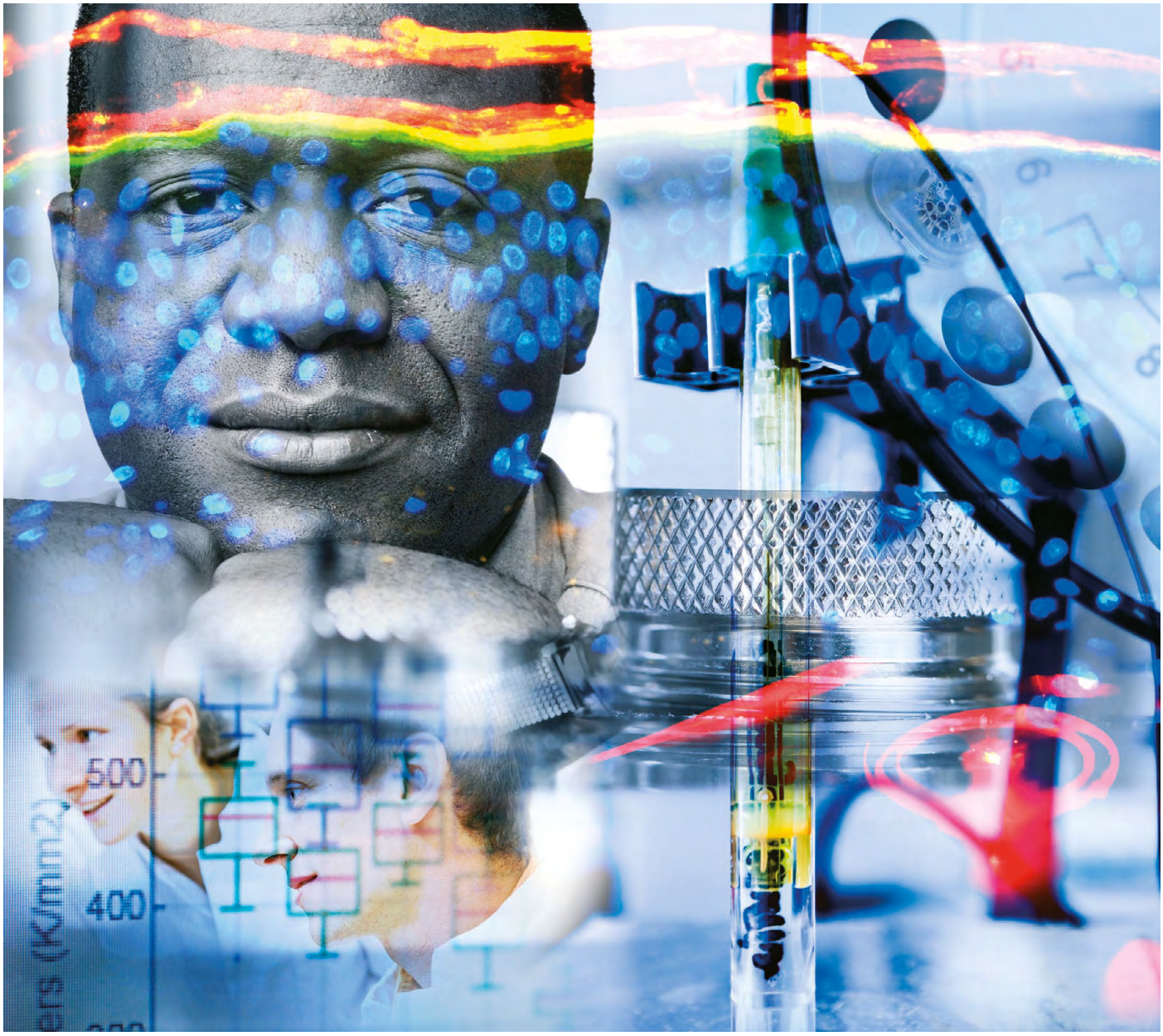
Radboud Institute for Molecular Life Sciences



Annual Report 2015

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

Design: Final Design

Front cover: The cover image depicts an artistic collection of photos of molecular life sciences

Photography: Theo Hafmans, Eric Scholten

Printed by: Janssen Repro b.v.

Foreword

In 2015, the Radboud Institute for Molecular Life Sciences (RIMLS), together with the other Radboudumc institutes, compiled the Research Agenda 2025. This document sets out our collective ambitions and objectives for the coming decennium to 'have a significant impact on healthcare'. The Research Agenda 2025 outlines our strategy for the years ahead and in particular the future path of RIMLS in understanding the molecular mechanisms of disease.

In last year, we conducted a baseline evaluation of our new research themes. Many themes demonstrate significant coherency and international visibility. The individual thematic objectives for the coming years have been defined setting clear goals for the site-visit evaluation in two years time. We visited all (junior) principal investigators of our institute to discuss how their research can be further supported. We were highly impressed and thankful by the conviction, dedication and determination by which all our scientists fulfil their individual ambitions, and ultimately make a difference for the patient.

The passion for research is, of course, evident by the number of RIMLS researchers that have been successful in obtaining European multi-partner subsidies, either as coordinators or participants, as well as prestigious grants and prizes awarded on individual merits for ground breaking new research projects and achievements. Of particular note are our young researchers who, in the last year, have acquired prestigious Netherlands Organisation for Scientific Research (NWO) and European Research Council grants. The impressive success rate is also due to the generous support given by colleague researchers to improve the applications and to improve the applicants' interview techniques. In our 2015 annual report, we proudly present the RIMLS highlights of an inspirational year.

Adrian Cohen
Scientific Manager

René Bindels
Scientific Director

Dagmar Eleveld
Scientific Manager

Table of contents

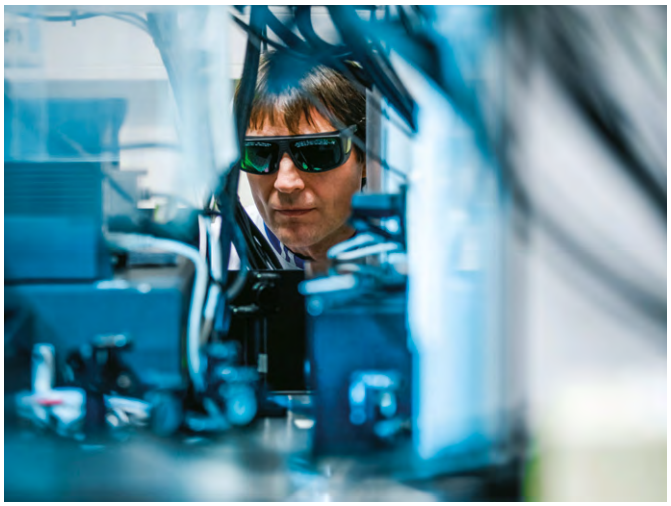
Research

Mission

Researchers at the Radboud Institute for Molecular Life Sciences (RIMLS) seek to achieve greater insights into the molecular basis of disease. This is achieved by integrating molecular and medical research to obtain multifaceted knowledge of normal and pathological processes. Findings are translated into clinical applications, into the development of diagnostics, and into the treatment of patients as part of personalized healthcare.

Themes

RIMLS – a leading research institute that focuses on the molecular mechanisms of disease – brings together research groups from the Radboud University Medical Center (Radboudumc) and the Faculty of Science (FNWI) of the Radboud University. Clinical and fundamental scientists, who specialize in diverse areas of the life sciences, work together closely in programmes designed to understand the underlying causes of disease. In line with the Radboudumc's strategic vision to have a significant impact on healthcare, research is bundled into clinically-orientated research themes ranging from molecule to man. The RIMLS Graduate School integrates a dedicated two-year Research Honours MSc programme in Molecular Mechanisms of Disease (MMD) and a PhD programme, thus creating a challenging yet enriching international learning environment where researchers at all levels are exposed to societally relevant multidisciplinary research questions related to the molecular basis of disease. RIMLS research comprises 13 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.

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.

Research

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; 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.

Sensory disorders

Research focuses on elucidation of the molecular mechanisms of retinal diseases, hearing impairment and deaf-blindness. By developing and improving diagnostic and predictive tests for sensory diseases, researchers hope to bring new personalized rehabilitation strategies and therapies, *e.g.* gene therapy and retinal implants, into the clinic.

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 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 (IRB, www.irbbarcelona.org) in Barcelona. An official agreement has been made to participate in each other's research and educational programmes. On 3 June 2015, Paul Smits, Dean of Radboudumc, signed an agreement with Joan Guinovart, the Director of IRB. This umbrella agreement paves the way for further strengthening of existing exchanges and exploring new opportunities for collaboration. Furthermore, IRB Masters students will be able to participate in the RIMLS Molecular Mechanisms of Disease (MMD) training programme.

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. The MMD master programme was rated first in the category Life Sciences in the Netherlands in 2012 and 2014 (Top-rated programme), and second in 2013 and 2015 (Keuzegids Masters), illustrating a strong commitment to excellent education at the institute.

RIMLS researchers contribute actively to the dissemination of research results via public conferences, teaching in schools and colleges as well as in the media. Some examples: Sanne Botden (Reconstructive and regenerative medicine) won the ZonMw Medical Innovation Prize for a patch that can be used to treat babies with a hole in the diaphragm (the patch received sixty percent of the over 19,000 'likes' on Facebook) and Frans Russel (Renal disorders) appeared regularly in the media to discuss recent innovative research on cholesterol-lowering drugs (statins). Public outreach is considered to be very important. RIMLS – together with researchers working on the sensory disorders theme – organized a patient evening on inherited blindness. Likewise, Jan Smeitink (Mitochondrial diseases) organized a patient information day for patients with mitochondrial disorders as well as their families and carers. On World Kidney Day a large multidisciplinary team of researchers working in the Renal disorder theme made a seminal public contribution to raising awareness about kidney disease.

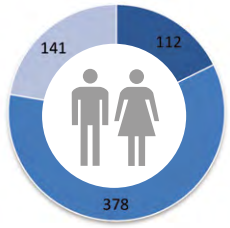
RIMLS researchers are actively involved in enhancing disease diagnosis, prevention and treatment. Their efforts have been acknowledged in high-level awards. Of particular note, Anneke den Hollander (Sensory disorders) received the Cogan Award, which recognizes promising researchers who have made important contributions to research in ophthalmology and visual science. Peter Friedl (Cancer development and immune defence) was awarded the 2015 Faculty Excellence Award by the MD Anderson Cancer Center, Texas, USA. Mihai Netea (Infectious diseases and global health) was elected as a member of the Academia Europaea.

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. Joost Drenth (Renal disorders), became an Honorary Member of the Hungarian Society of Gastroenterology. Leon Massuger (Women's cancer) launched the national charity "Ruby and Rose" to raise money and awareness for research into ovarian cancer.

Facts & Figures

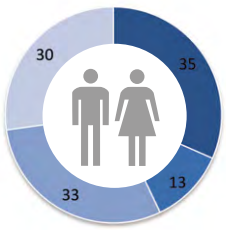
www.RIMLS.nl
70.000 page-views
400.00 unique page views
1 min average visit

Staff (fte) per appointment



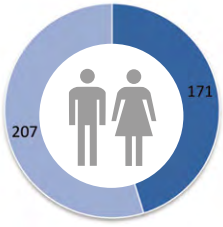
Tenured Non tenured Support

Tenured Staff (fte)



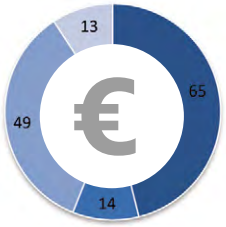
Professors Associate Professors
Assistant Professors Researchers

Non-Tenured Staff (fte)



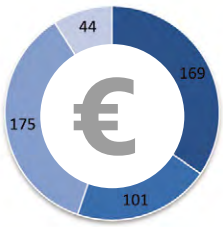
Researchers Doctoral Candidates

Non-Scientific Staff Funding (fte)



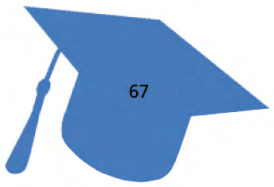
1st Funding Stream 2nd Funding Stream
3rd Funding Stream 4th Funding Stream

Scientific Staff Funding (fte)

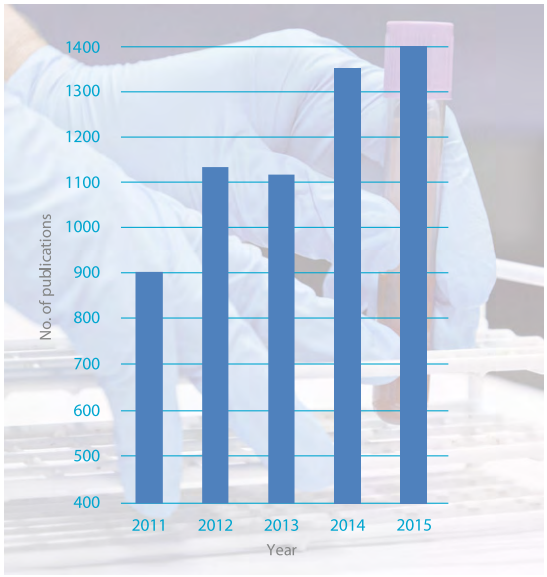


1st Funding Stream 2nd Funding Stream
3rd Funding Stream 4th Funding Stream

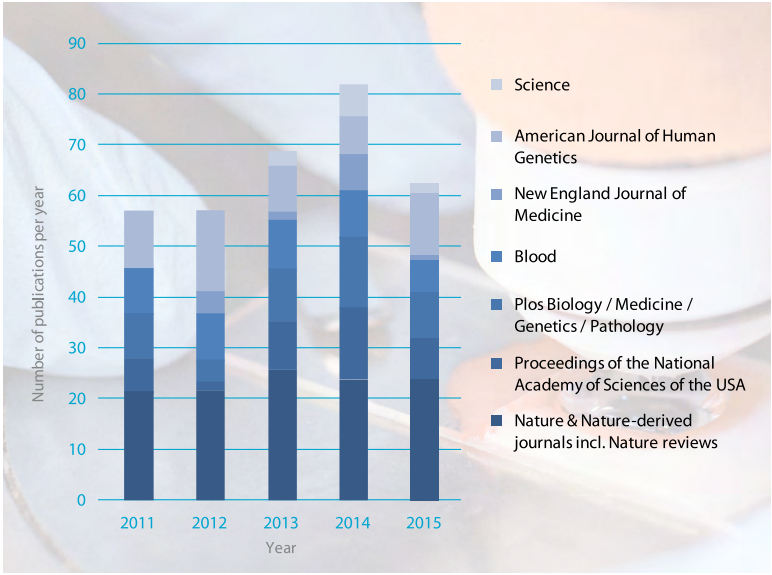
Number of graduations



Total RIMLS publications



Number of publications in selected top-international journals



RIMLS & Selected Awards

RIMLS Awards & grants

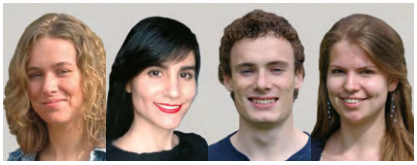
Best scientific report: Felix Fennemann (Cancer development and immune defence).
Best PhD thesis: Jeroen de Baaij (Renal disorders).
Best breakthrough paper of the year: Nicoline Hoogerbrugge & Robbert Weren (Tumours of the digestive tract): A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer. *Nat Genet.* 47:668-71, 2015.

Best oral lecturers (PhD retreat): Christian Büll (Cancer development and immune defence) & Katharina Becker (Infectious diseases and global health).
Best poster (PhD retreat): Sarah Weischer (Cancer development and immune defence).

Winners of the RIMLS challenge (PhD retreat): Giuliana Ascone (Inflammatory diseases), Christian Büll, Dylan Eikelenboom & Daniëlle Verboogen (Cancer development and immune defence), Ideke Lamers (Renal disorders), Christina Wefers (Women's cancers) & Christiane Zuconelli (Nanomedicine).

Travel grant: Brook Latour & Jenny van der Wijst (Renal disorders), René Marke & Lotte de Winde (Cancer development and immune defence), Pascal Miesen (Infectious diseases and global health), Wouter Touw (Nanomedicine).

Winners RIMLS-IRB Travel Award
Maartje Cleophas (Infectious diseases and global health), Tania Crisan (Infectious diseases and global health) & Steef Kurstjens (Renal disorders).



Best PhD project proposals:

- Gaby Eliesen (Renal disorders): Handling of biologicals by human placenta and the risk of their use during pregnancy.
- Shokoufeh Cheheili Sobbi (Infectious diseases and global health): The role of neuroinflammation in cognitive decline post-cardiac surgery. The FOCUS study.
- Jeroen Slaats (Cancer development and immune defence): Tumor immune escape: unravelling and overcoming the immunosuppressive mechanisms and niche in melanoma.
- Inge Wortel (Cancer development and immune defence): Computational reconstruction of the tumour microenvironment: towards personalized cancer immunotherapy.

New Frontiers symposium Poster Awards:

- Ruxandra Bachmann-Gagescu (University of Zurich, Institute for Molecular Life Sciences, Zürich, Switzerland), The Joubert syndrome protein CC2D2A associates with NINL and plays a role in RAB8A-MICAL3 regulated vesicle trafficking.
- Albane Bizet (Laboratory of hereditary kidney diseases, Paris, France), Mutations in *TRAF3IP1/IFT54* reveal a new role for IFT proteins in microtubule stabilization.
- Jeroen van Reeuwijk (Renal disorders), Systematic exploration of the ciliary protein landscape by large-scale affinity proteomics.

RIMLS & Selected Awards

Selected consortium grants

- Carl Figdor (Cancer development and immune defence) received a large EU H2020 consortium grant (PRECIOUS, €8.3 M) to develop and clinically test biodegradable nanomedicines for cancer immunotherapy.
- Henri Timmers (Vascular damage) and his colleagues obtained a H2020 consortium grant (ENSAT, €7.6 M) to develop 'omics-based strategies for improved diagnosis and treatment of endocrine hypertension.
- Anneke den Hollander (Sensory disorders) and colleagues were awarded an EU H2020 consortium grant, EYE-RISK (€6 M), to explore the combined roles of genetic and non-genetic factors in developing age-related macular degeneration.
- A large European study (MDS-RIGHT, €6 M) for better diagnosis and treatment of severe anaemia and myelodysplastic syndromes will be started to determine optimal treatment. The project will be coordinated by a core team from the Radboudumc consisting of Joop Jansen and his colleagues (Cancer development and immune defence).

- Niels Riksen (Vascular damage), Mihai Netea and Leo Joosten (Infectious diseases and global health) will partake in a large study (REPROGRAM, €6 M) of immune epigenetic reprogramming (trained immunity) in atherosclerosis. The aim of the study is to identify novel diagnostic targets and determine optimal treatment.
- Rogier Thurlings and Peter van Lent (Inflammatory diseases) will participate in a large EU consortium, ADIPOA-2, that is developing novel cellular therapies for treating osteoarthritis.

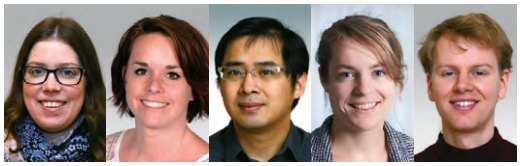
- An international training network (EU Marie Curie ITN) has been awarded to a consortium of European researchers coordinated by Jan van Hest (Nanomedicine). The focus of the network is to educate a new generation of young scientists in developments in nanomedicine, from particle synthesis and characterization to pharmacokinetics and bio-distribution.
- Gosse Adema (Cancer development and immune defence) received an EU Marie Curie ITN grant (IMMUTRAIN, €3.9 M) for development of immunotherapy against cancer.
- William Leenders (Nanomedicine) received a €1.9 M grant from Eurostars designed to develop diagnostic blood-based tests for detection of cancer-causing genes in patients.
- An Alpe d'HuZes grant (€1 M) was awarded to Jeroen van der Laak (Women's cancers) and Iris Nagtegaal (Tumours of the digestive tract) to develop advanced image analysis software as prognostic tools for colon, breast and liver cancers.

- Gerben Ferwerda and Marien de Jonge (Infectious diseases and global health) have been awarded an EU H2020 consortium grant (PHC-10) to develop advanced miniaturized diagnostics for respiratory syncytial virus infections in children.
- Toin van Kuppevelt and Willeke Daamen (Reconstructive & rege-regenerative medicine) received a €600,000 consortium grant to improve lung regeneration in emphysema patients. The grant is supported by McGowan Institute for Regenerative Medicine, Pittsburgh and Trinity College Dublin.

Veni, Vidi, Vici & ERC Awards

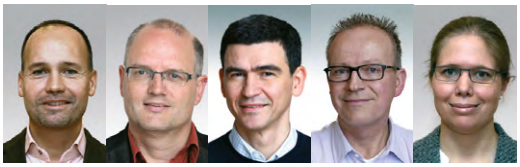
- Martijn Verdoes (Cancer development and immune defence) received a €1.5 M ERC starting grant for his research proposal titled *"Checkpoints in Check: Novel Chemical Toolbox for Local Cancer Immunotherapy"*. Martijn Verdoes was also successful in obtaining a €1.1M Tenure Track Fellowship from the Institute for Chemical Immunology (www.chemicalimmunology.nl), to further his research on chemical immunology.
- Three RIMLS researchers were awarded NWO Vidi grants - each worth €800,000 - to develop innovative lines of research. Geert van den Bogaart (Cancer development and immune defence): *"Activation of the immune system"*, Bas Dutilh (Tumours of the digestive tract): *"Bacteriophages in the human gut"* and Bart Smeets (Renal disorders): *"Damage control in progressive kidney disease"*.

RIMLS & Selected Awards



- Five RIMLS researchers were awarded NWO Veni grants, each worth €250,000 to develop innovative lines of research. Annemarie Boleij (Tumours of the digestive tract): *"Do intestinal bacteria increase the risk of colon cancer in ulcerative colitis?"*, Ellen van den Bogaard (Inflammatory diseases): *"Get rid of that itch!"*, Shih-Chin Cheng (Infectious diseases and global health): *"The role of energy metabolism in the immune system"*, Janna van Diepen (Mitochondrial diseases): *"The relationship between diabetes and arteriosclerosis"*, and Wouter Verdurmen (Nanomedicine): *"Protein therapeutics against cancer"*.

Selected personal grants



- Henri Timmers (Vascular damage) together with Peter Deen (Renal disorders) obtained a grant of €750,000 from the Paradifference Foundation to develop a treatment for paraganglioma's caused by mutations in the mitochondrial succinate dehydrogenase (SDH) B subunit.
- Mihai Netea and Leo Joosten (Infectious diseases and global health) received a ZonMw Top grant of €675,000 for a project entitled: *Immuno-metabolic circuits in sepsis: restoring host defense.*
- Tina Ritschel (Nanomedicine) received a €500.000 research grant (Netherlands eScience Center) for the development of eScience technologies to improve the integration of chemical and biological data for the prediction of polypharmacological action of drug molecules.

- Several researchers were successful in obtaining funding from the Dutch Cancer Society (KWF):
  - Nicoline Hoogerbrugge (Tumours of the digestive tract) and colleagues: *"Early TUbectomy with delayed oophorectomy to improve quality of life as alternative for salpingo-oophorectomy in BrcA mutation carriers: TUBA study"*.
  - Nicole Blijlevens (Rare cancers): *"The influence of the oral microbiome and salivary proteome on oral complications in hematopoietic stem cell recipients: the H-OME study"*.
  - Janneke-Hoogstad-van Evert (Women's cancers): *"Exploring the opportunities of natural killercell therapy against ovarian carcinoma"*.
  - Iris Nagtegaal (Tumours of the digestive tract): *"Intestinal bacterial biofilms in Lynch syndrome patients as disease markers for colorectal cancer"*.

  - Roland Kuiper, Nicoline Hoogerbrugge and Marjolijn Ligtenberg (Tumours of the digestive tract): *"Base excision repair defects: novel causes of adenomatous polyposis and (colorectal) cancer predisposition"*
  - Gosse Adema and Christian Büll (Cancer development and immune defence): have been awarded a 570.000 Euro KWF fundamental research grant: *"Blocking Sialic Acids to Boost Cancer Immunotherapy"*
  - Annemarie Boleij (Tumours of the digestive tract): *"Intestinal bacterial biofilms in Lynch syndrome patients as disease markers for colorectal cancer"*.

- René Bindels and Paco Arjona (Renald disorders) were awarded €250,000 by the Dutch Kidney Foundation for their project *"Mechanosensation of urinary flow by primary cilia regulating renal electrolyte reabsorption"*.
- Joost Hoenderop and Jeroen de Baaij (Renal disorders) were awarded €250,000 by the Dutch Kidney Foundation for their project *"Magnesium as novel therapeutic target for cardiovascular disease in CKD"*.
- Richard Rodenburg (Mitochondrial diseases) received a grant of €250,000 from the Prinses Beatrix Spierfonds to identify novel intervention targets to treat mitochondrial disease patients.

RIMLS & Selected Awards

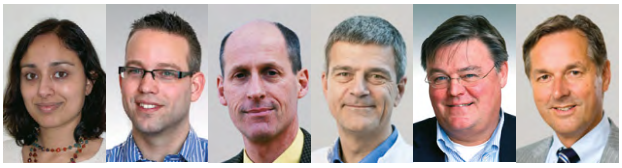
- Esmeralda Blaney Davidson (Inflammatory diseases) received a €240,000 grant from the Dutch Arthritis Foundation to carry out the project *"Inflammation-induced SOCS3 leads to deleterious chondrocyte behaviour by altering TGF-β signalling, resulting in progressive cartilage damage in osteoarthritis"*.
- Wiljan Hendriks and William Leenders, (Nanomedicine) received €125,000 from Stichting Stophersentumoren for their collaborative project: *"Tackling glioblastoma therapy resistance via exploitation of novel genetic concepts"*.

- Johan van der Vlag together with Marjolein Garsen (Renal disorders) received a €100,000 innovation grant from the Dutch Kidney Foundation to test therapeutic potential of heparanase 2 in glomerular diseases. Dorine Swinkels and Guus Kortman (Renal disorders) received an equivalent grant to investigate the pathogenic role of the gut microbiota in chronic kidney disease.
- Jeroen de Baaij (Renal disorders): *"Mighty Magnesium: Hope for diabetic patients?"* and Marjolein Meddens (Cancer development and immune defence): *"Four dimensions of the mast cell membrane"* have each been awarded a 2 year NWO Rubicon grant to conduct research at a foreign institute.

Selected Awards & Honours

- Joost Drenth (Renal disorders) was introduced as a Honorary Member of the Hungarian Society of Gastroenterology. He was bestowed with this honour for his leading role in protecting the interests of national societies at the European level and for his research achievements on polycystic liver disease.
- Peter Friedl (Cancer development and immune defence) received the award for Faculty Excellence 2015, from the MD Anderson Cancer Center (Texas, USA), in recognition of his innovative imaging research providing unprecedented insights into cancer metastasis.
- Mihai Netea (Infectious diseases and global health) was elected as a new member of the Academia Europaea. Membership is only by invitation after peer group nomination, scrutiny and confirmation as to the scholarship and eminence of the individual in their chosen field. In addition to Mihai Netea, John Jansen, Jan Smeitink, Carl Figdor, Jos van der Meer, Han Brunner, René Bindels and Han van Krieken are also members of the Academia Europaea.

Other selected news items



- The Health-Holland Venture Challenge was won by 'Conquest', represented by Mangala Srinivas (Reconstructive and regenerative medicine), Erik Aarntzen (Tumours of the digestive tract) and Frank Smeets (Valorisation). Together they won €25,000 for their nanoparticle diagnostic imaging technology.
- During the World Cancer Day the 4th February 2015 gynecological oncologist Leon Massuger (Women's cancer) gave a presentation on the new HPV (human papillomavirus) test that will be implemented in 2016 as the new standard for cervical cancer screening.
- Khondrion, the Dutch biopharmaceutical company focusing on small molecule therapeutics for mitochondrial diseases, announced that the European Commission has granted Khondrion Orphan Drug Designation (ODD) for its frontrunner compound KH176 to treat MELAS syndrome.
- On September 10th, a charity dinner was organized to celebrate 50 years of Academic Urology at Radboudumc. Jack Schalken and Peter Mulders (Urological cancers) handed a cheque of €200,000 to the chair of the Radboud Oncology Fund, Frans Corstens, and fundraiser Petra van Soest. The money will be used to further urological cancer research at the Radboudumc.

Appointments

- Annemiek van Spriel (Cancer development and immune defence) has been appointed Associate Professor in Immune Cell Signaling. Her research focuses on understanding membrane biology and signal transduction in immune cells during anti-tumor responses.

New Frontiers Symposium in Cilia Medicine

In front of a full auditorium, Paul Smits, Dean / vice-Chairman Radboudumc, opened the symposium aimed at discussing the current achievements and challenges ahead in cilia research. The keynote speaker Heymut Omran (Münster, Germany) presented in the first session Cilia disorders & therapeutics his impressive research about the role of motile cilia in disease. The Hans Bloemendal Medal for 2015 was awarded to him in recognition of his groundbreaking studies on ciliopathies.

Lotte Pedersen (Copenhagen, Denmark) described how the KIF13B and NPHP4 interact to establish a caveolin-enriched membrane domain at the ciliary transition zone. Esben Lorenzen (Martinsreid, Germany) discussed the structural studies of the IFT-B complex: implications for the IFT of tubulin-cargo. George Witman (Massachusetts, USA) talked about *in vivo* functions of specific intraflagellar transport (IFT) proteins and protein domains. Dennis Brown (Boston, USA) presented truly amazing super high resolution helium ion scanning microscopy images of the kidney depicting cilia majestically. The second session focused on Cilia & development. Martin Blum (Honenheim, Germany) discussed the evolution and conservation of left-right patterning followed by Jeremy Reiter (San Francisco, USA) who talked about ciliary lipids that modulate Hedgehog signaling. In the third session the speakers talked about the complixity of ciliopathies. The focus of session three was the complexity of ciliopathies. Dorien Peters (Leiden, The Netherlands) discussed about polycystic kidney disease followed by Rachel Giles (Utrecht, The Netherlands) about replication stress causes DNA damage and subsequent cilia loss in Joubert syndrome.

During the second day of the symposium, the fourth session focused on cilia disorders & therapeutics. Jing Zhou (Boston, USA) presented work on polycystin protein family and the primary cilia. Stefan Somlo (New Haven, USA) discussed his work on the increasingly complex relationship of polycystin and cilia function with autosomal dominant polycystic kidney and liver disease followed by Joost Drenth (Nijmegen, The Netherlands) who talked about cholangiocyte organoids as a model of polycystic liver disease. After the coffee break Uwe Wolfrum (Mainz, Germany) discussed about photoreceptor cilia function in health and disease. Rob Collin (Nijmegen, The Netherlands) presented his work on insight into disease mechanisms and new treatments for inherited blindness. Phil Beales (Londen, UK) talked about the question What good are cilia in the brain? Ronald Roepman (Nijmegen, The Netherlands) discussed systems biology of the cilium in health and disease followed by Oliver Blacque (Dublin, Ireland) who gave a lecture about TMEM107 recruits ciliopathy proteins to anchored subdomains of the ciliary transition zone membrane and causes Joubert syndrome. The symposium was drawn to a close with the keynote lecture by Cayetano Gonzelez (Barcelona, Spain) on centrobin function in terminal differentiation.

Bloemendal Medal 2015

The Hans Bloemendal Medal for 2015 was awarded to Heymut Omran, professor of pediatrics, in recognition of his groundbreaking studies on ciliopathies. Heymut Omran obtained his medical degree from the Albert-Ludwigs-University in 1994 and subsequently completed his habilitation in 1980 on kidney failure in children. Specifically, nephronophthisis, a rare genetic disorder affecting cilia function. This early work formed the basis of his interest in ciliopathies. Currently, Heymut's clinical and research specialty focuses on primary ciliary dyskinesia, (PCD) another ciliopathy that causes defects in cilia function in the respiratory tract. The diagnosis of PCD is a speciality in itself. Only a few centers worldwide have the necessary expertise. Heymut Omran is the Chief Medical Director of one such center at the University Hospital Münster. In his scientific quest to understand rare hereditary diseases, his group was able to decipher many genetic defects of ciliopathies and characterize the importance and molecular mechanisms of action of motile cilia / flagella. His research has significantly contributed to clarifying the aetiology of cystic kidney disease, chronic respiratory disease, retinal degeneration, infertility and hydrocephalus. Using molecular genetics and cell biological techniques he characterized evolutionarily conserved biological mechanisms involved in the setting of left & right body asymmetry and mucociliary cleansing of the airways. Heymut Omran has won numerous awards for his research activities, most recently in 2015 the Eva Luise Köhler Research Prize for Rare Diseases. He is also an elected fellow of the prestigious Leopoldina National Academy of Sciences, one of the oldest academies of science in the world. Heymut Omran is a passionate and devoted paediatrician with a clear ambition to make a significant impact on healthcare. An inspiration to all, he has trained and mentored many young scientists to follow in his footsteps.

Scientific Activities

PhD Retreat

The 21st edition of the annual RIMLS PhD retreat was again successfully organized, to great satisfaction of the participants and organisers. The retreat was held at the Conference Centre Koningshof and was attended by most PhD candidates of the RIMLS. Echoing the previous retreats, students from the Institute for Research in Biomedicine (Barcelona, Spain) joined the retreat, to stimulate collaborations and promote international visibility of RIMLS. Final year PhD candidates including the IRB students presented their data orally, highlighting the broad background of the PhD students. All other participants displayed their work in organized poster walks; every student presented their work to a group of 8-9 students, experiencing how to present science. After an intense first day of scientific presentations, there was time for relaxation and social activities, including a "30 seconds game". The pleasant atmosphere and the social interaction with other PhD students made this popular event a winner. Mark Post, professor of physiology, from the University of Maastricht provided an interesting keynote lecture on "Cultured Beef". During the retreat participants took part in the RIMLS challenge, where they were asked to pitch their idea on how to improve the research in our institute in groups. At the end of the retreat, the best oral presentations and best poster presentation were awarded to Christian Büll, Katharina Becker and Sarah Weischer, respectively (see page 11).

The Radboudumc Postdoc Initiative (RPI)

The RPI is a platform that represents Postdocs, research clinicians and final year PhD students. 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. 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, such as career development, transferable skills, and Postdoc policy. This year, two lunch seminars were organized with the topics: *"Academic skills: the building block of future career"*, featuring a foreign guest and three Radboudumc alumni (Alexandra Mark-Schwarz, Florianne Bauer, Ingrid Zeelenberg and Robbert van der Voort) and their career path from academia to event manager, advisor, lecturer, and medical writer, respectively. Finally, our Young Academy member Teun Bousema presented *"50 shades of ethics in science"* featuring an intriguing discussion on scientific integrity. The informal *"Pizza and beer"* event has been extended in 2015. The special guests have been invited to discuss the emerging topics, such employment regulations, the career development, the Art & Science initiative involving Postdocs in 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* and *RU get inspired*.

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 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. Continuous high quality of the programme is evident, in 2012 and 2014 the MMD programme was rated first, and in 2013 and 2015 second, in Life Sciences Master's programmes in the Dutch Master's programme information guide "Keuzegids Masters".

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. To date, students from 27 countries have started and successfully completed the MMD Master's programme, of whom the majority in 2 years.

Students' comments on MMD and RIMLS research:

Ramanil Perera – MMD graduate,
PhD student ETH Zurich
"My internship at the RIMLS was the turning point in my career"

As part of the MMD program, I conducted my first 6-month internship at the Department of Cell Biology in the group of Katarina Wolf associated with the Friedl group. My project focused on the role of nuclear lamins in protease-independent cancer cell migration and invasion through the 3D extracellular matrix (ECM) in vitro. I was trained in various techniques such as 3D cell culture, time-lapse microscopy, confocal microscopy, siRNA gene knockdown and Atomic Force Microscopy. My supervisors really took the time to explain the techniques and theory to me in great detail and I received a lot of feedback. I can confidently say that my internship at the RIMLS was the turning point in my career as a scientist as I gained a vast amount of knowledge and experience in the field of research. It added greatly to moulding my research interests into visualizing cancer cell migration, invasion and metastasis via molecular imaging. I personally had a great experience and highly recommend this lab to my fellow students.

Maxim Baranov – MMD graduate,
PhD student RIMLS, winner of 2015 Radboud University Academic Award
"MMD opened a lot of amazing opportunities to me after I moved to the Netherlands from Russia".

I loved the program structure and the valuable experience offered. The internship opportunities were amazing. I learned how to write grant proposals and carry out high complexity experiments. MMD prepared me for a successful scientific carrier. After graduating from MMD it was easy to transition into a PhD position. Due to my MMD training I feel comfortable and confident in my PhD. I am very thankful that MMD provided me with great training for winning a University Prize for the best internship project of 2013. MMD provides all the necessary training to navigate scientific world with confidence.

Lisanne Gommers – MMD student
"The decision to apply for the MMD programme has been one of the best I ever made - it is the perfect preparation for entering into a high-end PhD programme. But just as importantly, I have made friends for life!"

The MMD programme has encouraged and prepared me to perform my second research-training period in a prestigious and world-leading research group. Since the start of the MMD master I have been really inspired by the motivation and enthusiasm of my fellow MMD students, who immediately became my family. The international setting of the Master is highly motivating. We started with a very intensive period of fundamental- and translational courses given by some of the best and most highly motivated teachers in the field. I immediately experienced that we were part of the RIMLS/Radboudumc community and we always had nice discussions during the lectures. A unique and distinctive feature of the MMD Master is that it helps us gain competence in scientific skills, such as presenting scientific data, reading and writing scientific articles and writing research proposals. I truly believe that these skills are of great importance to become an independent scientist and I could already use these 'scientific skills workshops' in my first research-training period. The small-scale and the international - and interactive nature of the MMD programme make it an excellent preparation for a successful scientific career.

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 inter-disciplinary training programme 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 Gradaute School Certificate and financial bonus.

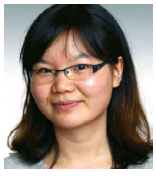
The RIMLS motto is 'to understand molecular mechanisms of disease'. What does this mean to some of our PhD candidates?

Rianne Hendriks (Urological cancers) *With a better understanding of molecular mechanisms of disease we can develop new diagnostic methods and therapies for a number of diseases and improve the quality of life of patients.*

Machteld Oud (Renal disorders) *Current treatment for nephronophthisis and related ciliopathies is just not good enough. We need to understand the underlying mechanisms of this disease in order to start thinking about possible therapies.*

Mieke Roeven (Cancer development and immune defence) *Although my career is not even that long, I have seen the introduction of new therapies which make a real difference for patients. For me, understanding the molecular mechanisms of disease means hope for a longer and improved life for people with currently incurable diseases.*

Paulo Urbano (Inflammatory diseases) *Our body is a complex and, sometimes, an imperfect universe leading to disease. Every day women and men in the scientific community try to connect the pieces (molecular interactions) to understand the causes and ultimately remedy or prevent those diseases.*



Jiangyan Yu (Cancer development and immune defence) *If we can clearly understand the evolutionary process of relapse in leukemia, we will provide novel strategy for future routine diagnosis. Patients can then get proper treatment and live for a longer life.*

Ralph Slijkerman (Sensory disorders) *On one side we try to gain more knowledge on the molecular signaling cascades of Usher proteins and on the other side we try to use the available knowledge to develop new treatments.*

The RIMLS as Graduate School

Jitske Jansen (Renal disorders) *Elucidating molecular pathways involved in the renal excretion of waste products will contribute to the development of novel renal replacement therapies to treat patients suffering from kidney disease.*

Mani Diba (Reconstructive and regenerative medicine) *Understanding the molecular mechanisms of disease will help us design synthetic materials with enhanced biological function, for example to develop better materials for bone tissue regeneration in osteoporotic conditions.*

Amrish Baidjoe (Infectious diseases and global health) *Without comprehensive understanding of all the complex mechanisms behind diseases, adequate solutions will remain elusive.*

Marije Sloff (Urological cancers) *Understand molecular signaling pathways will help us to develop innovative treatments that are better than the currently available ones. Ultimately we need to be able to prevent disease from occurring in the first place.*

Luuk Versteegden (Reconstructive and regenerative medicine) *It is essential to understand the molecular mechanisms of diseases in order to develop novel therapies in a efficient manner and not rely on the serendipity-like discoveries such as penicillin.*

René Raavé (Reconstructive and regenerative medicine) *With novel insights into disease-related molecular mechanisms, new therapies may become available that eventually will help patients, but can also serve as a platform for discovering new drug targets and drug delivery systems.*

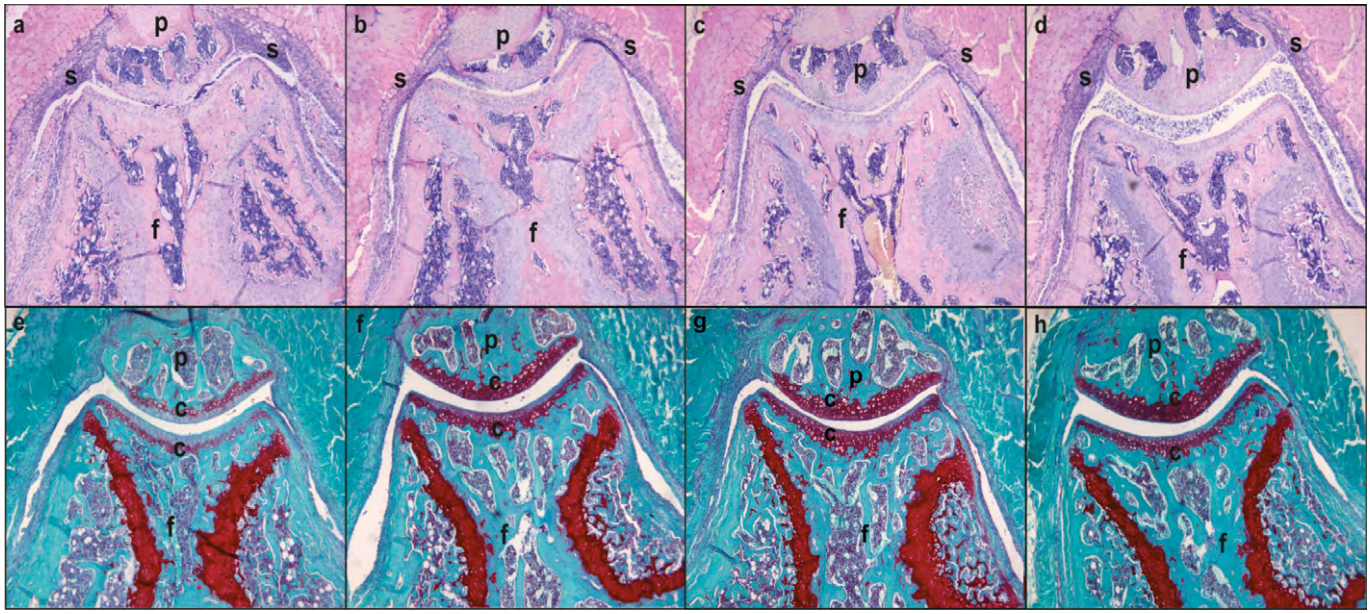
Kioa Wijnsma (Renal disorders) *During medical school I was mostly taught to look at the "clinical" side of diseases. In the coming years I hope to supplement this outlook with understanding mechanisms behind diseases.*

Ilse Dingjan (Cancer development and immune defence) *I work at the level of molecular mechanisms in immune (dendritic) cells during activation (by pathogens or tumour antigens). So, the motto really fits my work. Furthermore, I think you can only start with testing medical interventions, if you know how the intervention works at a molecular level.*

Heinz-Peter Janke (Urological cancers) *Understanding molecular mechanisms is an important piece of the puzzle to find novel treatments and ways to regenerate diseased tissues and organs.*

Patents requested

Title	Lead Inventor
3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors which do not affect the mitochondrial complex III activity – including modified statins and new chemical entities	Frans Russel (Renal disorders), Jan Smeitink (Mitochondrial diseases)
A renal cell line with stable transporter expression	Martijn Wilmer (Renal disorders)
Improved method for ex vivo expansion CD34 + HSPC's into NK cells using an hydrocarbon	Harry Dolstra (Cancer development and receptor antoganist immune defence)
Method for enhancing HIFU-induced ablation	Carl Figdor, Jolanda de Vries (Cancer development and immune defence) & Mangala Srinivas (Nanomedicine)
Method for inducing adipogenic differentiation of stem cells	Wout Feitz (Reconstructive and regenerative medicine)
Method for inducing growth and/or differentiation of stem cells (US- grace period)	Wout Feitz (Reconstructive and regenerative medicine), Egbert Oosterwijk, Silvia Mihaila (Urological cancers)
Method for inducing osteogenic differentiation of stem cells	Wout Feitz (Reconstructive and regenerative medicine) & Egbert Oosterwijk (Urological cancers)
Method for inducing osteogenic differentiation of stem cells	Wout Feitz (Reconstructive and regenerative medicine), Egbert Oosterwijk (Urological cancers)
Method for inducing vascularization of stem cells	Wout Feitz (Reconstructive and regenerative medicine)
Method for the prediction of progression of bladder cancer	Toine van der Heijden (Urological cancers)
Novel inhibitors of p-glycoprotein	Roland Brock & Marco Favretto (Nanomedicine)



Selected Research Highlights

RIMLS 2015


Theme: Nanomedicine

Anneke Navis
William Leenders

Acta Neuropathol. 130:131-44, 2015.

A novel *MET* mutation in diffuse glioma with implications for therapy

Diffuse gliomas are incurable primary brain tumors characterized by the highly invasive spread of tumor cells through the brain. The MET receptor and its ligand HGF are attractive targets for glioma treatment since the receptor is involved in a myriad of tumor-promoting activities including invasion. We previously showed that one of our glioma cell lines is MET-addicted in a ligand-independent way. This prompted us to further investigate the underlying mechanism of activation. Genetic analysis revealed a *MET* amplification, but also a 2-Kb intronic deletion, resulting in a mutant protein ($MET^{\Delta 78}$) lacking 80 amino acids in the Ig-like domains. Because $MET^{\Delta 78}$ is retained intracellularly (Figure 1), it is insensitive to MET-targeting antibodies. Small molecule MET-specific tyrosine kinase inhibitors do inhibit $MET^{\Delta 78}$ signaling. We identified $MET^{\Delta 78}$ in 6% of the diffuse gliomas; screening in other tumor types is ongoing. Our study is the first describing $MET^{\Delta 78}$ and reveals that subcellular localization of the protein is altered, thereby hiding it from MET- and HGF-targeting antibodies. A patent application has been filed and licensed to a biotech company.

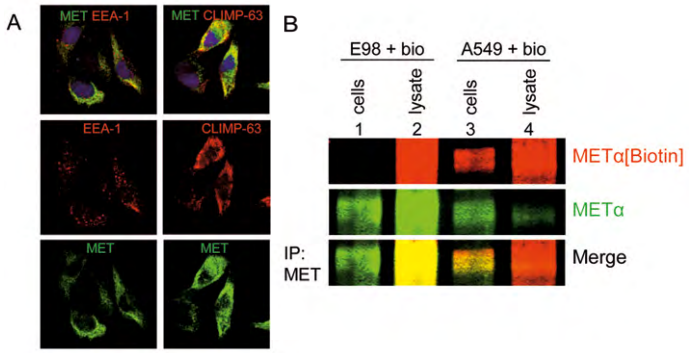


Figure: *$MET^{\Delta 78}$* mutation alters subcellular MET protein localization in glioma cells. (A) Double staining for MET with the early endosome marker EEA-1 and RER-marker CLIMP-1 suggests an intracellular localization of MET in the MET-addicted E98 cell line that does not correlate with early endosomes and only partly with the ER. (B) NHS-biotin labeling of proteins in intact E98 and A549 cells and lysates, followed by immune-precipitation with MET antibodies and protein blotting for MET and biotin. In intact cells, only extracellular proteins will be labeled. MET is biotinylated in A549 cells (wild type *MET*), but not in E98 cells. Complete cell lysates were biotinylated as well, as control for MET labeling.


Theme: Nanomedicine

Sandra Heskamp
Otto Boerman

Cancer Res. 75:2928-36, 2015.

Non-invasive imaging of immune checkpoints in cancer

Immune checkpoints play a critical role in regulating the anti-cancer immune response. Programmed death ligand 1 (PD-L1) is one of the major inhibitory immune checkpoints. By up-regulating PD-L1, tumor cells can escape immune recognition and attack. Antibodies that block PD-L1 have shown impressive and durable anti-tumor responses. However, only a subgroup of patients responds to this therapy. To prevent unnecessary treatment costs and treatment-associated side-effects, there is a urgent need for predictive biomarker. Currently, PD-L1 expression is measured immuno-histochemically. One of the major limitations of this technique is that PD-L1 can be expressed heterogeneously within or between tumor lesions. This leads to misinterpretation if only a single biopsy is analyzed. To overcome this, we have developed a novel imaging technique using radiolabeled anti-PD-L1 antibodies and SPECT/CT to non-invasively determine PD-L1 expression of whole tumors, their microenvironment, and metastases. In the future, this technique can be used as biomarker to select patients for anti-PD-L1 anti-cancer treatment. Furthermore, the technique will allow monitoring of disease progression and therapy.

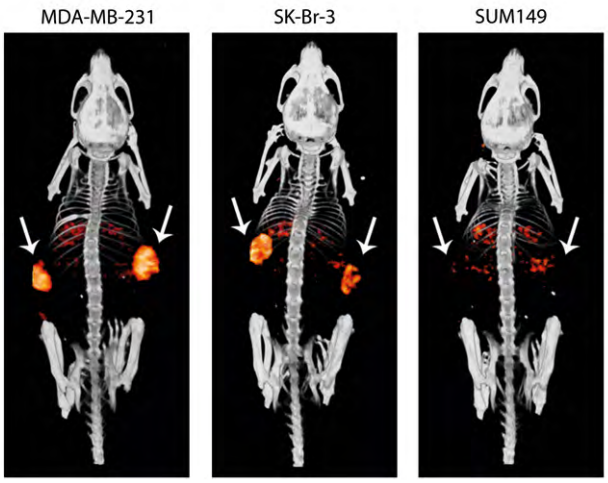


Figure: SPECT/CT scans of mice bearing subcutaneous human breast cancer xenografts on both flanks (white arrows). PD-L1 SPECT/CT was able to distinguish between tumors with high, moderate, and low PD-L1 expression levels. Furthermore, heterogeneous uptake was observed within and between tumors lesions.


Theme: Cancer development and immune defence

Christian Büll
Gosse Adema

Nano. 9:733-45, 2015.

Sialic acid blocking nanoparticles stop cancer spread in mice

Cancer metastases, rather than primary tumors, are responsible for the largest percentage of cancer deaths. Sialic acid sugars are overexpressed by cancer cells and contribute to the metastatic cascade at multiple levels. Therapeutic interference with sialic acids, however, has been difficult to achieve because of the absence of dedicated tools. Here we show that a rationally designed sialic acid-blocking glycomimetic (P-3F_{ax}-Neu5Ac) successfully prevents cancer metastasis. Formulation of P-3F_{ax}-Neu5Ac into nanoparticles coated with tumor-specific antibodies allowed targeted delivery of P-3F_{ax}-Neu5Ac to melanoma cells, slow release, and long-term sialic acid blockade. Most importantly, injections of melanoma-targeting P-3F_{ax}-Neu5Ac nanoparticles prevented metastasis formation in a murine lung metastasis model (Figure 1). These findings stress the importance of sialoglycans in cancer metastasis and advocate that sialic acid blockade using glycomimetics targeted to cancer cells can effectively prevent cancer metastases. Targeting strategies to interfere with sialic acid-dependent processes are broadly applicable not only for different types of cancer but also in infection and inflammation.

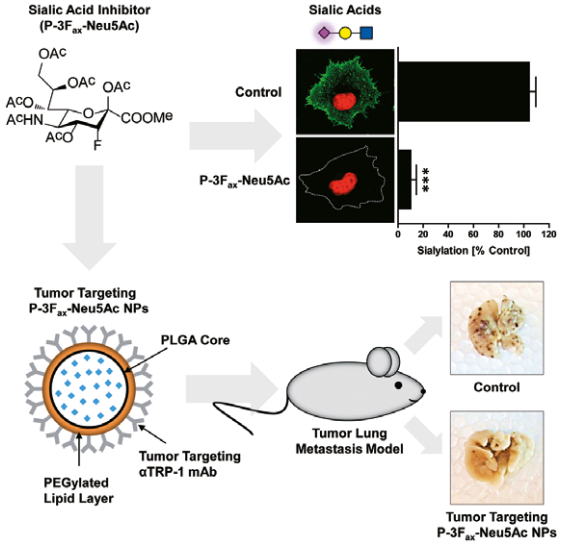


Figure: Structural representation of TRP-1-targeting nanoparticles containing the sialic acid blocking glycomimetic P-3F_{ax}-Neu5Ac. Intravenous injection of the nanoparticles largely prevented metastatic spread of melanoma cells to the lung in a mouse tumor model.


Theme: Cancer development and immune defence

Carl Figdor
Martijn Verdoes

J Am Chem Soc. 137:4771-7, 2015.

Imaging cancer using cathepsin S

The cysteine cathepsins are a family of 11 proteases. These enzymes are important regulators of both health and disease. Due to its distinctive expression profile in immune cells and involvement in antigen presentation, cathepsin S has attracted significant attention from scientists, both in the pharmaceutical industry and in academia. To investigate mechanisms important for cathepsin S mediated pathology, reliable molecular tools that can monitor cathepsin S activity are needed. Furthermore, the activity of cathepsin S is upregulated in both cancer and inflammation, making it a suitable target to image these conditions. We designed and synthesized the first near-infrared quenched activity-based probe (qABP) (Figure 1A) that selectively targets cathepsin S (BMV157). We have used this probe to non-invasively image cancer in mice (Figure 1B). Furthermore, combined with a new complementary pan-reactive green-fluorescent cysteine cathepsin qABP (EM053) we performed dual color live cell imaging studies to show for the first time the specific localization of cathepsin S activity in dendritic cells (Figure 1C).

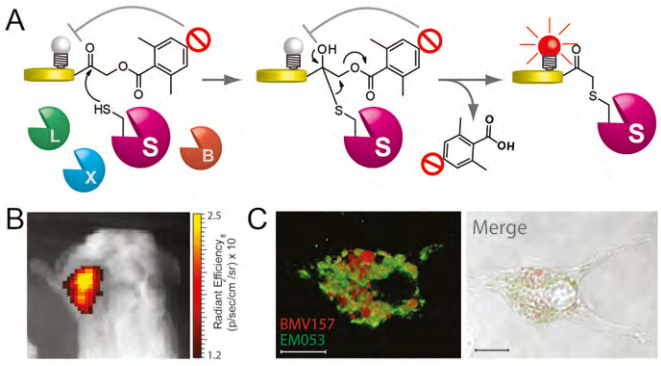


Figure: (A) Mechanism of qABP action. (B) Non-invasive tumor detection with BMV157. (C) Live cell dual color cathepsin activity imaging showing specific localization of cathepsin S activity in dendritic cells.


Theme: Cancer development and immune defence

Hendrik Marks
Henk Stunnenberg

Genome Biology. 16:149, 2015.

Spreading of silencing over the X chromosome during X inactivation in female cells

In mammals, gender is determined by "sex" chromosomes. Considering the X chromosome, males have a single X chromosome, whereas females have two copies of the X chromosome. To compensate for this difference, female cells shut off one X chromosome during early embryonic development in a process called X inactivation.

Thus far, it was unclear how such a silencing process spreads along a full chromosome. To study this, we used female mouse embryonic stem cells and initiated X inactivation by means of differentiation. With the latest technologies, we were able to keep the two X chromosomes apart based on differences in nucleotide composition between the two X chromosomes, and measured in detail all RNA of the X chromosome that got inactivated. At daily intervals we checked which parts of the chromosome had been switched off. The whole process took eight days, and we could show that the inactivation spread out from the centre of the X chromosome towards the ends. The inactivation spreading moves in a jumpy fashion along domains of around 1Mb (Figure 1). Furthermore, we collected strong evidence that a similar process occurs in humans.

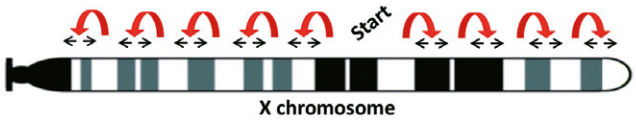


Figure: Spreading of silencing (arrows) over the X chromosome.


Theme: Tumors of the digestive tract

Chella van der Post
Marjolijn Ligtenberg

Gastroenterology. 149:897-906.e19, 2015.

Accuracy of hereditary gastric cancer testing criteria

Patients with a germline *CDH1* mutation have a high lifetime risk to develop diffuse gastric cancer and lobular breast cancer for which preventive measures can be undertaken. In the Netherlands germline mutations were detected in only 18 of 499 (4%) families tested after referral by a clinical geneticist between 1999 and 2014. In close collaboration with all Dutch clinical genetic centers, the tested individuals were categorized according to the international hereditary diffuse gastric cancer (HDGC) criteria that were accepted in 2010 (Figure 1). These criteria are based on age at diagnosis, histology and family history. Sixteen of the 118 (14%) families that fulfilled the HDGC criteria were tested positive for a pathogenic germline *CDH1* mutation. Therefore, if these criteria would have been strictly applied 3.5 times fewer patients would have been tested with a sensitivity of 89%. The results led to modified international HDGC criteria that were implemented in 2015.

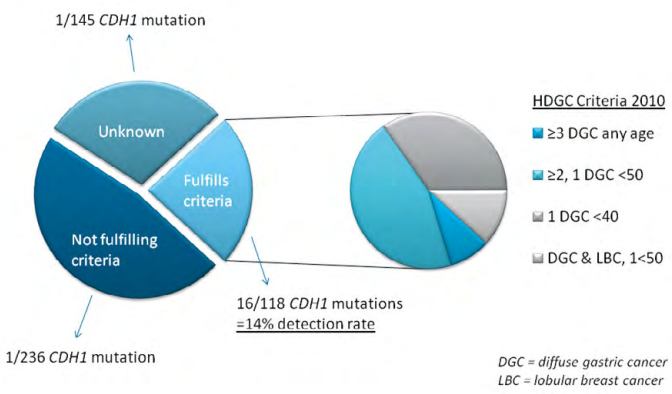


Figure: Schematic overview of the families tested.


Theme: Tumors of the digestive tract

Robbert Weren
Nicoline Hoogerbrugge

Nat Genet. 47:668-71, 2015.

Novel genetic cause for adenomatous polyposis and cancer

Patients diagnosed with adenomatous polyposis are at high risk of colorectal cancer (CRC). Adenomatous polyposis (AP) is strongly associated with heritable germline aberrations, but a significant subset of these patients cannot be explained by known predisposing genes. We performed whole-exome sequencing on a stringently selected cohort of unexplained AP patients (*n*=51) and identified a novel predisposing gene: *NTHL1*. A deleterious germline mutation, p. Gln90*, in the base excision repair gene *NTHL1* was homozygously present in seven patients from three different families. This mutation is rare and heterozygous in controls. All families showed recessive inheritance, complete co-segregation of the homozygous p. Gln90* mutation with development of adenomatous polyposis and progression to CRC in at least one member. Somatic mutation analysis of CRC and adenomas from affected members revealed enrichment of cytosine-to-thymine transitions, strongly reflecting a defect in the base excision repair pathway (i.e. *NTHL1*). All affected women also developed endometrial (pre)malignancies, pointing towards a broader tumour spectrum. Future research will be performed to establish the tumour spectrum and incidence of this novel adenomatous polyposis and cancer predisposing syndrome.

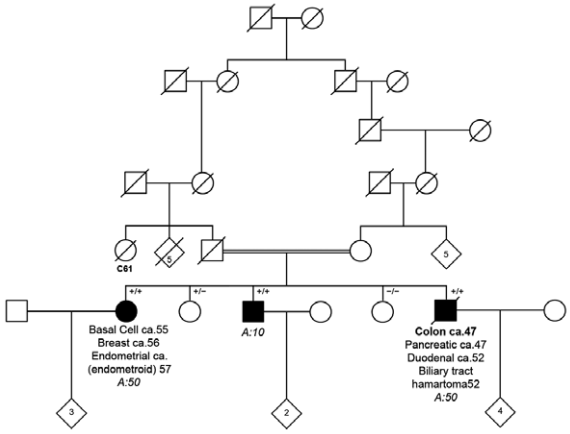


Figure: Pedigree of one family with individuals homozygous for *NTHL1* p.Gln90*. Individuals with adenomatous polyposis were all tested positive for the homozygous p.Gln90* mutation in *NTHL1* (+/+) and are indicated by filled symbols. Age of onset is indicated for each malignancy. Number of colorectal adenomatous polyps (A) present at time of diagnosis are in italic. C, colon cancer; Ca.: carcinoma. +/–) heterozygous carrier of the p.Gln90* mutation in *NTHL1*. –/–) non-carrier of the p.Gln90* mutation in *NTHL1*.


Theme: Urological cancers

Gisele Leyten
Jack Schalken

Clin Cancer Res. 21:3061-70, 2015.

A liquid biopsy for the early detection of prostate cancer

Prostate cancer is most common malignancy in the male population. The main challenge is, therefore, to identify patients who need treatment, i.e. those with clinically significant prostate cancer. The commonly used serum PSA test has led to over-treatment. We have identified a panel of mRNAs, that can be measured in urine, to predict the presence of a clinically significant cancer. The panel was validated in a large prospective study. In particular for men with a slightly elevated serum PSA 3-10 mg/ml), the test can be used to further select patients for whom a prostate biopsy is needed. Thus, the test can lead to a significant reduction of the number of (unnecessary) biopsies. This new test was launched in November 2015 as the SelectMDx test (www.mdxhealth.com).

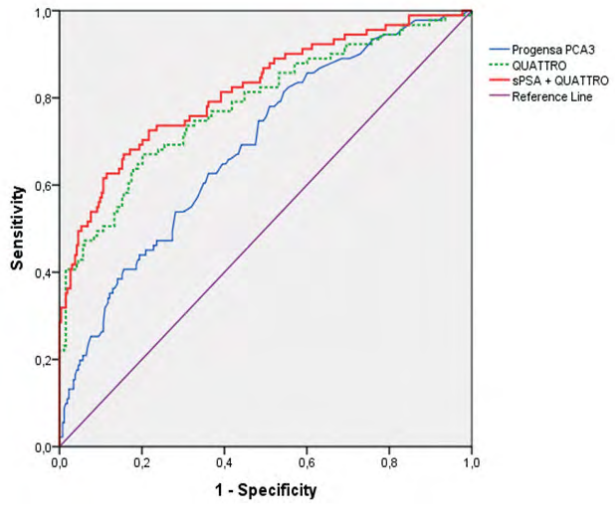


Figure: The ROC curves (sensitivity graphs for evaluation of diagnostic tests) for four models: Progensa PCA3 (purple line, AUC = 0.688; 95% CI 0.63 – 0.75), QUATTRO (red line, AUC = 0.78; 95% CI 0.72 – 0.84) and sPSA + QUATTRO/SelectMDx (green line, AUC = 0.82; 95% CI 0.73 – 0.87) for the prediction of Gleason score ≥7 PCa diagnosis upon biopsy.


Theme: Infectious diseases and global health

Pascal Miesen
Ronald van Rij

Nucleic Acids Res. 43:6545-56, 2015.

Defining a new class of small RNAs in arbovirus infection of mosquitoes

Aedes mosquitoes transmit a substantial number of viruses, collectively called arthropod borne viruses (arboviruses), between vertebrate hosts. Therefore, antiviral pathways that limit virus replication in mosquitoes critically influence virus spread within the vertebrate population. RNA-interference, with at its core small interfering RNAs (siRNAs), is such a potent antiviral mechanism (A). We recently identified an additional class of viral small RNAs, known as PIWI-interacting RNAs (piRNAs), raising the exciting possibility that viruses are targeted by two independent RNA silencing pathways in *Aedes* mosquitoes (A). The piRNA pathway was initially only implicated in transposon defense and little is known about the biogenesis and function of virus-derived piRNAs. We identified the PIWI proteins Piwi5 and Ago3 as key biogenesis factors for viral piRNAs (B). Interestingly, whereas the production of virus-derived piRNAs is almost exclusively dependent on Piwi5 and Ago3, the biogenesis of the 'classical' transposon-derived piRNAs is more versatile and involves additional PIWI proteins. These findings suggest that specialized arms of the piRNA pathway recognize and produce piRNAs from endogenous or exogenous parasitic RNAs (B).

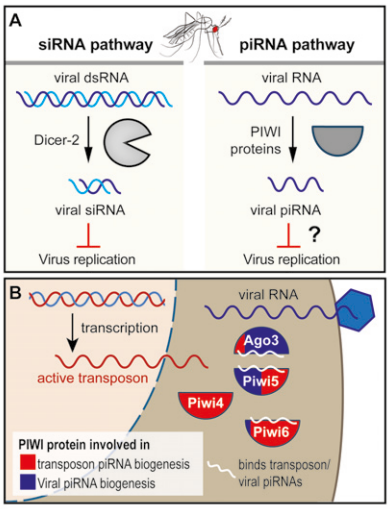
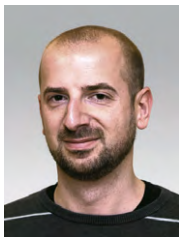


Figure: (A) siRNA and piRNA pathways target viral RNA in *Aedes* mosquitoes. (B) piRNA biogenesis in mosquitoes involves multiple PIWI proteins. The blue/red color code indicates whether a PIWI proteins primarily acts in viral or transposon piRNA biogenesis.




Theme: Infectious diseases and global health

Wout Megchelenbrink
Richard Notebaart

Proc Natl Acad Sci U S A. 112:12217-22, 2015.

Targeting cancer cells by metabolic network simulation

Synthetic dosage lethality (SDL) denotes a genetic interaction between two genes whereby the under-expression of gene A combined with the overexpression of gene B is lethal (Figure 1). SDLs offer a promising way to kill cancer cells by inhibiting the activity of SDL partners of oncogenes in tumors, which are often difficult to target directly. We introduced a network-level computational modeling framework that quantitatively predicts human SDLs in metabolism. For each enzyme pair (A, B) we systematically knocked out the flux through A combined with a stepwise flux increase through B and searched for pairs that reduce cellular growth more than when either enzyme is perturbed individually. We found 12,000 SDLs and demonstrated that, as expected, SDLs are significantly underrepresented in tumors. Moreover, breast cancer tumors with SDLs active have smaller sizes and the survival times of these patients are increased. Finally, we reported that patient survival improves when multiple SDLs are present, pointing to a cumulative effect. This study lays the basis for quantitative identification of cancer SDLs in a model-based mechanistic manner.

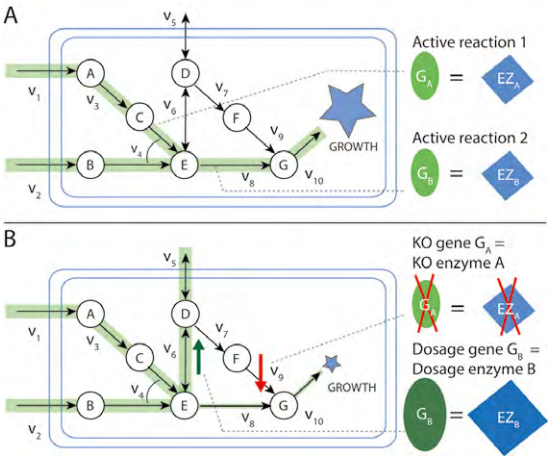


Figure: Cancer metabolic state vs SDL metabolic state. (A) Cancer gene activity routes metabolic flux to tumor growth. (B) Knock-out of gene A and overexpression of enzyme B routes flux away from growth and is lethal to the cell.

Theme: Inflammatory diseases

Heleen de Koning
Anna Simon

J Allergy Clin Immunol. 135: 561-4, 2015.

Myeloid-lineage-restricted mosaicism in variant Schnitzler's syndrome

Schnitzler's syndrome is a rare autoinflammatory syndrome characterized by a chronic urticarial rash, fever, bone pain, arthralgias, increased inflammatory markers and a monoclonal gammopathy. High efficacy of treatment with interleukin-1 beta (IL-1β) blockers suggests involvement of the IL-1β pathway. Based on its late onset and absence of familial clustering, the syndrome was considered acquired rather than genetic, a concept we challenged here.

Whole exome sequencing revealed an *NLRP3* mutation in a patient. NLRP3 is part of an inflammasome that activates IL-1β. Targeted resequencing revealed *NLRP3* mutations in whole blood DNA from two patients. Remarkably, these mutations were exclusively present in subsets of neutrophils and monocytes (Figure 1). Lesional skin is infiltrated by these myeloid cells. Further, patient peripheral blood mononuclear cells showed excessive spontaneous *in-vitro* IL-1β production.

By identifying myeloid-lineage-restricted mosaicism of *NLRP3* mutations in Schnitzler's syndrome, we clarified the clinical response to IL-1β blockade. This is the first report on myeloid-lineage-restricted mosaicism in a non-malignant disorder, and we predict that mosaicism is involved in many other late-onset disorders.

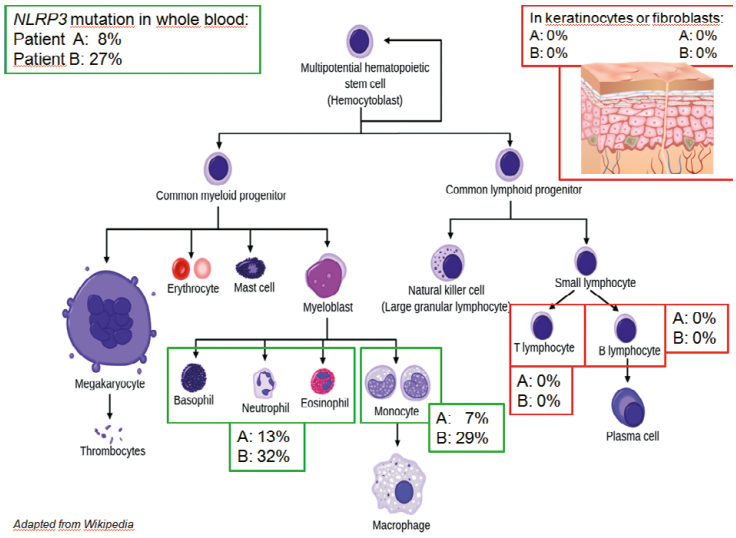


Figure: Percentages of the presence of *NLRP3* mutations in different cell subsets of patient A and patient B show myeloid-lineage restricted mosaicism.

Theme: Inflammatory diseases

Mathijs Broeren
Eline Vermeij

Ann Rheum Dis. 74:2084-91, 2015.

Inducible interleukin-10 gene therapy for arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease, affecting the joints of 1% of the world population. Patients are often treated with weekly systemic injections of immunosuppressive biological drugs, which can lead to side effects. We have therefore developed a gene therapy vector, which allows autoregulated production of the anti-inflammatory protein interleukin-10 (IL-10) by cells in the joint. To limit exposure to flares of inflammation, the IL-10 expression is driven by a disease-responsive promoter. Based on microarray analysis of synovial biopsies of arthritic mice, we selected the promoter of the SAA3 gene (early inflammation response gene) and the promoter of the MMP13 gene, which is activated several days after an inflammatory stimulus. The viral vectors were injected in mouse joints prior to induction of experimental arthritis. As expected, mice that received a control treatment showed signs of immune cell infiltration (Figure 1a) and loss of cartilage proteoglycans (Figure 1e). The mice receiving IL-10 gene therapy showed reduced signs of arthritis (Figure 1 b-d, f-h). These results show that the SAA3 and MMP13 promoter allow disease-regulated overexpression of therapeutic levels of biologics in arthritic joints.

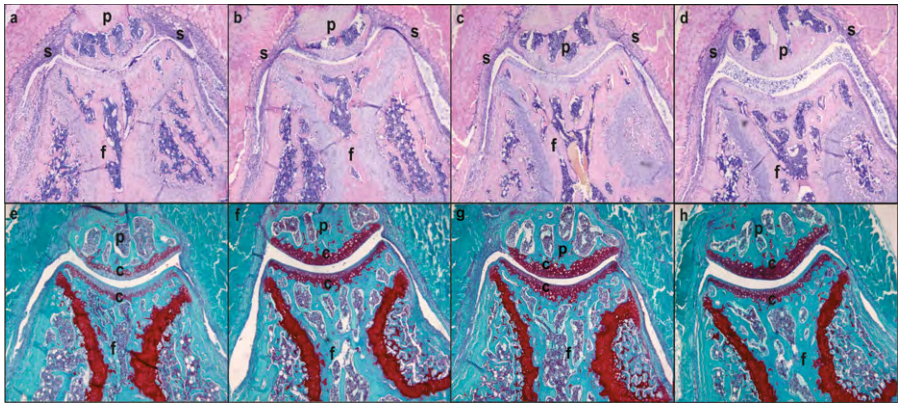


Figure: Histology of knee joints using HE-staining for analysis of synovial inflammation (A-D), visible as infiltration of purple immune cells. Safranin-O was used for red staining of the cartilage proteoglycans (E-H). Knee joints were injected with control viral vector (A, E), PGK-IL10 (B, F), SAA3-IL10 (C, G) or MMP13-IL10 (D, H). Histology from day 4 (A-D) or day 7 (E-H) after arthritis induction is shown. p=patella, f=femur, s=synovium, c=cartilage.


Theme: Inflammatory diseases

Esmeralda Blaney Davidson
Peter van der Kraan

Ann Rheum Dis. 74:1257-64,2015.

Bone Morphogenetic Protein 2: boosting bone spurs, but not cartilage damage in osteoarthritis

Osteoarthritis (OA) is a joint disease that is characterized by cartilage degradation and osteophyte formation (bone spurs developing through endochondral bone formation at the rim of the joint). Previously, we found that Bone Morphogenetic Protein 2 (BMP2) was expressed in high levels near cartilage lesions, but its function there was unclear. In addition, we had shown a potential role for BMP2 in osteophyte formation. Since cartilage-specific research *in vivo* is a challenge due to the multitude of tissues in a joint, we generated a unique transgenic mouse with chondrocyte-specific, inducible BMP2 expression. Our experiments revealed that in normal healthy young mice elevated BMP2 levels in chondrocytes did not result in pathology. However, when experimental OA was induced, BMP2 induction led to a severe aggravation of osteophyte formation, which was not observed without the OA as a trigger (Figure). Despite the severe osteophytes, no changes in cartilage damage were observed. This revealed not only that BMP2 was not deleterious for cartilage, but also disconnects cartilage damage and osteophyte formation.

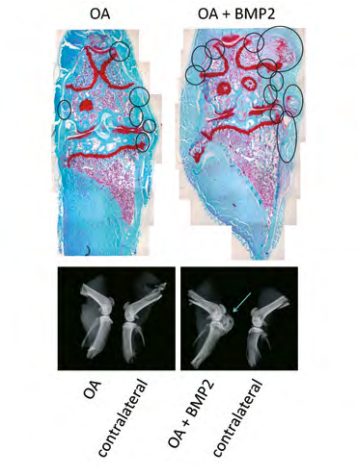


Figure: The left side of the figure shows representative images of murine knee joints with experimental OA, whereas the right side shows that of experimental OA with BMP2 overexpression. Top part shows the histology, bottom shows X-ray images of the knee joints. Circles and arrows indicate osteophytes.


Theme: Mitochondrial diseases

Tom Schirris
Frans Russel

Cell Metab. 22:399-407, 2015.

Statin-induced myopathy is associated with mitochondrial complex III inhibition

Statins are commonly prescribed cholesterol-lowering drugs that effectively reduce the risk of major cardiovascular events. Myopathy is the most important adverse effect, but the underlying mechanism was unknown. In the body statins exist in two forms: acid and lactone. Here, we describe that the lactone form, which opposed to the acid form does not contribute to the cholesterol-lowering effect, reduced mitochondrial respiratory capacity in C2C12 myoblasts. The observed dysfunction was explained by inhibition of mitochondrial complex III (CIII) activity. We could confirm CIII inhibition in muscle tissue of patients suffering from statin-induced myopathies (Figure). In-depth *in silico* and biochemical studies identified the Q_o binding site of CIII as off-target of the statin lactones. Moreover, respiratory inhibition could be attenuated by convergent electron flow into CIII, providing a rationale for L-carnitine supplementation. This enables us to explore strategies for improved prevention of these adverse effects. In addition, we are exploring and patenting novel compounds, which inhibit the cholesterol synthesis without impacting muscle bioenergetics.

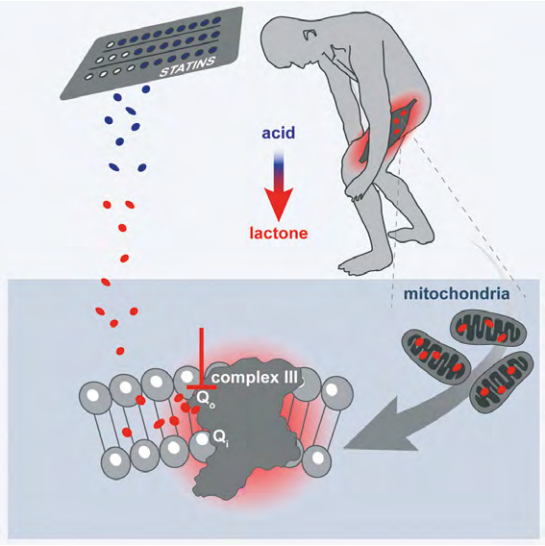


Figure: Schematic overview of the statin lactone interaction with mitochondrial complex III and the association with the clinically observed statin-induced myopathies.

Theme: Mitochondrial diseases

Ulrich Brandt

Science. 347:44-9, 2015.

Mechanistic clues from the X-ray structure of mitochondrial complex I

Complex I of the mitochondrial respiratory chain creates a membrane-potential across the inner mitochondrial membrane driving ATP production. Complex I is also a source of deleterious reactive oxygen species and is involved in many hereditary and degenerative disorders. Here we describe the X-ray structure and mechanistic details of mitochondrial complex I at 3.6-3.9 Å resolution. With 84 transmembrane helices and a mass of 1 MDa, mitochondrial complex I is the largest membrane protein complex ever solved by X-ray crystallography. A continuous axis of protonable residues running centrally through the membrane arm connects the ubiquinone reduction site in the hydrophilic arm to four putative proton-pumps. The structure provides deep insights into a concerted structural rearrangement at the ubiquinone-reduction site explaining the pumping mechanism and the associated regulatory active/deactive transition. The clues obtained on the structure and mechanism of this giant molecular machine will help understanding the functional defects underlying the numerous diseases involving complex I deficiencies and to design preventive and therapeutic strategies.

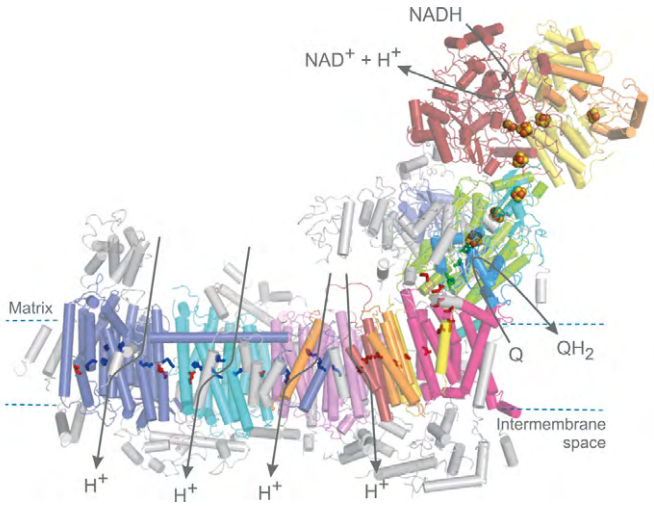


Figure: Structural overview and functional topology of mitochondrial complex I. Accessory subunits in grey. Iron-sulfur clusters in space fill and protonable residues of central axis in stick representation.

Theme: Reconstructive and regenerative medicine

Henk Hoogenkamp
Willeke Daamen

Acta Biomaterialia. 12:113-21, 2015.

Directing collagen fibers using counter-rotating cone extrusion

Although fiber direction and alignment of collagen fibers are important for cellular behavior, methods that can guide the orientation of native insoluble collagen fibers are limited. In this study, we applied a controlled counter-rotating cone extrusion technology to engineer tubular collagen constructs with defined anisotropy. We utilized second harmonic generation microscopy in combination with quantitative image analysis to visualize the collagen fibers, as samples up to 1 mm can be penetrated with this technique without any staining. A clear correlation was found where the direction and extent of collagen fiber alignment during extrusion were a function of the shear forces caused by a combination of cone rotation and flow direction. A change in the fiber direction, starting at +50° and gradually changing to -40°, was observed through the tube wall. With variations in cone speeds, the collagen constructs showed differences in mechanical properties such as elasticity and toughness.

Rotational extrusion presents an enabling technology to create and control the (an)isotropic architecture of collagen constructs for applications in regenerative medicine.

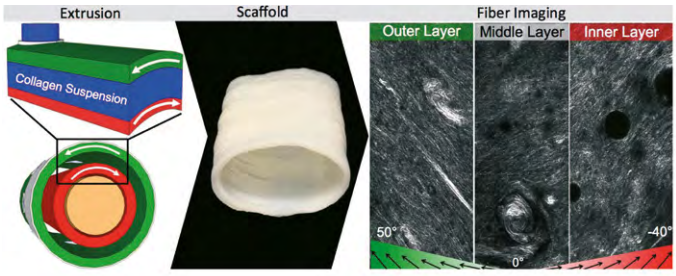


Figure: Extrusion setup showing counter-rotating cones with collagen suspension in between, the tubular scaffold formed in the extrusion process, and the microscopical images with fiber alignment at different angles through the wall of the scaffold.

Theme: Renal disorders

Miriam Schmidts

Nat Commun. 6:7074, 2015.

Novel gene identified for Jeune Syndrome

Cilia are antenna-like cells involved in a large number of signaling pathways crucial for multiple developmental processes. Many inherited so-called "ciliopathy" diseases have been identified to date, one of which is a disabling condition called "Jeune Syndrome". Affected individuals have short ribs causing smaller than normal lungs at birth resulting in severe breathing problems. Also, kidney and liver problems occur frequently. Using next generation DNA sequencing of human patients, in parallel with proteomics techniques, as well as zebrafish and a flagellated green algae, *"chlamydomonas rheinhardtii"* models, we have identified a novel gene causing Jeune Syndrome, *TCTEX1D2*. Loss of TCTEX1D2 impairs retrograde intraflagellar transport (IFT) in humans, a process essential for proper cilia function and by destabilization of the retrograde IFT dynein motor (cytoplasmic dynein 2). TCTEX1D2 encodes for a light chain of the cytoplasmic dynein 2 complex and is required for correct vertebrate skeletal formation but may be functionally redundant under certain conditions. Our findings enable better genetic counselling for patients with Jeune Syndrome and have led to the identification of a potential novel therapeutic target for future improvement of patient care.

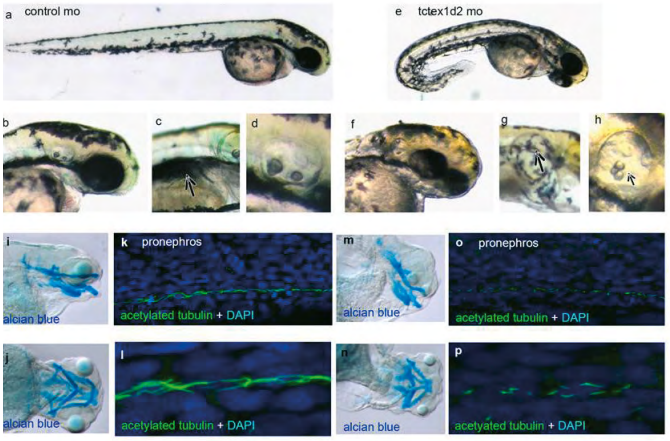


Figure: Zebrafish phenotype using a tctex1d2 morpholino to knockdown the gene function

Theme: Renal disorders

Carolien Schophuizen
Bert van den Heuvel

Acta Biomater. 14:22-32, 2015.

Towards a bio-artificial kidney device

The need for improved renal replacement therapies has stimulated innovative research for the development of a cell-based renal assist device. A key requirement for such a device is the formation of a "living membrane", consisting of a tight kidney cell monolayer with preserved functional organic ion transporters on a suitable dialysis membrane surface. In this work, we have grown conditionally immortalized proximal tubule epithelial cells (ciPTEC) on polyethersulfone (PES) dialysis membranes by making use of an optimized coating. PES membranes were double coated with combinations of dopamine polymers and human collagen IV. The optimal coating time and concentrations were determined to preserve retention of vital blood components while still facilitating high water transport and optimal ciPTEC adhesion. Tight ciPTEC layers formed when using the optimized combined coating. Furthermore, active transport of (14)C-creatinine through the developed membrane, indicated the presence of functional renal transmembrane transport processes. In conclusion, this study shows the first successful development of a living, cation transporting, ciPTEC based, membrane. These findings are important step in the development of a bioartificial kidney devices.

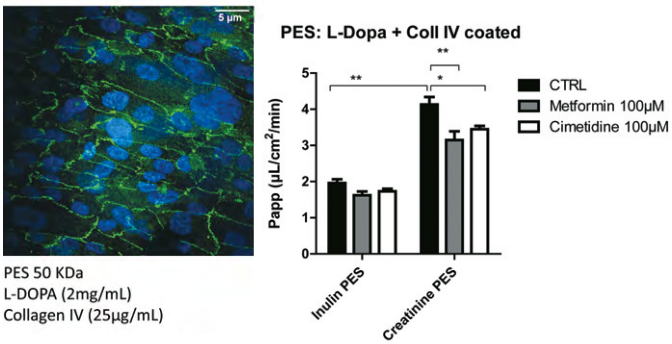


Figure: Left: example of a ciPTEC cell layer cultured on double coated PES dialysis membranes. Cell-cell connections are shown in green, and nuclei are shown in blue. Right: active transmembrane transport of ^{14}C labeled creatinine over the ciPTEC cell layer exceeds the leakage of the ^{3}H labeled inulin (leakage marker). Furthermore, the inhibitors metformine en cimetidine significantly reduce creatinine transport, indicating involvement of active processes.


Theme: Vascular damage

Hedi Claahsen-van der Grinten
Karijn Pijnenburg-Kleizen

Endocrinol. 156: 3504-10, 2015.

Adrenal steroid metabolites in congenital adrenal hyperplasia

In congenital adrenal hyperplasia (CAH), a rare congenital disorder of the adrenal cortex, one of the enzymes involved in adrenal steroid synthesis is deficient, usually 21-hydroxylase. This results in impaired production of cortisol and aldosterone, while the synthesis of adrenal androgens is increased (Figure 1). We observed that patients are clinically often less severely affected by cortisol deficiency, than anticipated from their enzymatic defect. In our study we show that the adrenal steroid hormone precursors that accumulate in untreated CAH patients can bind to, translocate and transactivate the human glucocorticoid receptor *in vitro* (Figure 2). 21-deoxycortisol, a compound specifically produced in CAH, shows the highest glucocorticoid activity. 17-hydroxyprogesterone and progesterone have glucocorticoid properties as well when present in higher concentrations. These steroid precursors, mainly 21-deoxycortisol, may therefore partially compensate the cortisol deficiency in untreated CAH patients. Our results lead to new insights in the understanding of the molecular mechanisms of CAH. Further studies will mainly focus on the clinical relevance and consequences of our findings.

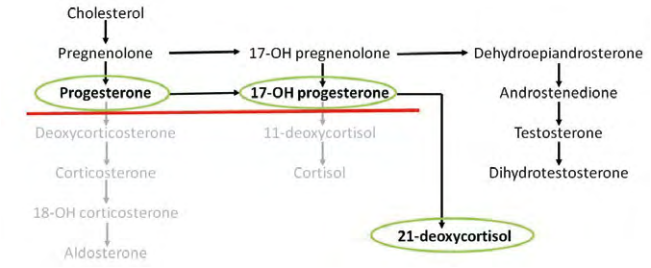


Figure 1: Steroid hormone synthesis in the adrenal cortex in CAH patients. The red line represents the enzymatic block due to the deficiency of 21-hydroxylase.

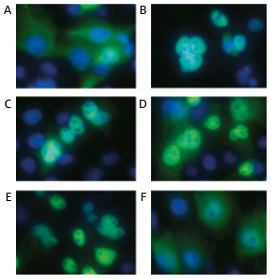


Figure 2: Localization of the human glucocorticoid receptor (hGR) in COS-7 cells transfected with the hGR, without steroids (A) and after incubation with various steroids in a concentration of 10^{-6} M (B-F). The nucleus is stained blue, the hGR is tagged with a green fluorescent protein. B cortisol, C 17-hydroxyprogesterone, D progesterone, E 21-deoxycortisol, F androstenedione.

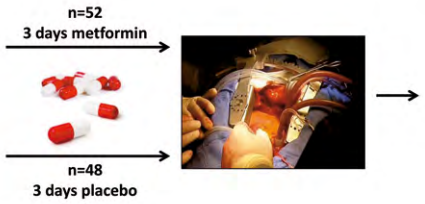

Theme: Vascular damage

Saloua El Messaoudi
Niels Riksen

Lancet Diabetes Endocrinol. 3(8):615-23, 2015.

Metformin does not protect the heart in patients undergoing cardiac surgery

During coronary artery bypass graft (CABG) surgery, blood supply to the heart is temporarily interrupted. This period of ischaemia and subsequent reperfusion can damage myocardial tissue, and an increased postoperative plasma troponin concentration, a biomarker for myocardial damage, is associated with worse outcome. Various animal studies have consistently reported that the blood glucose-lowering drug metformin reduces myocardial infarct size by limiting ischemia-reperfusion injury. We now investigated for the first time in humans whether metformin can limit cardiac injury by performing a double-blinded randomized controlled trial in patients without diabetes scheduled for CABG. Patients were pretreated with metformin or placebo for three days before surgery. Myocardial damage was measured with the postoperative plasma troponin concentration. Although metformin did activate pivotal prosurvival proteins in myocardial tissue, including AMPK and Akt, this did not translate into a reduced postoperative troponin concentration. Short-term metformin pretreatment, therefore does not seem to be an effective strategy to reduce periprocedural myocardial injury in patients without diabetes undergoing CABG surgery.



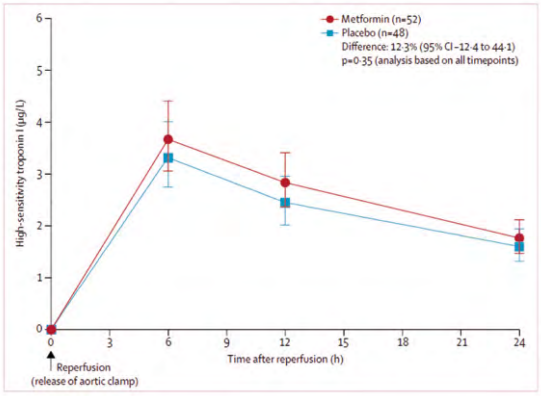


Figure: Schematic overview of the experimental design and primary endpoint of the study.

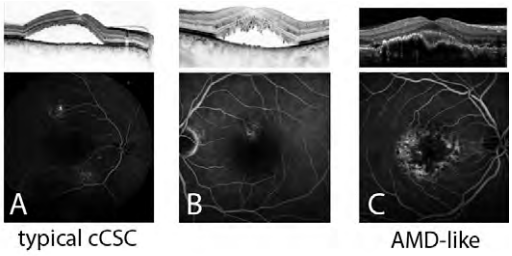
Theme: Sensory disorders

Eiko de Jong
Anneke den Hollander

Ophthalmology. 122:562-70, 2015.

Chronic central serous chorioretinopathy is associated with genetic variants implicated in age-related macular degeneration

Patients with chronic central serous chorioretinopathy (cCSC) suffer from blurred vision. This is a consequence of a fluid bubble generated from the vascular layer underneath the retina, distorting vision. The etiology of the disease is unknown. Historically, cCSC was often diagnosed as a subtype of age-related macular degeneration (AMD). The genetic architecture of AMD is well known and because of the apparent clinical overlap, we investigated whether AMD-associated genes also associate to cCSC. We discovered that cCSC is distinct from AMD and identified three phenotype groups ranging from typical cCSC to atypical cCSC which overlaps with AMD. Importantly, variants in the genes *ARMS2* and *CFH* that associate to AMD inversely associate to cCSC. Thus, risk variants for AMD offer protection against cCSC and *vice versa*. These results may impact patient care in the future as therapies for cCSC and AMD are different; a phenotype-genotype assessment of the patient will better determine appropriate treatment for each patient. Our future work aims to further uncover the molecular genetic background of cCSC to better understand the disease mechanism.



Gene Variant	frequency in A	frequency in B	frequency in C
ARMS2 (rs10490924)	17%	26%	31%
CFH (rs800292)	31%	26%	15%

Figure: We identified three distinct groups of cCSC ranging from typical (A), intermediate (B) to AMD-like (C). Top panels in each figure demonstrate fluid accumulation underneath the retina. Bottom panels represent visible abnormalities such as fluid leakage (A and B) to lesions (C) on retinal imaging of the back of the eye. Carrier frequencies of genetic variants rs10490924 and rs800292 are significantly different compared to controls, but are also significantly different between the three distinct subgroups (Table underneath figure).

Theme: Sensory disorders

Celia Zazo Seco
Hannie Kremer

Am J Hum Genet, 97:647-60, 2015.

Genetic cause of unilateral and asymmetric hearing impairment

Familial unilateral or asymmetric hearing impairment without other symptoms is rare. We identified a large Dutch family with this type of hearing impairment inherited in a dominant pattern. Sequencing of all known genes (whole exome sequencing) identified a truncating defect in the *KITLG* gene which encodes the KIT-ligand. In embryonic development KITLG-KIT signaling is essential for melanocyte migration and differentiation. In the inner ear, melanocytes contribute to establishing the endocochlear potential and thus to the transformation of sound waves into auditory nerve firing. In a second family with a missense mutation in the *KITLG* gene, leading to the substitution of a single amino acid in the KITLG protein, unilateral hearing impairment was accompanied by pigmentation abnormalities in the skin and iris of the eye (Figure 1) which are likely to be due to partial absence of melanocytes at these sites. We hypothesize that the missense mutation in this family affects the normal KITLG protein encoded by the second *KITLG* gene copy which was found to be unlikely for the truncating mutation in the hearing loss-only family.

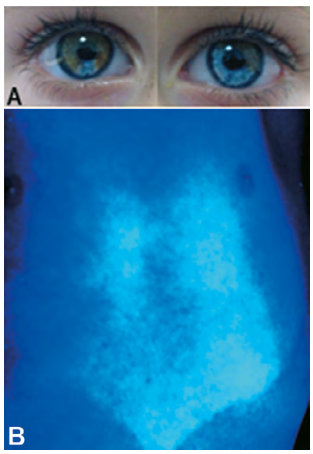


Figure: Pigmentation abnormalities of the eyes (A) and skin (B) of a patient with a missense mutation in *KITLG*.

Researchers at the Radboud Institute for Molecular Life Sciences (RIMLS) seek to achieve greater insights into the molecular basis of disease. This is realized by integrating molecular and medical research to obtain multifaceted knowledge of normal and pathological processes. Findings are translated into clinical applications, into the development of diagnostics, and into the treatment of patients as part of personalized healthcare.

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