Graduate School Certificate and financial bonus.

The RIMLS motto is 'to understand molecular mechanisms of disease'. What does this mean to some of our PhD candidates?

Lotte de Winde (Cancer development and immune defense)
There is still a lot we don't know and I think it is really important to understand the molecular mechanisms behind a disease before we can develop new or improve current therapies. This means we should stimulate fundamental research in order to discover novel molecular mechanisms.

Jelle Vriend (theme Renal disorders)
For me the RIMLS motto means to establish a functional 3D renal model and use this model to understand nephrotoxicity.

Dorien Feyaerts (Inflammatory diseases)
The immune system is a complex interplay of numerous molecular mechanisms and is far from understood. It needs to be unraveled piece by piece to solve the puzzle. Understanding the mechanisms behind this tolerance and development in healthy and complicated pregnancies will help to find treatment options for women who suffer from pregnancy complications, like recurrent miscarriages.

Gert-Jan Bakker (Cancer development and immune defense)
Biology occurs along many different scales, at the one end there is the molecular scale, with many different molecules acting upon each other in a very dynamic fashion, all in a tiny environment. At the other end, many diseases are systemic, with the whole organism or even society involved. I want to combine established building blocks in biology, physics and other disciplines to visualize the molecular mechanisms of disease along these different scales, with a particular interest in microscopy.

The RIMLS as Graduate School

Joep Joosten (Infectious diseases and global health)

To construct a model of disturbances of a molecular system, e.g. in the case of disease, we must first have a thorough understanding of the system in its healthy state.

Michelle Damen (Infectious diseases and global health)

It is actually the reason why I do research. How does it work and why do certain people become sick where others do not and what is causing this difference?

Corina van den Heuvel (Nanomedicine)

I've always been interested in how the human body works in general and, in particular the underlying mechanisms that cause disease. It is the ultimate challenge to unravel exactly how a disease manifests, and to utilize this knowledge to find a therapy that targets such critical 'survival mechanisms'....without side effects of course.

Iris Hagemans (Cancer development and immune defense)

For me, chemistry becomes interesting when it has an application 'in real life'. The most interesting projects are those where you can combine chemistry and molecular biology, or those projects that aim at answering a fundamental molecular biology question.. For me, that means the aims are relevant, not just in a scientific context but also in a 'real life' context.

Susan Schuster (Infectious diseases and global health)

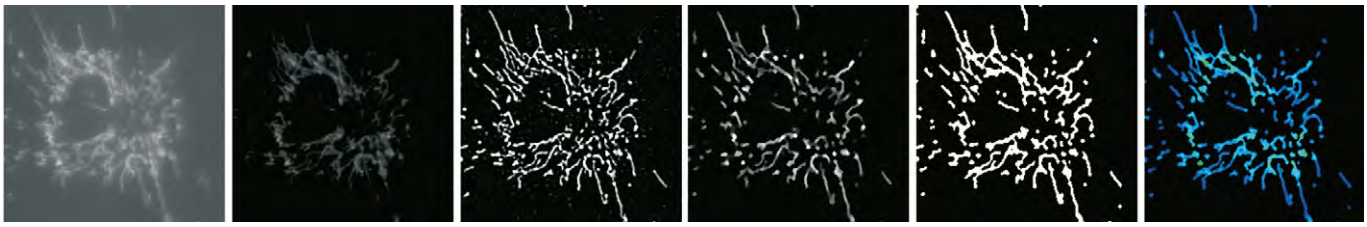
In my opinion, understanding the molecular mechanisms of disease is critical to improving patient care. It is difficult to translate findings into the clinic without a good understanding at the molecular and cellular level. Therefore fundamental research is essential.

Eligio Iannetti (Mitochondrial medicine)

I have always had a mechanistic conception of life and I love to break down complex problems in smaller issues that I can better deal with, therefore the RIMLS motto means a lot for me. I love it.

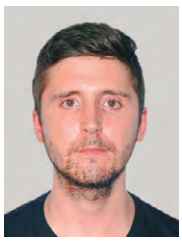
Patents Requested

Title	RIMLS lead inventor(s)
Fiber reinforced Hap	Sander Leeuwenburgh
3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors which do not affect the mitochondrial complex III activity - including modified statins and new chemical entities.	Tina Ritschel, Tom Schirris, Jan Smeitink, Floris Rutjes, Frans Russel.
Process for preparation of beads for imaging	Mangala Srinivas, Jolanda de Vries, Carl Figdor, Chris de Korte
Fusion protein comprising Pneumococcal antigen	Marien de Jonge, Kirsten Kuipers
Patent appl. created under existing licence Oxfordimmunotec/Radboudumc - patent T10-0003 - "new diagnostic method wherein IL-12 is added and IFNg is the read out"	Leo Joosten, Mihai Netea, Ian Durrant (Oxford Immunotec), Wolfgang Pieken (Boulder Diagnostics)
Selective cell penetrating peptides	Harry Dolstra, Jan van Hest



Selected Research Highlights

RIMLS 2016




Theme: Cancer development and immune defense

Boris Novakovic
Henk Stunnenberg

Cell 167:1354–1368, 2016.

Candida albicans derived β-glucan re-instates macrophage function after immune-suppression caused by E. coli LPS

Tolerance is a phenotypic state of innate immune cells, such as monocytes and macrophages, in which they are incapable of mounting a pro-inflammatory response. This state is often observed in sepsis patients, where an initial high bacterial burden renders the cells incapable of responding to pathogens, leading to high susceptibility to infection and death. As part of the BLUEPRINT consortium, we employed a comprehensive epigenomics approach to study how monocytes become tolerant after exposure to a bacterial compound called lipopolysaccharide (LPS). Our analysis revealed a specific set of pathways and genomic regions that are repressed by LPS exposure. We further found that these same pathways and regions are strongly activated by another microbial compound, β-glucan. This led us to hypothesize that LPS-induced tolerance could be reversed by β-glucan exposure. Our collaborators at Radboud UMC used an in vivo model of LPS induced tolerance and showed that β-glucan exposure can re-instate a pro-inflammatory phenotype *ex vivo* (Figure). This is the first time that the tolerant state has been reversed and this discovery paves the way for future clinical trials in sepsis patients.

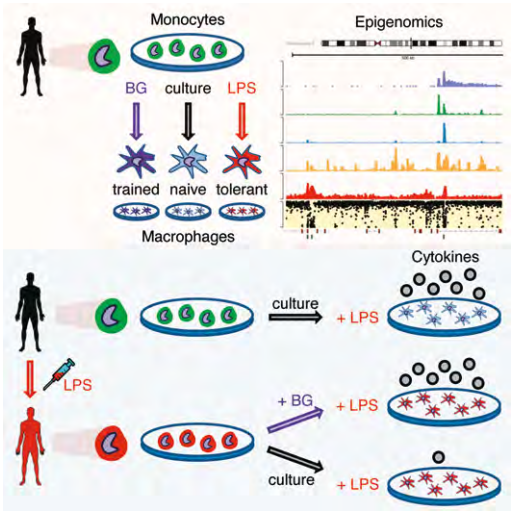


Figure: Monocytes were exposed to E. coli derived lipopolysaccharide (LPS) or C. albicans derived β-glucan and analyzed at the epigenome level (histone marks, RNA, DNA methylation, open chromatin). We show that LPS-tolerized monocytes can be re-wired to a steady state by exposure to β-glucan. The steady-state is defined as high cytokine release at LPS re-exposure *ex vivo*.


Theme: Cancer development and immune defense

Charlotte de Winde
Annemiek van Spriel

J Clin Invest 126:653–666, 2016.

Tetraspanin CD37 protects against B cell lymphoma development

B cell lymphoma is the most common hematological malignancy worldwide, and molecular mechanisms leading to B cell lymphoma are not well understood. We discovered that tetraspanin CD37, a membrane-organizing receptor important for B cell function, protects against B cell lymphomagenesis. CD37-knockout mice spontaneously developed B cell lymphoma in lymphoid organs, which was associated with hyperactivation of the IL-6 signaling pathway. The underlying mechanism is a molecular interaction between CD37 and SOCS3, an intracellular cytokine suppressor that inhibits IL-6 signaling (Figure A). In patients with diffuse large B cell lymphoma (DLBCL), CD37 expression was lost in ~50% of lymphomas (Figure B), which was directly correlated with enhanced IL-6 signaling. Importantly, patients with CD37-negative tumors had a significant worse overall survival than patients with CD37-expressing tumors (Figure C). Our study identifies CD37 as a novel tumor suppressor in B cell lymphomagenesis. Furthermore, it provides a strong rationale for blocking the IL-6 signaling pathway in patients with CD37-negative B cell lymphoma as a new therapeutic intervention.

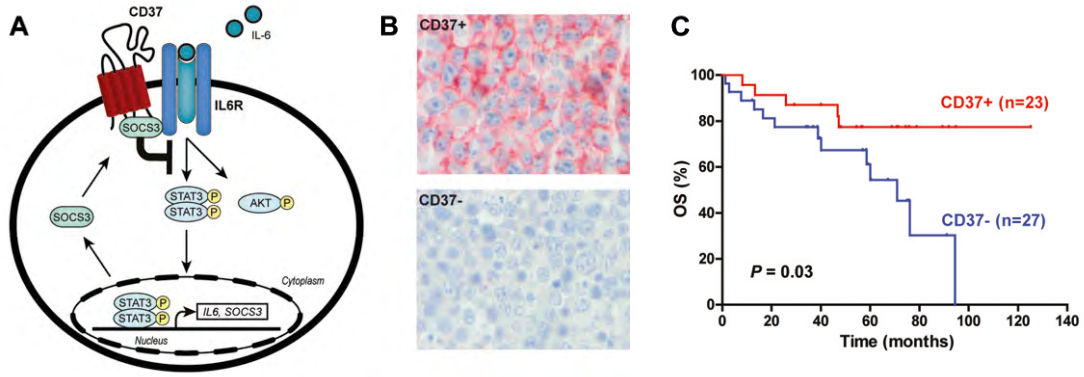


Figure: **(A)** Tetraspanin CD37 inhibits the IL-6 signaling pathway via direct interaction with SOCS3. **(B)** Human DLBCL tissue stained for CD37 (red) and nucleus (blue) demonstrating a CD37-positive (upper) and CD37-negative (lower) tumor. **(C)** Patients with CD37-negative DLBCL (blue line) have poor overall survival.

Theme: Infectious disease

Taco Kooij

Nat Commun 7:10519, 2016.

Functional profiles of membrane transporters in the life cycle of the malaria parasite

Assigning function to orphan membrane transport proteins and prioritizing candidates for detailed biochemical characterization remain fundamental challenges and are particularly important for medically relevant pathogens, such as malaria parasites. We performed a comprehensive genetic analysis of 35 orphan transport proteins of *Plasmodium berghei* during its life cycle in mice and *Anopheles* mosquitoes (Figure). Six genes, including four candidate aminophospholipid transporters, are refractory to gene deletion, indicative of essential functions and highlighting these as potential drug targets. Using our advanced flow cytometry-based approach, we generate and phenotypically characterize 29 mutant strains with deletions of individual transporter genes, presenting the largest collection of mutant malaria parasite lines published to date. Whereas seven genes appear to be dispensable under the experimental conditions tested, deletion of any of the 22 other genes leads to specific defects in life cycle progression *in vivo* and/or host transition. Our study provides growing support for a potential link between heavy metal homeostasis and host switching and reveals potential targets for rational design of new intervention strategies against malaria, including a new lead for a genetically attenuated whole-parasite vaccine.

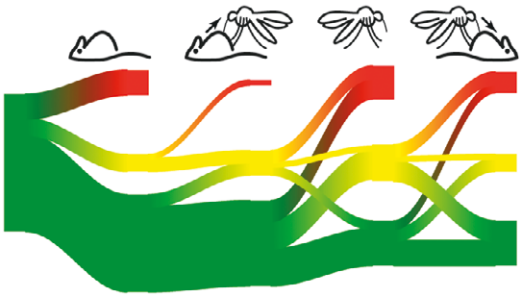


Figure: **Experimental genetics screen of malaria parasite orphan membrane transport proteins.** Sankey diagram for parasite development at four life cycle checkpoints looking at (a) blood-stage growth in the mouse, (b) mouse-to-mosquito transmission, (c) development in the mosquito, and (d) mosquito-to-mouse transition and ability to complete the full life cycle. Parasite lines are enumerated and colored according to complete arrest (red), slow development (<10% percentile; yellow), and normal growth (green).

Theme: Infectious disease

Marije Doppenberg-Oosting
Mihai Netea

Nat Med 22:952-960, 2016. – Cell 167:1125-1136, 2016.
Cell 167:1111-1124, 2016. – Cell 167:1099-1110, 2016.

To get more understanding of the human immune response

The human immune system is represented by a complex network consisting of several players including immune cells and organs. Between individuals large variability in immune responses is observed, leading to different clinical outcomes in disease and changes in susceptibility to disease. There is an urgent need to understand this variability of these responses in the human population and how this variability relates to susceptibility to immune-mediated diseases and to responses to immune-based therapies.

In these studies, we aimed to characterize and understand interindividual variation of human immune responses more comprehensively by combining 'omics' technologies with in-depth functional phenotyping of the immune responses in healthy and diseased individuals (http://www.humanfunctionalgenomics.org/).

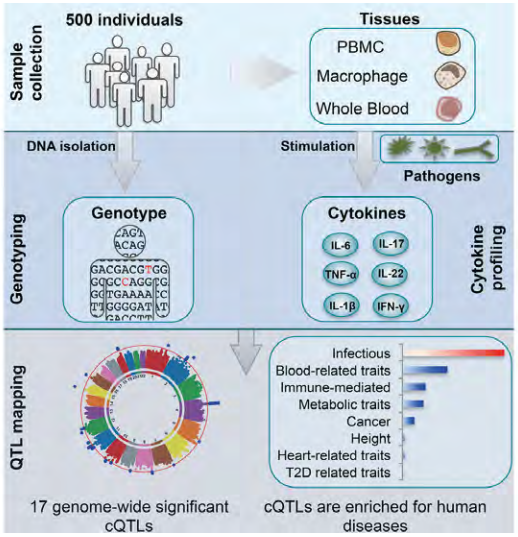


Figure: Overview of the study design. 500 healthy individuals were included in the study and on the one hand genotyped but also immunological assessed. By using quantitative trait loci (QTL) analysis, 17 genome-wide cytokine-QTLs were discovered in this population leading to changes in susceptibility to infectious diseases.

Theme: Inflammatory diseases

Bram van Cranenbroek
Irma Joosten

Blood 127:1976-1986, 2016.

Platelets as regulators of the immune response in inflammation

Regulatory T-cells (Treg), suppressive by nature, are important for the prevention of auto-immunity acting as modulators of inflammation. However, depending on environmental stimuli, these cells can inadvertently change function and turn into IL-17 producing cells that lose suppressive capacity. Stabilizing Treg is important to prevent immunepathology. While platelets are critical for hemostasis, recent insights reveal that they can also modulate immune responses. Upon activation, platelets release plasma membrane platelet-derived microparticles (PMP) into the circulation. These PMP were shown to be actively involved in (pathogenic) immune responses. In our work, we show that PMP prevent the deleterious switch of Treg from a suppressive towards a pro-inflammatory profile in a cell-contact dependent way. We identified two receptors on Treg, PSGL-1 and CXCR3, involved in this interaction. In functional studies, the immunomodulatory effect was established in a well-defined subset of HLA-DR$^+$ CCR6$^+$ Treg. Together, these findings open the exciting possibility that PMPs actively regulate the immune response at sites of (vascular) inflammation, where they are known to accumulate and interact with leukocytes, consolidating the (vascular) healing process.

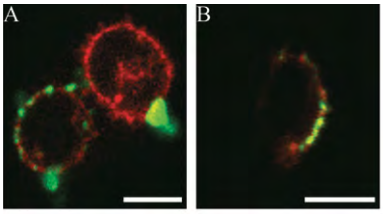


Figure 1: Confocal laser scanning of activated Treg co-cultured with PMP; (A) binding of CD41+ PMP (green) to Treg (CD25 (red)); (B) adherent P-selectin positive PMPs (green) co-localize with PSGL-1 (red) on Treg.

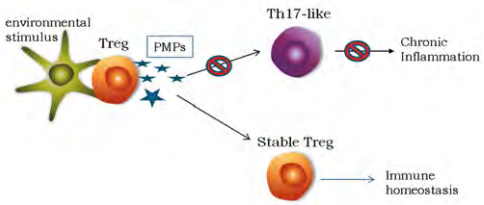


Figure 2: Schematic overview of the Treg – PMP interaction preventing Treg turning into IL-17 producing cells.

Theme: Inflammatory diseases

Edwin Geven
Peter van Lent

Arthritis Res Ther 18:247, 2016.

Sounding the alarm in seronegative arthritis. Novel molecular imaging markers for predicting joint destruction

Seronegative joint diseases are characterized by the lack of autoantibodies, which are relevant biomarkers for predicting disease activity in rheumatoid arthritis, and no validated biomarkers are available yet. Promising alternative biomarkers are the alarmin proteins S100A8 and S100A9 which are specifically released by infiltrating phagocytes. We have therefore investigated the biomarker potential of serum S100A8/A9 and *in vivo* imaging of synovial S100A8 to assess joint inflammation and damage in the IL-1 receptor antagonist deficient (IL-1Ra$^{-/-}$) mice, a mouse model for seronegative arthritis in which serum autoantibodies are not correlated to disease activity. We showed that serum levels of S100A8/A9 were significantly increased in IL-1Ra$^{-/-}$ mice and correlated to macroscopic joint swelling and histological parameters of inflammation, bone erosion and cartilage damage. The increased serum S100A8/A9 levels were reflected by an increased expression of S100A8 within the ankle joint, as visualized by molecular imaging (Figure). In addition, increased synovial S100A8 expression, coincided with increased cartilage damage, MMP-mediated neoepitope expression and *in vivo* imaging of activated MMPs. Our data underline the potential of S100A8/A9 as a systemic and local imaging biomarker tool in seronegative arthritis, not only for assessing inflammation but also for severity of inflammatory joint destruction.

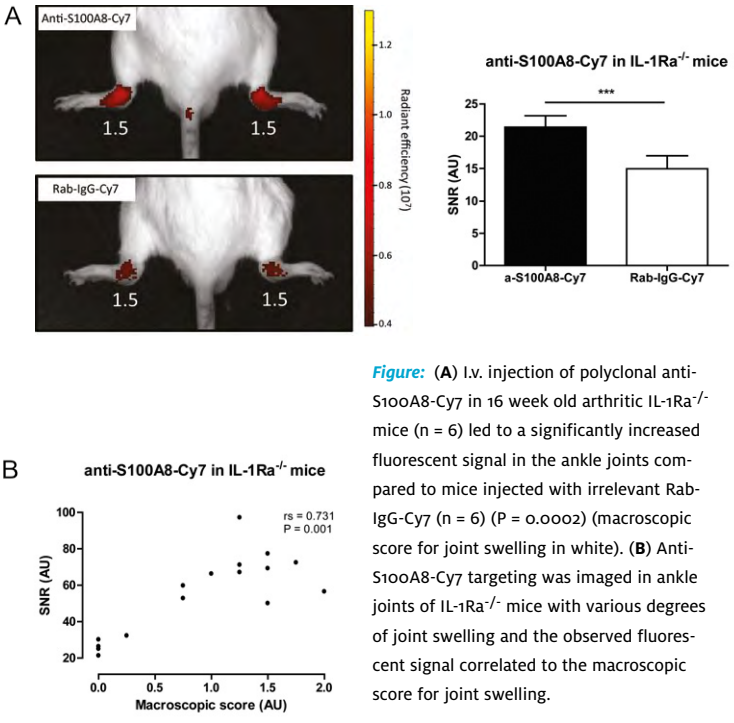


Figure: (**A**) I.v. injection of polyclonal anti-S100A8-Cy7 in 16 week old arthritic IL-1Ra$^{-/-}$ mice (n = 6) led to a significantly increased fluorescent signal in the ankle joints compared to mice injected with irrelevant Rab-IgG-Cy7 (n = 6) (P = 0.0002) (macroscopic score for joint swelling in white). (**B**) Anti-S100A8-Cy7 targeting was imaged in ankle joints of IL-1Ra$^{-/-}$ mice with various degrees of joint swelling and the observed fluorescent signal correlated to the macroscopic score for joint swelling.


Theme: Mitochondrial diseases

Eligio Iannetti
Werner Koopman

Nat Protoc 11:1693-1710, 2016.

Automated microscopy analysis of mitochondria in human metabolic disorders

Mitochondria function as the powerhouses in virtually every cell of the human body and play a central role in a wide variety of diseases including cardiovascular disease, neurodegeneration, chronic autoimmune diseases, inflammation, cancer and metabolic disorders. Individual mitochondria are motile and possess a high morphological plasticity and variability. Much needs to be learned about how mitochondrial morphology and function ("morphofunction") are quantitatively coupled to each other and to cell functioning at the mechanistic level. To address this issue we developed an integrated live-cell microscopy strategy for unbiased automated quantification of mitochondrial morphofunction in multi-well plates (**Fig. 1**). This information was obtained at the single-organelle level in living fibroblasts from healthy individuals and patients with mitochondrial disease. Cells are stained with fluorescent reporter molecules allowing simultaneous readout ("multiplexing") of nuclear, cytosolic and mitochondrial parameters (44 descriptors in total). The descriptor data is subjected to an automated quality control algorithm based upon principal component analysis and interpreted using univariate, bivariate and multivariate statistical analysis. Our strategy is suited for application in fundamental research, mitochondrial drug development and mitochondrial toxicity analysis.

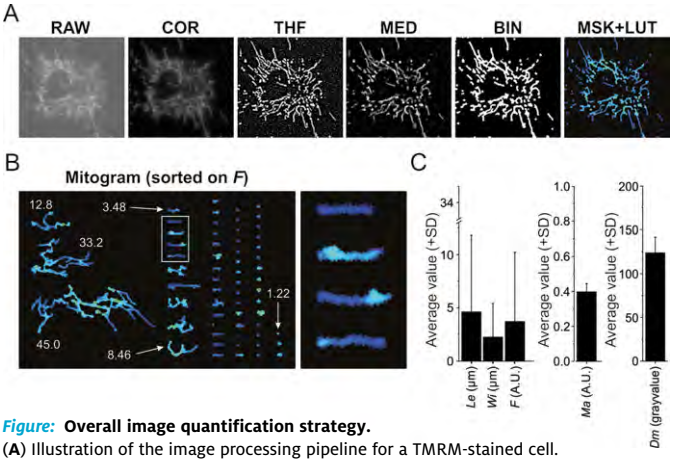


Figure: **Overall image quantification strategy.**
(**A**) Illustration of the image processing pipeline for a TMRM-stained cell. The intensity of the TMRM signal is color-coded from low (blue) to high (green). (**B**) "Mitogram" calculated from the last image in panel A. In the left panel mitochondrial objects are depicted according to their length and degree of branching ("Formfactor" *F*, values indicated by numerals). The right panels shows 4 individual mitochondrial and signal heterogeneity. (**C**) Average value of six descriptors calculated for the 61 objects in the last image in panel A: mitochondrial length (*Le*), width (*Wi*), *F*, margination (*Ma*) and average TMRM intensity (*Dm*). **Abbreviations:** A.U., arbitrary units; BIN, Binary image; COR, Background-corrected image; MED, Median-filtered image; MSK, Masked image; RAW, Image directly from microscope; LUT, look-up table; THF, Top-hat filter.


Theme: Mitochondrial diseases

Laura Sánchez-Caballero
Leo Nijtmans

Am J Hum Genet 99:208-216, 2016.

New cause for a mitochondrial complex I assembly defect

Mitochondrial complex I is a key enzyme in cellular metabolism. As major entry-point of electrons in the respiratory chain it contributes to the cellular ATP production and to the formation of reactive oxygen species. Dysfunction causes hereditary metabolic disorders but is also implicated in Parkinson's and Alzheimer's disease as well as in cancer development and ageing. To understand how this complex is regulated and how mutations lead to disease, it is vital to understand how the 44 different subunits are assembled and which factors are required in this process (Figure 1). Our recently developed mitochondrial complexome profiling approach revealed a novel complex I assembly protein called TMEM126B. Here we identified mutations in this gene to cause a complex I deficiency with an unusual mild clinical phenotype. Our analysis pinpointed the role of TMEM126B to the assembly of the complex I-membrane part. In addition, this analysis revealed a potential compensatory protein possibly explaining the relative mild phenotype (Figure 2). These insights in complex I assembly allow identification of underlying defects and better understanding of disease progression.

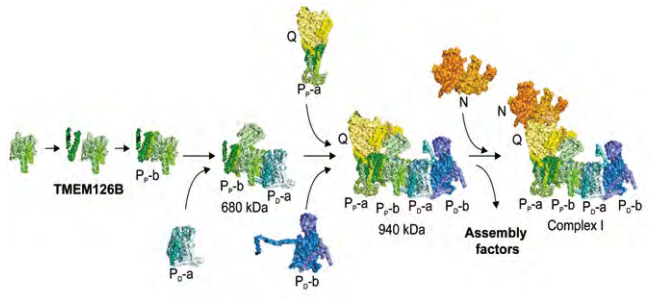


Figure 1: Schematic assembly pathway of mitochondrial complex I.

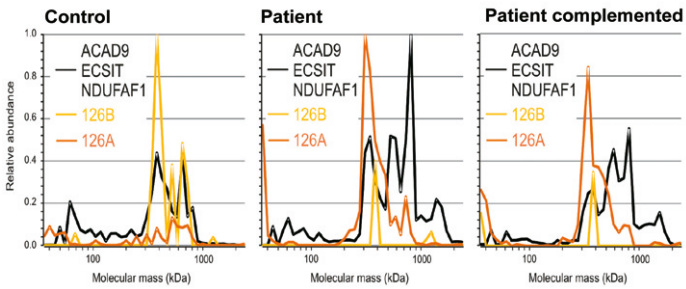


Figure 2: Migration profiles of complex I assembly intermediates obtained by complexome profiling of mitochondria isolated from (complemented) TMEM126B-patient and control fibroblasts. The replacement of TMEM126B by its paralogue TMEM126A in the patient cells might suggest a compensatory mechanism.


Theme: Nanomedicine

Marjolein Meddens
Alessandra Cambi

Nat Commun 7:13127, 2016.

How dendritic cells probe the environment

Podosomes are small protrusions generated from the cytoskeleton of osteoclasts, activated endothelial cells as well as antigen-presenting cells such as macrophages and dendritic cells (DCs). Like small feet, hundreds of podosomes spatially organize in diversely shaped clusters in DCs, mediating adhesion and slow migration. The mechanism and relevance of podosome clustering for DC migration is unknown. Here we combined advanced fluorescence microscopy with quantitative image analysis and demonstrated that actin and actin-associated proteins exhibit directional and correlated flow patterns over multiple proximal podosomes throughout the cluster. Flow pattern formation and velocity depend on a functional actomyosin machinery. Super-resolution microscopy revealed myosin-decorated actin filaments interconnecting multiple neighboring podosomes, demonstrating a previously unappreciated structural connectivity throughout a podosome cluster. This allows coordinated movement and mechanical force redistribution, making podosome clusters mechanosensitive platforms enabling environment probing by DCs. Understanding how cells probe the environment can teach us how immune cells travel through the body or how skin cells move to heal wounds. Finally, podosomes are closely related to cancer cell invadopodia. Unraveling architecture and dynamics of protrusive structures may provide novel leads to improve specificity and efficacy of experimental anti-cancer therapies.

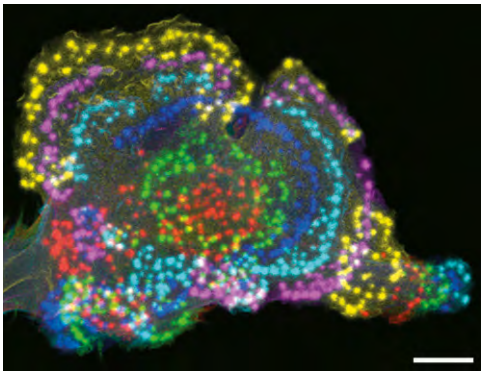


Figure: This image shows a dendritic cell moving over a glass surface. Each color indicates the position of the podosome cluster at a different time point. The podosome cluster exhibits impressive spatial rearrangements over time that seem to guide the dendritic cell during exploration of its environment. Scale bar is 10 μm.


Theme: Nanomedicine

Jessie van Buggenum
Klaas Mulder

Sci Rep 6:22675, 2016.

Sensitive protein detection via immuno-PCR using antibody-DNA conjugates

Antibody-DNA conjugates can be used in a broad range of research fields for multiplexed quantification of specific proteins or molecules. In order to successfully implement this technology, it is essential to have *i*) a cost-efficient conjugation approach that is applicable to all antibodies; *ii*) specific immuno-staining of targeted epitopes; *iii*) sensitive detection of the DNA "barcode" after immuno-staining. Therefore, we developed a broadly applicable protocol to conjugate antibodies to double stranded DNA. Moreover, we included a disulphide-containing cleavable linker that allows release of the dsDNA and efficient detection in qPCR after immunostaining. We show specific and sensitive protein detection in immuno-PCR for human epidermal stem cell markers (ITGA6 and ITGB1) and the differentiation marker Transglutaminase 1 (TGM1). The described approach can in principle be used to conjugate any antibody to dsDNA, and is thus applicable to many different fields of research where multiplexed and sensitive protein detection is of interest.

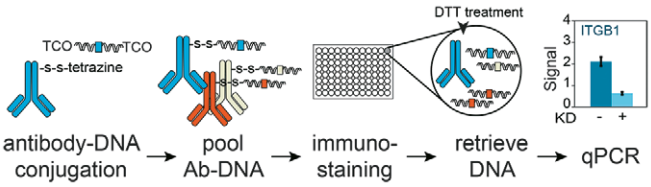


Figure: Schematic overview of our novel antibody-DNA conjugation strategy and immuno-PCR method for sensitive protein detection.


Theme: Rare cancers

Annelieke Willemsen
Wim Oyen

Eur J Cancer 56:54-58, 2016.

PERCIST criteria for FDG-PET/CT to assess cancer treatment response: all that glitters is not gold

Early assessment of response to cancer treatment is of great importance. Quantitative analysis of [^{18}F]-FDG-PET/CT has high potential to assess early response. The PERCIST criteria are considered a preferred method to perform this analysis. However, we argue that these criteria are insufficient to deliver generally applicable results. Here, we illustrate two limitations.

Firstly, a lesion qualifies as a target lesion if it is sufficiently FDG-avid, as measured relative to mean liver activity. Unfortunately, this criterion prohibits inclusion of the majority of lung lesions, even though these lesions can be easily discriminated from the very low background of normal lung (Figure A). Secondly, measurement of Total Lesion Glycolysis (TLG) is recommended by PERCIST. When tumor delineation is based on an absolute threshold, this may not adequately differentiate tumor from normal tissue. Using a proportional threshold can result in a paradoxically overall larger TLG, despite evident response (Figure B).

To improve the applicability of PERCIST, we recommend to use organ-specific background cut-off values for selecting target lesions and TLG. Consensus should be reached on a more feasible and clinically useful methodology for data analysis.

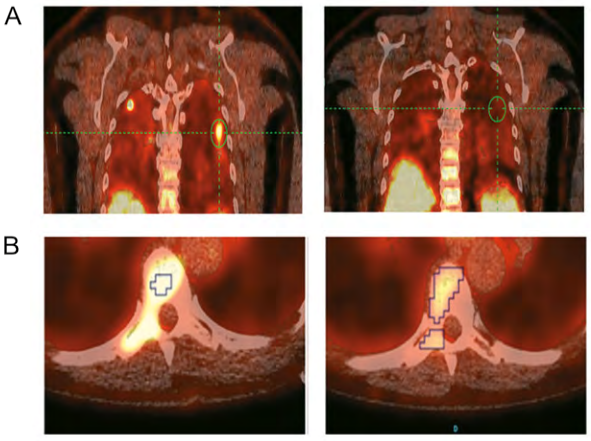


Figure: A: Pulmonary metastasis of sarcoma patient at baseline (A, left) and after 8 weeks of anti-angiogenesis treatment (A,right): this particular lesion cannot be included according to PERCIST, as its FDG-avidity is too low at baseline, although response during follow-up seems obvious
B: Bone metastasis of breast cancer patient at baseline (B, left) and after 14 days of treatment with everolimus and exemestane (B, right): strong decrease in SUV_{max}, but blue delineation shows increase in TLG based on isocontour of 70% of SUV_{max}


Theme: Rare cancers

Theo Plantinga
Romana Netea-Maier

Autophagy 12:1195-1205, 2016.

Low autophagy activity is associated with radioactive iodide resistance in thyroid cancer

Non-medullary thyroid cancer (NMTC) is the most common endocrine malignancy. Following surgical removal of the tumor, treatment with radioactive iodide (RAI) represents the main treatment for metastatic disease. About 20-30% of NMTC patients have a persistent or recurrent disease requiring subsequent therapy and face increased risk of death when the tumor becomes inoperable and when it loses RAI avidity. NMTC cells become RAI unresponsive due to dedifferentiation and concomitant loss of membrane expression of the intrinsic sodium-iodide symporter (NIS, SLC5A5), the sole membrane channel for (radioactive) iodide uptake by thyroid cells. The underlying mechanisms of dedifferentiation remain elusive. Autophagy is an intracellular recycling mechanism involved in pathways of proliferation and differentiation. By retrospective assessment of LC3-II expression as measure of autophagy activity in patient tumor material, we observed that tumors with high membranous NIS expression and high RAI-sensitivity also exhibited high autophagy activity and that this activity is lost in RAI-resistant, NIS-negative tumors. These findings identify for the first time autophagy activity as biomarker of RAI-resistance, potentially with mechanistic implications to elucidate the underlying processes driving NMTC dedifferentiation.

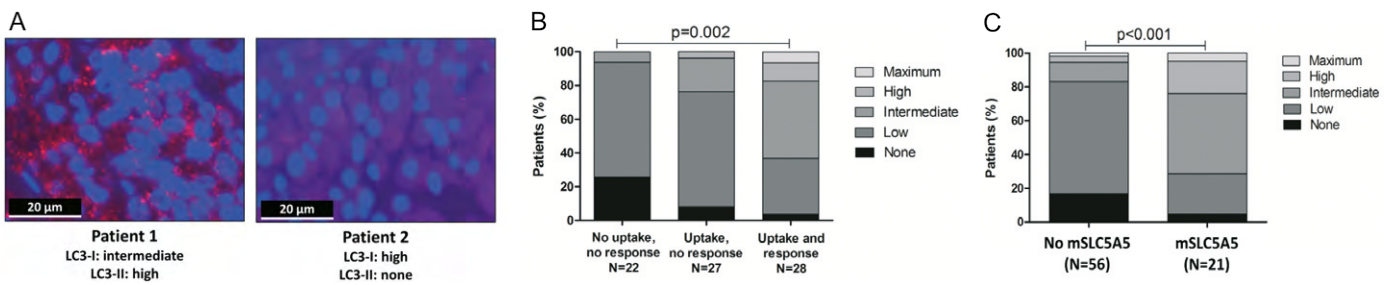


Figure: **A.** Examples of LC3 staining patterns and autophagy scoring in tissue samples of two NMTC patients with highly different autophagy activity (1000x magnification). **B.** Distribution of LC3-II positive puncta scores in NMTC patient tissues and its correlation with uptake of and clinical response to RAI treatment. **C.** Correlation of membranous SLC5A5 (mSLC5A5), i.e. NIS, expression with LC3-II-positive puncta scores in NMTC tissues.


Theme: Reconstructive and regenerative medicine

Luuk Versteegden & Henk Hoogenkamp
Toin van Kuppevelt & Willeke Daamen

Acta Biomater 44:277–285, 2016.

Elastic collagen scaffolds for regeneration of dynamic organs

Resections of damaged tissue may be needed in the case of cancer, congenital abnormalities or trauma. In order to stimulate regeneration of tissue in the damaged area, biodegradable scaffolds can be applied. Type I collagen is widely used as a scaffold component, as collagen also gives structural support component to native tissue. Collagen, however, does not provide elasticity, a characteristic crucial for dynamic organs.

In this article, a methodology is presented to introduce elasticity to biomaterials consisting of type I collagen only. The method comprises physical compression and corrugation in combination with chemical crosslinking (Fig. 1A). This procedure induces elastic-like properties in scaffolds which could be repeatedly stretched to five times their original length for at least 1000 cycles (Fig. 1A, right panel). The elasticity is likely based on newly established hydrophobic interactions between collagen fibrils in the scaffold and is entropy driven (Fig. 1B).

The straightforward technique endows unique elastic characteristics to scaffolds prepared from solely type I collagen and may be useful for the regeneration of dynamic tissues such as blood vessels, ligaments, and lung.

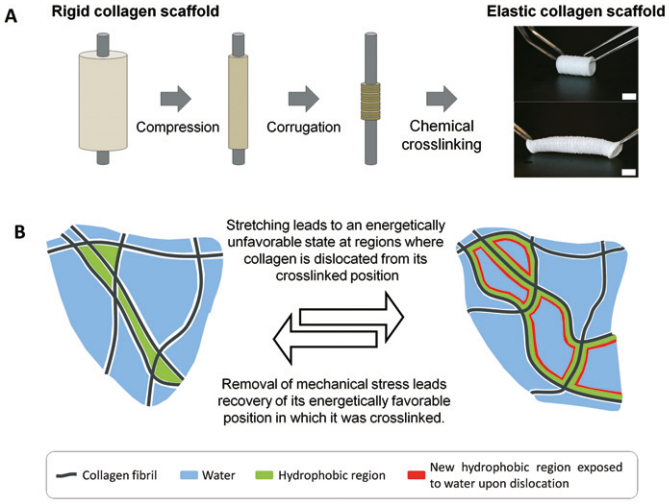


Figure 1: **Elastic collagen scaffolds.** A) The elastic scaffolds are prepared by compression, corrugation and chemical crosslinking of porous tubular collagen scaffolds. The scaffold can be extended up to 5 times its original length and instantly returns to its corrugated state. Scale bar = 5 mm B) Elasticity is entropy driven and based on newly established hydrophobic interactions between the collagen fibrils.


Theme: Reconstructive and regenerative medicine

Jiankang Song
Fang Yang

Nanomedicine 12:1357-1364, 2016.

Nanofibrous membranes with a long-term antibacterial effect for infection prevention

Percutaneous medical devices, such as external fixation devices, urinary catheters, and intravenous catheters are indispensable in clinical practice. These percutaneous devices, however, are particularly susceptible to bacterial infections due to their penetration through the skin, the body's primary defence against infection.

To prevent percutaneous device associated infections (PDAIs), we developed a novel and simple one-step electrospinning method (Figure 1) to prepare chitosan/poly(ethylene oxide) nanofibrous membrane (Figure 2a) containing silver nanoparticles as an implantable delivery vehicle for the dual release of antiseptics chlorhexidine (CHX) and silver ions. We observed that the silver nanoparticles were distributed homogeneously throughout the fibres (Figure 2b-c), and a fast release of CHX in 2 days and a sustained release of silver ions for up to 28 days (Figure 2d).

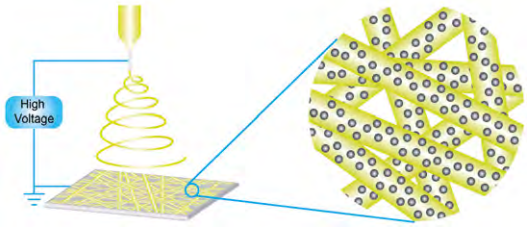


Figure 1: Schematic diagram of the one-step electrospinning method.

Upon loading with $AgNO_3$ and CHX, the membranes exhibited a clear inhibition zone against Staphylococcus aureus, one of the most common bacteria to cause skin infections (Figure 2e-f). These results suggest that the membranes have strong potential to act as an active antibacterial dressing for local delivery of antibacterial agents to prevent PDAIs.

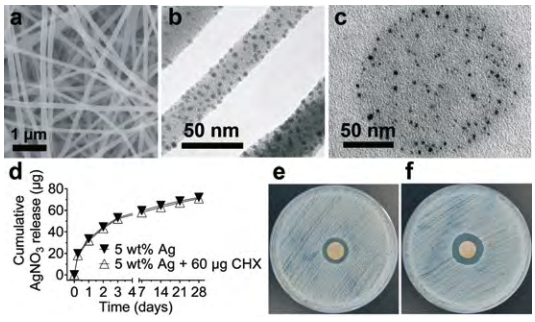


Figure 2: Characterization, drug release and antibacterial effects of the electrospun nanofibrous membranes. Scanning electron microscopy of the nanofibrous membrane (a), transmission electron microscopy of the nanofibers containing silver nanoparticles in longitude (b) and cross-section (c) (black dots in b and c indicate silver nanoparticles), cumulative silver ions release from the nanofibrous membranes (d), the zone of inhibition test of the nanofibrous membranes with 5 wt% of $AgNO_3$ (e) and membranes with both 5 wt% of $AgNO_3$ and 60 μg chlorhexidine (f) against *Staphylococcus aureus*.

Theme: Renal disorders

Jeroen van Reeuwijk
Ronald Roepman

Nat Commun 7:11491, 2016.

A protein landscape of the cell's antenna

As a coordinating partner in an international team of researchers (funded by EU FP7 Health project SYSCILIA), we have systematically identified and mapped new protein components related to cilia (dys)function.
Cilia are slender organelles projecting from the cell surface. They act either as a fluid propeller (motile cilia), or as the cell's antenna or signaling hub (primary, immotile cilia). Inherited dysfunction of cilia underlies a wide range of hereditary disorders called ciliopathies, affecting 1 in 1000 people. Common symptoms of ciliopathies are kidney failure, blindness, brain defects, skeletal abnormalities, and even cancer.
The study gives detailed insights into the connectivity of over 1300 proteins as part of structural ciliary protein complexes or signaling pathways (Figure). We developed specific algorithms to define new molecular machines that underlie proper cilium function. Dysfunction of these machines resulting from genetic mutations may result in defective cilia and cause ciliopathies. Additionally, it helped us to classify known inherited disorders, like the 3M syndrome, as ciliopathies, which is essential knowledge for translational research towards therapies.

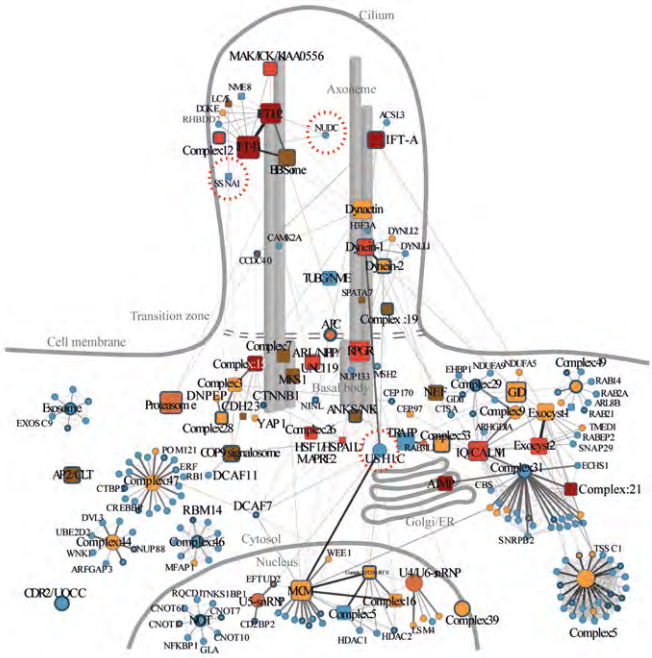
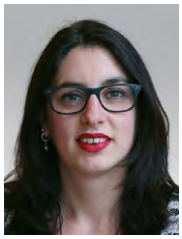


Figure: Overview of the ciliary landscape. Complexes and proteins identified in this study are depicted by circles and rounded boxes, respectively.



Theme: Renal disorders

Rachel van Swelm
Dorine Swinkels

J Am Soc Nephrol 27:2720-2732, 2016.

Hepcidin protects against acute kidney injury

Postoperative acute kidney injury (AKI) is an increasingly common life-threatening complication in up to 30% of the patients undergoing major surgery with cardiopulmonary bypass (CPB). Currently, adequate preventive measures or specific treatment modalities are lacking. It is now well-established that haemolysis is an essential mechanism that contributes to postoperative AKI. Findings from clinical studies showed an association between high urinary hepcidin concentrations and reduced risk of AKI in CBP patients. Therefore, (urinary) hepcidin might protect against AKI. However, renal handling of hepcidin remains elusive and a causal relation between hepcidin and renal protection lacks. We demonstrated that systemic circulating hepcidin is filtered in the kidney and reabsorbed in the proximal tubules via megalin in mice (Figure). In addition, hepcidin is also produced in the distal part of the renal nephron. Systemic hepcidin administration abolished haemoglobin-induced AKI in mice. At the same time, increased hepcidin synthesis was observed in the distal nephron, suggesting that both systemic and renal synthesized hepcidin are essential for protection along the entire nephron.

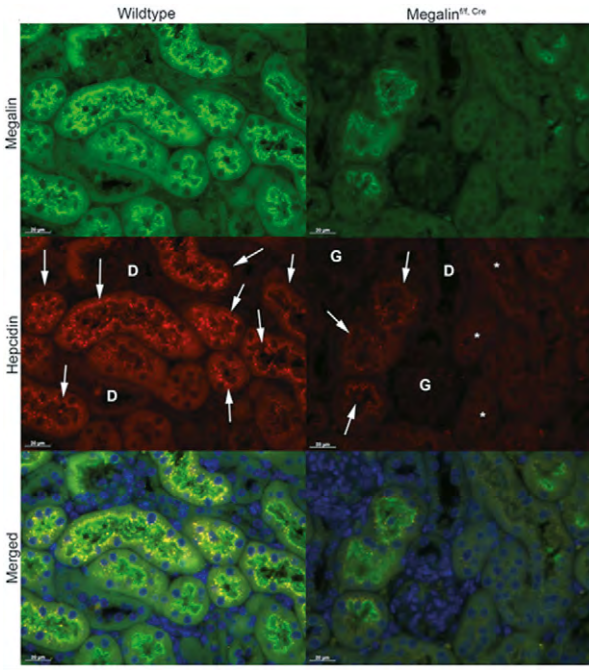


Figure: Co-localization of injected hepcidin (red) and renal megalin (green) in kidney sections of wildtype and megalin deficient mice (Megalin $^{f/f}$, Cre). Arrows: hepcidin; asterisk: megalin-deficient tubules, D: distal tubule,G: glomerulus.


Theme: Tumors of the digestive tract

Richarda de Voer
Marjolijn Ligtenberg

PLoS Genet 12:e1005880, 2016.

Novel candidate genes for colorectal cancer susceptibility

Individuals who develop colorectal cancer (CRC) at an early age in life are suspected of having a genetic predisposition, but only in a small set of patients causative germline mutations are identified. This means that we still need to capture the genetic predisposition of many patients and their relatives. A cohort of individuals (*n*=55) that developed CRC before the age of 45 years were whole-exome sequenced. We focused on genes with multiple variants present in cases, but not in controls, that have a functional link to cancer development. Based on this strategy, targeted re-sequencing, and functional analyses, *LRP6* and *PTPN12* were identified as novel candidate genes for CRC susceptibility. LRP6 is involved in Wnt/β-catenin signaling, which is activated in most CRCs, and two of the three variants that were identified showed increased WNT signaling activity *in vitro* (Figure). Our results suggest a polygenic model of CRC susceptibility in which patients with early-onset CRC carry a set of rare, pathogenic variants in their germline that pose them at risk to develop CRC.

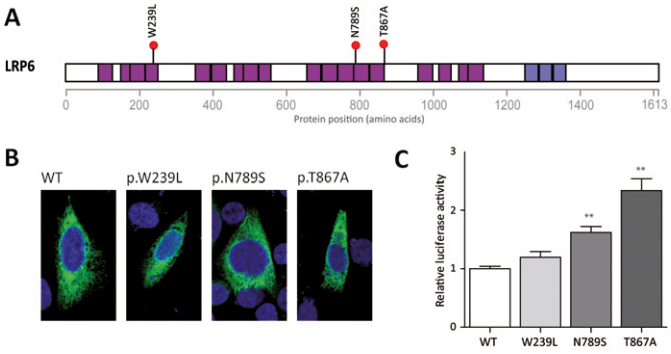


Figure: Rare variants in LRP6 in three cases. (A) Distribution of identified missense LRP6 variants (red dots). (B) Immunofluorescence analyses of LRP6 wild-type and mutant proteins showing similar subcellular localizations. (C) *In vitro* analyses of wild-type and mutant LRP6 to determine their effects on the WNT signaling pathway. Both p.N789S and p.T867A mutants reveal a significant increase in activation compared to the wild-type LRP6 protein.


Theme: Tumors of the digestive tract

Nikki Knijn
Iris Nagtegaal

Oncotarget 7:31699-31707, 2016.

The role of lymph node metastases in colorectal cancer

The presence of regional lymph node metastases in colorectal cancer (CRC) is associated with a decreased outcome. Whether these nodal metastases function as a sign of advanced disease, or whether nodal metastases are actually involved in the metastatic process is unclear. If the latter is true, different metastatic patterns should be present in patients with and without lymph node metastases. We evaluated the metastatic pattern of CRC according to the lymph node status of the primary tumor in large patient cohorts with metastatic disease. We found that lymph node positive CRC show a slightly different dissemination pattern, with a higher rate of peritoneal metastases and metastases to distant lymph nodes. The comparable incidences of liver and lung metastases in regional lymph node positive and regional lymph node negative CRC support the hypothesis that metastases to distant organs occur independently of lymphatic spread.

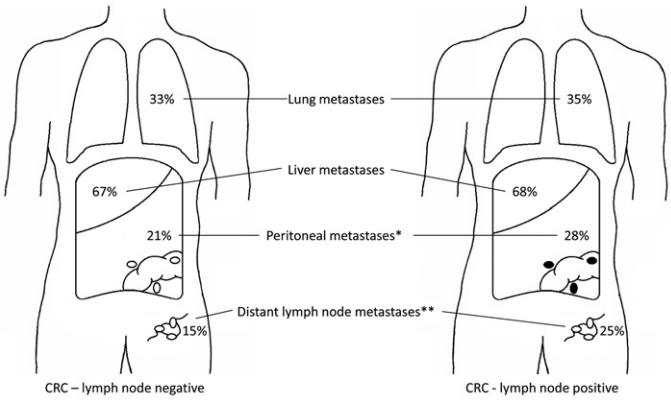


Figure: Distribution of CRC metastases according to regional lymph node status. Left figure shows the distribution of metastases for regional lymph node negative primary tumors, right figure shows the distribution of metastases for regional lymph node positive primary tumors. * $p = 0.003$, ** $p < 0.001$.


Theme: Urology

Toine van der Heijden
Fred Witjes

Eur J Cancer 64:127-136, 2016.

A five-gene expression signature to predict progression in bladder cancer

Two third of all bladder tumors are non-muscle invasive at diagnosis. One out of five patients will eventually progress to muscle-invasive bladder cancer. Progressive patients deserve careful attention, particularly because the clinical outcome of patients who progress to invasive cancer is much worse compared to de novo muscle invasive bladder tumors. Since histopathology is inadequate to accurately predict the behavior of non-muscle invasive tumors, there is a clear need for predictive biomarkers that can distinguish progressive from non-progressive non-muscle invasive bladder cancer.

We found that progressive and non-progressive bladder tumors have different gene expression patterns. Subsequently, a five-gene signature to predict progression in high risk non-muscle invasive bladder cancer was identified. This signature was developed in close collaboration with the University Hospital of Barcelona and validated in patients from both hospitals. This test can select patients with a high risk of progression in which a complete removal of the bladder (radical cystectomy) should be considered. The secondary validation study is currently recruiting patients.

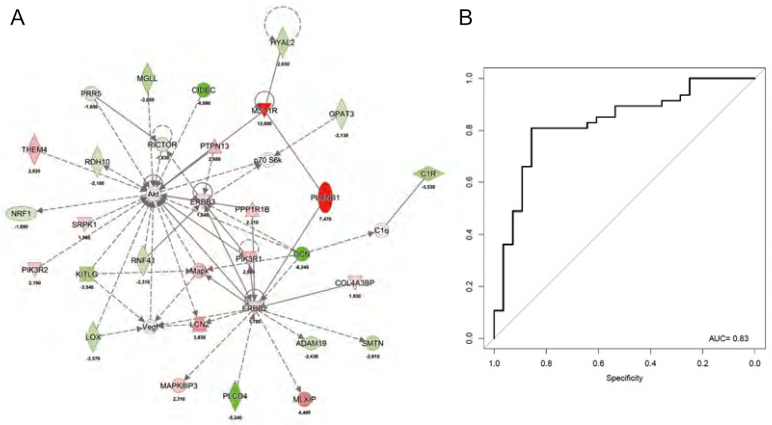


Figure: a. Ingenuity pathway analysis (IPA). Network associated with Cell Death and Survival, Cancer, Organismal Injury and Abnormalities derived from our set of genes differentially expressed in progressive bladder cancer patients (Green and red nodes indicate up-regulated and down-regulated, respectively. b. Curve analysis based on the predicted probabilities derived from the five-gene model.


Theme: Urology

Rianne Hendriks
Jack Schalken

Eur Urol 70:740-748, 2016.

Detection of high-grade prostate cancer using a urinary molecular biomarker-base risk score

The major challenge in prostate cancer diagnostics is to improve the detection of clinically significant or high-grade prostate cancer in an early stage. Ideally, specific biomarkers could be measured in a sample that is noninvasively obtained (e.g., in urine). In a previous study, a stepwise approach was described for the identification and selection of new urinary biomarkers using messenger RNA (mRNA) expression profiling. In this study, we used two independent clinical cohorts to validate the gene panel-based mRNA test performed on whole urine and developed a model combining molecular profiling with clinical risk factors. The developed model combining HOXC6 and DLX1 mRNA expression levels with clinical risk factors (PSA density, digital rectal examination, PSA, age, history of prostate biopsy and family history) outperformed the Prostate Cancer Prevention Trial risk calculator (PCPTRC) and urinary PCA3 (Figure). In conclusion, the two-gene risk score was able to detect high-grade, clinically significant prostate cancer accurately. Therefore, this risk score could be used in decision making, reducing the number of unnecessary prostate biopsies and potential overtreatment.

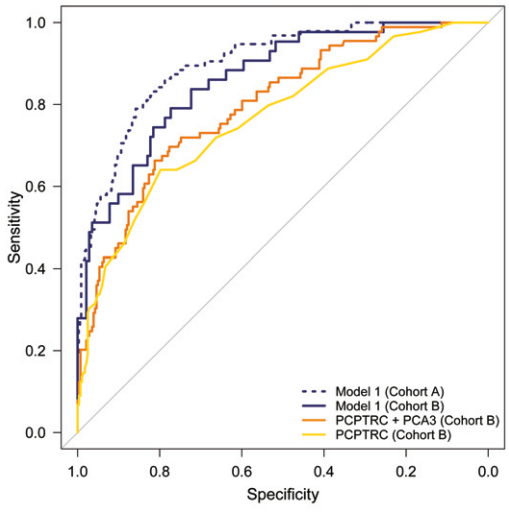


Figure: Receiver operating characteristic curves comparing model 1 (HOXC6+DLX1 risk score) in cohorts A and B with the Prostate Cancer Prevention Trial risk calculator (PCPTRC) alone and the combined PCPTRC and PCA3.


Theme: Vascular damage

Siroon Bekkering
Niels Riksen

Atherosclerosis 254:228-236, 2016.

Innate immune cell activation in patients with (a)symtomatic atherosclerosis

Atherosclerosis is an inflammatory disease, in which cells from the innate immune system (e.g. monocytes) contribute to the progression of disease. Recently it was described that monocytes can undergo functional reprogramming towards a long-term pro-inflammatory phenotype. This process is termed 'trained immunity' and is mediated by metabolic and epigenetic reprogramming We now studied whether monocytes from subjects with symptomatic and asymptomatic atherosclerosis show a trained immunity phenotype. We measured ex vivo cytokine production, RNA expression levels of important metabolic enzymes as well as activating and repressive histone marks in monocytes from these subjects (Figure). Monocytes from patients with symptomatic atherosclerosis showed an increased ex vivo cytokine production upon stimulation compared to matched controls. Interestingly, monocytes from subjects with asymptomatic atherosclerosis did not show an increased cytokine production upon stimulation. Further analysis of cells from patients with symptomatic atherosclerosis showed an increased expression of rate limiting enzymes of the glycolytic pathway. This was accompanied by less repressive histone marks in patients with symptomatic atherosclerosis. Since epigenetic remodeling is reversible, this might be an interesting future topic for drug development.

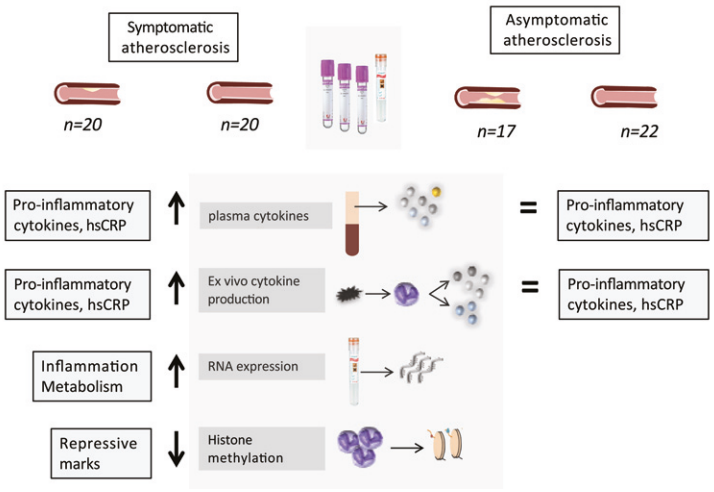


Figure: Schematic overview of the experimental design and results of the study.


Theme: Vascular damage

Siroon Bekkering
Niels Riksen

Circulation 134:611-624,2016.

Increased arterial wall inflammation through oxidized phospholipids on lipoprotein(a)

Elevated lipoprotein(a) [Lp(a)] is an independent risk factor for cardiovascular disease, but the underlying mechanisms is poorly defined. Lp(a) is the prominent carrier of pro-inflammatory oxidized phospholipids (oxPLs) in the circulation. It was recently described that monocytes can undergo functional reprogramming towards a long-term pro-inflammatory phenotype after brief *in vitro* exposure to atherogenic stimuli such as oxidized LDL. This process is termed 'trained immunity'. We now hypothesized that Lp(a) activates the innate immune system and thereby increases atherosclerosis in these patients.

Subjects with elevated circulating Lp(a) have increased arterial wall inflammation as measured by (18)F-FDG-PET/CT and enhanced PBMC trafficking to the arterial wall as measured by SPECT/CT compared to subjects with normal Lp(a). In addition, monocytes from subjects with elevated lp(a) produced more pro-inflammatory cytokines upon stimulation, resembling a trained immunity phenotype (Figure). In vitro studies showed that Lp(a) can indeed induce reprogramming of healthy monocytes. This effect appeared to be dependent on the oxPL moiety of Lp(a). These findings provide a novel mechanism by which Lp(a) mediates cardiovascular disease and might lead to novel therapeutic targets.

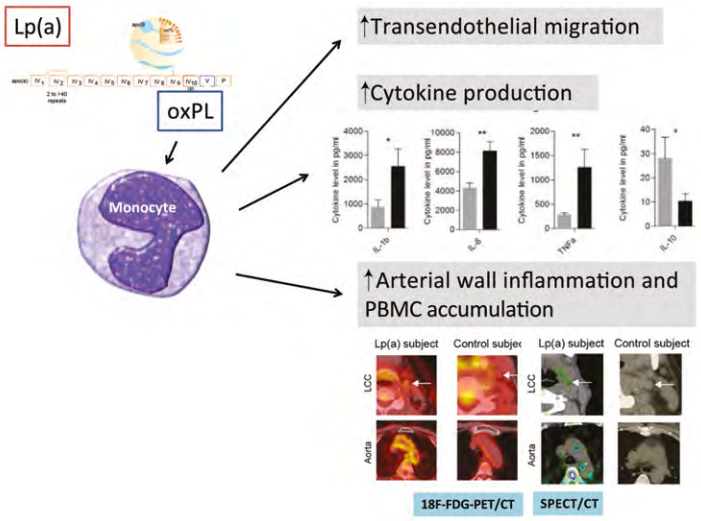


Figure: Oxidized phospholipids on Lipoprotein(a) induce increased monocyte activation in patients with elevated lipoprotein(a)


Theme: Women's cancers

Louis van der Putten
Hanny Pijnenborg

Brit J Cancer 115:716-724, 2016.

The prognostic value of L1CAM expression in endometrial carcinomas

Endometrial carcinoma is the most common gynecological malignancy, affecting around 2000 women in the Netherlands annually. Based on histology, these can be divided into endometrioid and more aggressive non-endometrioid carcinomas. Tumor histology and disease stage are important in deciding whether complete surgical staging and adjuvant treatment are necessary. However, additional risk factors are required for a better selection of high risk. We therefore studied the prognostic value of the immunohistochemical expression of the L1 cell adhesion molecule (L1CAM) in 1199 endometrial carcinomas, collected in 11 ENITEC hospitals. L1CAM expression was strongly related to the presence of other markers of poor prognosis, especially the presence of non-endometrioid histology. Moreover, it was a strong independent predictor of reduced disease-free and overall survival in the endometrioid cases, but did not have additional value in the non-endometrioid cases (Figure 1). L1CAM expression is therefore a very valuable marker in the identification of non-endometrioid and aggressive endometrioid cases, and the subsequent individualization of the treatment.

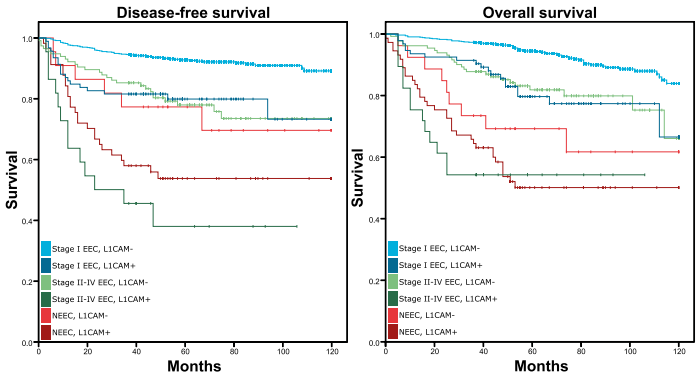


Figure: Kaplan-Meier plots of the 10-year disease-free and overall survival of the stage I endometrioid (stage I EEC), advanced stage endometrioid (stage II-IV EEC), and non-endometrioid cases (NEEC), with respect to L1CAM expression.


Theme: Women's cancers

Renée Ebisch
Willem Melchers

Int J Cancer 139:691-699, 2016.

The clinical value of HPV genotyping in triage of women with high-risk-HPV-positive self-samples

A persistent cervical infection with a high-risk human papillomavirus (hrHPV) is a necessary cause for the development of cervical intraepithelial neoplasia and cervical cancer. In 2017 the population-based screening for cervical cancer in the Netherlands will completely transform from morphological-based screening with cervical cytology, to molecular-based screening with hrHPV testing. The Radboud university medical center will become one of the 5 screening facilities. Primary hrHPV-based screening has a relatively low specificity, due to the assays inability to distinguish persistent from transient hrHPV infections. Additional triage is therefore required to identify women with high-grade cervical precancer or cancer. In our study, we assessed the clinical value of HPV16/18 genotyping as triage strategy for hrHPV positive women, compared with liquid based cytology testing. HPV16 and HPV18 are the two most carcinogenic HPV types, and together they cause 70% of all cervical cancers. Three triage strategies including HPV16 and/or HPV18 genotyping combined with cytology at different thresholds showed an increased specificity with maintenance or improvement of sensitivity, and a lower referral rate. High referral rates of hrHPV positive women without abnormalities due to transient hrHPV infections could be reduced by improving triage with HPV16/18 genotyping. This will personalize screening and could have a major impact on general healthcare by cost reduction and lowering pressure on limited resources.

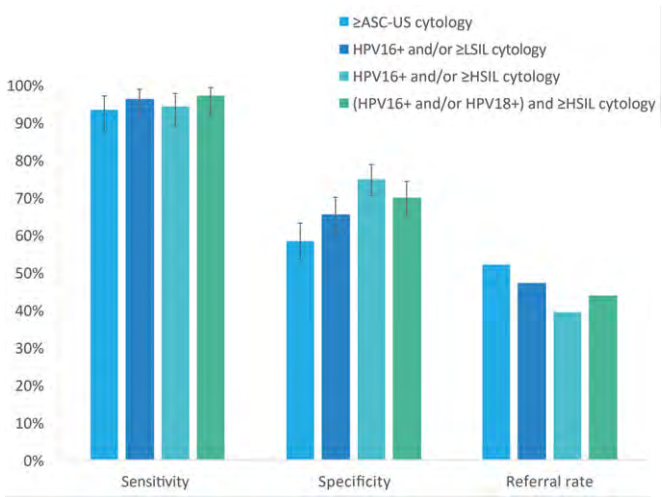


Figure: **Sensitivity, specificity and referral rate of different triage strategies for hrHPV positive women**
ASC-US: atypical cells of undetermined significance, hrHPV: high-risk human papillomavirus, HSIL: high-grade squamous intraepithelial lesion, LSIL: low-grade squamous intraepithelial lesion.

Researchers at the Radboud Institute for Molecular Life Sciences (RIMLS) seek to achieve greater insights into the molecular basis of disease. By integrating molecular and clinical research, the institute obtains multifaceted knowledge of normal and pathological processes. Within the general concept of personalized healthcare, findings are translated into clinical applications, into the development of diagnostics and into the treatment of patients. The institute offers a challenging and enriching learning environment, where researchers of all levels are exposed to societal-relevant medical research questions.

Radboud Institute for Molecular Life Sciences (RIMLS)

Postal address
259 RIMLS
P.O. Box 9101
6500 HB Nijmegen
The Netherlands

Visiting address
Geert Grooteplein 28
6525 GA Nijmegen

T: +31 (0)24 361 07 07
E: rimls@radboudumc.nl
I: www.rimls.nl