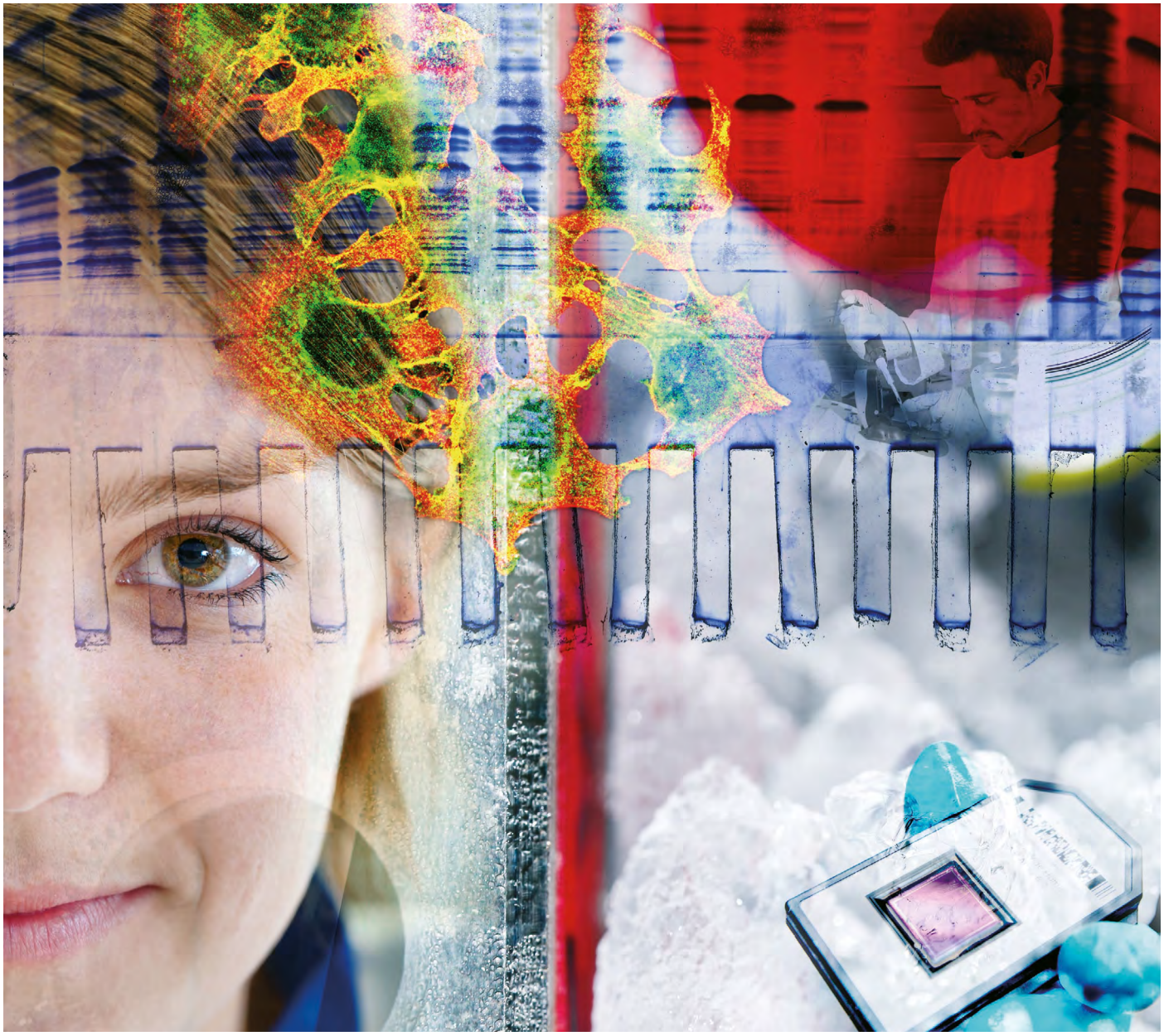
Radboud Institute for Molecular Life Sciences



Annual Report 2014

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: René Bindels, Judith Burgers, 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

Our first year with a new name…Radboud Institute for Molecular Life Sciences. To many, perhaps, a new name that is just as unpronounceable as the old one. So why change? Our new name stands for unity with the rest of Radboud, specifically for integration with the academic hospital and the University. Radboud proud, as some may say. Our mission remains largely the same. Curiosity-driven research and translational research from molecule-to-man, and vice versa, remains at our core. It's been a hectic year of defining and implementing the new Radboudumc research themes, and in this respect it's a great pleasure to present the successes of our scientists, in this new structure.

The highlight for RIMLS was two groundbreaking publications in Science by Henk Stunnenberg (Cancer development and immune defence) and Mihai Netea (Infectious diseases and host response), who published seminal contributions to our understanding of (1) epigenetics and (2) energy metabolism in host defence and immunity. Both papers received wide media coverage due to their importance for medical science. Other top publications are highlighted in the following pages of our annual report. Furthermore, numerous researchers have successfully obtained European multi-partner subsidies either as coordinator or participant. The impressive success rate is thanks to the ambition of our researchers, as well as the personal coaches that dedicated their time and energy into improving applications and interview techniques. Our excellence was further illustrated by esteemed awards including royal accolades, KNAW and Academia Europaea memberships and various advisory board positions.

In 2015, with the foundations laid for RIMLS, we look forward to moving our attention to developing improved policies for our talented researchers. Training the new generation of researchers is one of our core tasks, and one that we do with pride. From Masters and PhD to postdoc and senior group leaders, the pressures to perform are only increasing. We hope, in discussion with the relevant partners, to be able to support our researchers even more, especially in these time when focus on excellence and performance criteria, seems to be at its highest. Perhaps a serious note for a foreword, but nonetheless, an important one.

For now, a look back to a successful 2014.

Dr. Adrian Cohen
Scientific Manager

Prof. René Bindels
Scientific Director

Dr. 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 a multifaceted knowledge of normal and pathological processes. Findings are translated into clinical applications, into the development of diagnostics and into the treatment of patients within the general concept of Personalized Healthcare.

Themes

RIMLS is a leading research institute within the domain of molecular mechanisms of disease accommodating research groups from the Radboud university medical center (Radboudumc) and the Faculty of Science (FNWI) of the Radboud University (RU). As such, clinical and fundamental scientists from diverse areas of life sciences are in close interaction 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 mainly into clinically-orientated research themes from molecule-to-man (M-2-M). The RIMLS international Graduate School integrates a dedicated 2-year research honours MSc degree in Molecular Mechanisms of Disease (MMD) and a follow-up 4-year PhD program, thereby creating a challenging yet enriching learning environment where researchers of all levels are exposed to societal-relevant multidisciplinary research questions along our central theme of understanding the molecular basis of disease.

Cancer development and immune defence

The primary goal is to gain insight into the molecular, genetic and epigenetic processes that lead to the transformation of normal (stem) cells to malignant cancer cells. The knowledge gained on tumour microenvironment and interactions between the immune system and cancer is translated into the development of specific forms of therapy, targeting the affected molecular pathways, and by using (modified) immune cells targeting the tumour cells.

Disorders of movement

Disorders of movement are common in patients with neurological abnormalities in the central or peripheral nervous system. A deeper understanding of these aberrations will help improve the diagnostic, prognostic and therapeutic strategies in these patients. The emphasis lies on understanding the behavioural characteristics, the underlying pathophysiology, and the associated neuroplasticity.

Infectious diseases and host response

Infections are caused by infectious agents, such as viruses, bacteria, fungi, and parasites. Researchers aim to understand the interaction of the host immune system with pathogens by combining cutting edge research in immunology, microbiology and systems biology, with translational and implementation research. The ultimate goal is to identify personalized approaches in the diagnosis and treatment of patients with infections.

Inflammatory diseases

In the Western world, chronic inflammation is among the leading causes of morbidity and mortality. Core to the theme is understanding and controlling inflammatory disease for the benefit of each individual patient through (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) identification of druggable targets and biomarkers; (iv) developing clinical grading tools; and (v) performing pharmacogenetic and epidemiological studies.

Mitochondrial diseases

The mission of this theme is to understand the cellular bioenergetics in health and disease at all levels of complexity. The knowledge gained will enable us to develop preventive measures and make substantial contributions towards the development of rational treatment strategies for mitochondrial diseases.

Nanomedicine

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

Research

Rare cancers
Despite the rarity of each of the 186 rare cancers, they represent in total about 22% of all cancer cases. Examples include head and neck cancer, sarcoma, thyroid cancer, neuroendocrine cancer, brain tumours, lymphoma, and paediatric cancer. The mission is to improve diagnosis and prognosis for this patient group in an (inter)national collaborative setting.

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

Renal disorders
The present and future care of patients with renal and renal-related disorders can be highly improved. To achieve this the theme aims (i) to increase knowledge on the molecular and immunological basis of rare glomerular and tubular disorders; (ii) to develop biomarkers for optimal prediction of prognosis; and (iii) to apply strategies for the prevention and improvement of renal replacement therapy.

Sensory disorders
Research aims to improve our understanding 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 into the clinic e.g. gene therapy and retinal implants.

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 (i) the development of diagnostic tools for staging and therapy response; (ii) innovation in surgical techniques and immunotherapy. Increasing knowledge of the aetiology, epidemiology and genetics of these tumours will improve cancer therapy in high-risk patients.

Urological cancers
Research aims 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. Additionally, it is aimed to evaluate new and existing prevention and treatment modalities in these types of cancer. Synergistic multidisciplinary research collaboration, from molecular life sciences to population sciences, is the tool to keep the theme's focus on 'utility' for the patient and/or public health.

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. Researchers in this theme probe the causes and consequences of vascular injury and translate this knowledge into improved personalized cardiovascular healthcare.

Women's cancers
Central to the theme is improving patient centred quality of care in women's cancers (breast, ovarium, cervix, vulva, endometrium and pregnancy-related) in partnership with patients involved by means of prevention, early diagnosis or implementation of new management strategies supported by a better understanding of carcinogenesis and tumour development, with special attention for hereditary causes, preservation of fertility and post treatment individualised care.

Research

Collaboration

This multidisciplinary nature of RIMLS ensures not only high-quality research within the molecular life sciences, but also ensures excellent education at BSc, MSc and PhD level. Building options for inter-institutional collaboration e.g. visiting professorships/lecturers, exchange possibilities for Masters and PhD students, technology workshops, is a key ambition for the years ahead and contacts in this regard are welcome. The aim is to complete 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 Dutch UMCs and universities as well as with Dutch public- private partnerships. Within Europe, there is increasing cooperation with the University of Duisberg-Essen, specifically the Graduate School of Biomedical Science (BIOME). A recently awarded EU COST grant will serve as a forum for building partner relationships with other participants from universities in Münster, Glasgow, Poland and beyond. As part of the Glasgow-Radboud Memorandum of Understanding, there have been several exchanges (visiting lectureships) between RIMLS and the Institute of Molecular, Cell and Systems Biology, University of Glasgow, Scotland. These exchanges will be further developed as an integral part of the Masters and PhD programmes. In 2014, a double PhD retreat exchange was organized with the Institute for Research in Biomedicine (IRB), Barcelona, in which first students from IRB attended the Nijmegen PhD retreat, and then *vice versa*. This successful formula, built on experiences in 2013, will be extended in 2015.

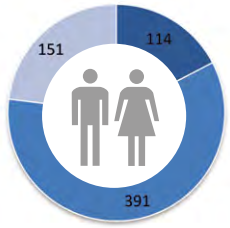
Societal impact

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 the University. The importance of molecular life sciences-related research in society is emphasised in education and research at RIMLS. In 2014, the RIMLS Research Master MMD was chosen as the best MSc programme in the life sciences in the Netherlands, according to the 2014 Dutch Master's programme information guide, illustrating a strong commitment to excellent education. Anneke den Hollander and Carel Hoyng (Sensory disorders) were awarded the Radboud Science Award 2014 by the University's Science Node (Wetenschapsknooppunt) to allow them to translate their research on teaching materials suitable for primary school pupils. Other examples of media appearances in 2014 included: a new gene discovered in blood formation (Bert van der Reijden, Cancer development and immune defence), the safety and efficacy of a new malaria drug combination (Teun Bousema, Poverty-related diseases) and a new vaccine for bowel cancer (Jolanda de Vries and Nicoline Hoogerbrugge, Cancer development and immune defence). John Jansen (Reconstructive and regenerative medicine) and Jelle Barentsz (Urological cancers) were honoured with the Knight of the Order of the Dutch Lion in light of their services to medical research. John Jansen also received the Isaac Schour Memorial Award for his valuable contributions to tissue engineering, tissue regeneration, stem cell and biomaterials research. Together with Han van Krieken (Cancer development and immune defence) they were both elected as members of the Academia Europaea. Han van Krieken was recently ranked by Lab Times magazine is among the top 30 European pathologists. Joost Drenth (Renal disorders) was elected as a member of the Governing Council of the World Gastroenterology Organisation (WGO) as chairman of the National Society Committee of the United European Gastroenterology Federation (UEG).

Facts & Figures

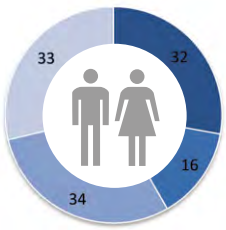
www.RIMLS.nl
410,000 page-views
60,000 unique visitors
2 min average visit

Staff (FTE) per appointment



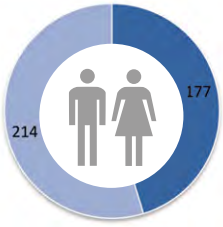
■ Tenured ■ Non-tenured ■ Support

Tenured Staff (FTE)



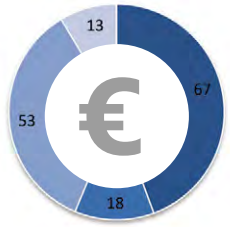
■ Professors ■ Associate Professors
■ Assistant Professors ■ Researchers

Non-Tenured Staff (FTE)



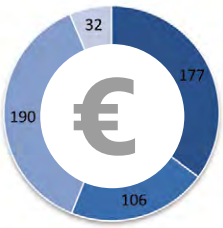
■ Researchers ■ Doctoral Candidates

Non-Scientific Staff Funding (FTE)



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

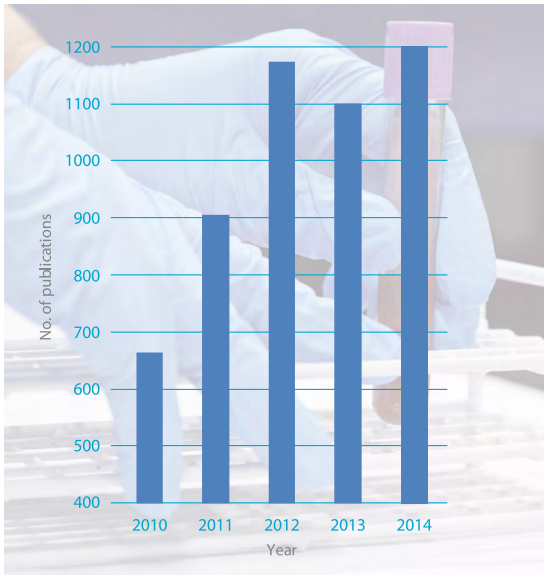
Scientific Staff Funding (FTE)



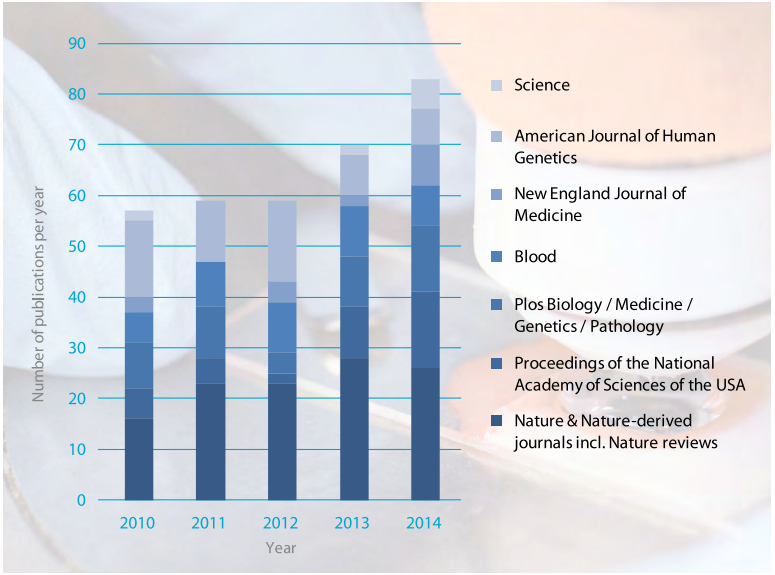
■ 1st Funding Stream ■ 2nd Funding Stream
■ 3rd Funding Stream ■ 4th Funding Stream

Number of graduations

Total RIMLS publications 2010-2014



Number of publications in selected top-international journals



RIMLS & Selected Awards

RIMLS Awards & grants

Best scientific report: Bart van Beusekom (Nanomedicine), Re-refinement in protein structure validation.
Best thesis: Ellen van den Bogaard (Inflammatory diseases), From skin development to disease pathogenesis and therapeutics - The power of 3D skin models.
Breakthrough paper of the year: Mihai Netea (Infectious diseases and host response), mTOR- and HIF-1α-mediated aerobic glycolysis as metabolic basis for trained immunity. *Science* 345: 1250684, 2014 (see page xx).
Best lecturer (PhD retreat): Jeroen de Baaij (Renal disorders), CNNM2 mutations cause impaired brain development and seizures in patients with hypomagnesemia.
Best poster (PhD retreat): René Raavé (Reconstructive and regenerative medicine), Biodistribution of lyophilisomes after intravenous injection in mice.

Travel grant: Michele Fedecostante (Renal disorders), Tessa van der Geest (Nanomedicine), Lisanne van Oppen (Mitochondrial diseases), Christian Büll (Cancer development and immune defence), Alex Garanto Iglesias (Sensory disorders), Kirsten Kuipers (Infectious diseases and host response), Marije Sloff (Reconstructive and regenerative medicine), Sophieke van der Steen (Women's cancers) and Florian Wimmer (Cancer development and immune defence) went to the IRB-PhD retreat in Barcelona.

Best PhD project proposals:

- Renal disorders: Peter Deen, Age-related macular degeneration Sucs: from understanding to personalized therapy. Joost Drenth, A comprehensive, molecular approach to generate improved patient care for polycystic liver disease. Johan van der Vlag, Deathly kisses: Apoptotic blebs and neutrophil extracellular traps cooperate in the pathogenesis of Systemic Lupus Erythematosus.
- Sensory disorders: Anneke den Hollander, Chronic central serous chorioretinopathy: Piecing it (back) together.
- Cancer development and immune defence: Peter Friedl, Tissue-guided cancer cell invasion: molecular biophysics and implications for therapy.

- Mitochondrial diseases: Martijn Huijnen, From the nucleoid to man and back.
- Reconstructive and regenerative medicine: Sander Leeuwenburgh, Combating bone metastases by delivering bone-seeking, theranostic platinum-based anticancer drugs.
- Tumours of the digestive tract: Iris Nagtegaal, Tumor promotion or inhibition? The effect of gut bacteria on colorectal cancer.
- Nanomedicine: Gert Vriend, A holistic approach to the analysis of genetic variation in patients.
- Disorders of movement: Bé Wieringa, Ribostasis problems in degenerative disease: Understanding myotonic dystrophy pathobiology through analysis of repeat-RNA structure.

New Frontiers symposium poster awards: Mani Diba (Reconstructive and regenerative medicine), Quantitative evaluation of interaction forces between building blocks of colloidal hydrogels. Jitske Jansen (Renal disorders), Functional organic cation transporters in human proximal tubule epithelial cells cultured on hollow fibre membranes. René Raavé (Reconstructive and regenerative medicine), Biodistribution of lyophilisomes after intravenous injection in mice.

RIMLS & Selected Awards

Selected Coordination grants

- An STW 'Perspective' grant of 4.3 M Euros to form the Biomarker Development Center, a public-private partnership to accelerate the validation and development of biomarkers, was awarded to Alain van Gool (Urological cancers) and colleagues.
- Frans Russel and Rick Greupink (Renal disorders) are the successful co-applicants of an NWO/ZonMW consortium grant of 1.6 M Euros. The project will integrate molecular mechanisms and clinical data to support non-animal based hazard and risk assessment for chemicals and drugs, concerning cholestasis, allergic contact dermatitis and liver cancer as endpoints. The consortium builds upon a strong public-private partnership, which is led by TNO, and in addition to RadboudUMC, consists of partners from universities of Groningen and Maastricht, RIVM, Jansen Pharmaceutica NV, and SimCyp Ltd.
- John Jansen, Jeroen van den Beucken and Sander Leeuwenburgh (Reconstructive and regenerative medicine) received $ 700,000 as part of a US Army Medical Research and Material Command consortium aiming to make the transition from a calcium phosphate based bone substitute research material into a medical device for clinical applications.

- Diederik de Bruijn (Tumours of the digestive tract), has been awarded an International Collaborative Grant from the Liddy Shriver Sarcoma Initiative (LSSI). This grant (totaling $ 250,000) was given to an International consortium of four research groups from Vancouver (CA), and New York (USA), focusing on the mechanisms of disease in synovial sarcoma and the identification of novel therapeutic targets.
- Gosse Adema (Cancer development and immune defence) and Mihai Netea (Inflammatory diseases) obtained COST European funding for a new research network aimed at standardising immune regulation biomarkers. The Mye-EUNITER concept stems from an IRUN biomedical initiative which held meetings in Duisburg-Essen (2011), Münster (2012) and Nijmegen (2013).

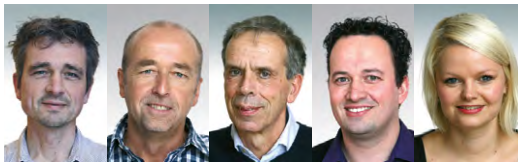
Veni, Vidi & Vici Awards

- Jolanda de Vries (Cancer development & immune defence) has been awarded a NWO Vici grant of 1.5 M Euro for her proposal entitled: Theranostics for the development of successful natural dendritic cell vaccines to combat and prevent cancer.
- Three RIMLS researchers were awarded NWO-Vidi grants, each 800,000 Euro, to develop their own innovative lines of research. Sander Leeuwenburgh (Reconstructive and regenerative medicine): Towards load-bearing bioceramics: smart toughening of calcium phosphate cements. Taco Kooij (Poverty-related disorders): Unravelling the *Plasmodium* mitochondrion: systematic functional characterization of an essential organelle for anti-malarial drug target identification. Jelle Goeman (Cancer development & immune disorders): Making uncertainties in rankings visible.
- Marleen Ansems (Cancer development & immune defence) received a NWO Veni grant of 250,000 Euro for her proposal looking at how certain cells of our immune system can be primed to use them as cancer therapy.

Selected personal grants

- Theo Plantinga (Rare cancers) and Anniek van der Waart (Cancer development and immune defence) each received a Bas Mulder Award 2014 (850,000 Euro) from the Alpe d'HuZes fund of the Dutch Cancer Society (KWF) to perform research on therapy resistance mechanisms in thyroid cancer and on optimized treatment in stem cell transplantation, respectively.
- Harry Dolstra, Jeannette Cany and Michel Schaap (Cancer development & immune disorders), have received a 567,000 Euro KWF Grant for translational Natural Killer (NK) cell research in acute myeloid leukemia. Annemiek van Spriel (same theme) has also been awarded a KWF Grant (566,000 Euro) to unravel the function of CD37, as key plasma membrane organizer in B-cells, in protection against development of B-cell lymphoma.

RIMLS & Selected Awards



- Roland Kuiper (Tumours of the digestive tract), has received a KiKa grant of Euro 566,000 to study therapy resistance and relapse in acute lymphoblastic leukemia (ALL). Together with Frank van Leeuwen and Peter Hoogerbrugge (Cancer development and immune defence), and Alexander Hoischen (Neurodevelopmental disorders), the project will provide novel strategies for the implementation of next generation sequencing technology in future routine diagnostics and relapse prediction.
- Richarda de Voer (Tumours of the digestive tract) has been awarded a KWF-fellowship (357,000 Euro) for fundamental research into genetic predisposition to colorectal cancer.

- Three young researchers within the Renal Disorders theme of the Radboudumc have been awarded with a Kolff start-up post doc grant of the Dutch Kidney Foundation (Nierstichting). The Kolff start-up program aims to support young talented researchers who have just completed their PhD. This prestigious grant allows them to perform a two-year research project within the field of nephrology. The award of three grants to the Radboudumc underlines the strength of the Renal disorders theme in Nijmegen.
  - Jeroen de Baaij (left)- The Magnesium Miracle: Preventing Calcification in Patients with CKD?
  - Rachel van Swelm (middle)- The role of iron in progression of proteinuric tubulointerstitial injury in an experimental model for focal segmental glomerulosclerosis: mechanisms and interventions.
  - Jan van den Brand (right)-Chronic kidney disease causes progressive decline of kidney function.

- Bolomini-Vittori (Mitochondrial diseases) has been awarded a 360.000 Euro grant for a three year project to develop novel RNA-based biosensors for the study of membrane lipid remodeling during leukocyte adhesion and migration.
- Erik Toonen (Mitochondrial diseases) and Leo Joosten (Infectious diseases and host response), together with Trian Chavakis (Dept. of Clinical Pathobiochemistry, Technische Universität Dresden), have been awarded a EKFS research grant (313.000 Euro) to investigate the potential therapeutic interventions with alpha1-antitrypsin fatty liver disease.
- Rob Collin (Sensory disorders) and colleagues from the Donders Institute of Neuroscience (Paul Tiesinga, Richard van Wezel and Francesco Battaglia) have been awarded a 300.000 Euro research grant from the NWO program Light, Cognition, Health and Behavior.
- Rick Wansink (Disorders of movement) and Roland Brock (Nanomedicine), have been awarded 250,000 Euro by the Prinses Beatrix Spierfonds. This project will be directed at the targeted delivery of antisense oligonucleotides to eliminate toxic molecules in myotonic dystrophy, a fatal neuromuscular disorder.

- Fang Yang (Reconstructive and regenerative medicine) has received 108.000 Euro funding from the Foundation NutsOhra to perform a 4-year research project related to the prevention of infection around skin penetrating limb prostheses. The research will be performed in collaboration with Dr. Henk van de Meent (Disorders of movement), Dr. Jan Paul Frölke (Reconstructive and regenerative medicine) and Prof. Pieter Buma (Reconstructive and regenerative medicine).
- William Leenders and Bastiaan Tops (Nanomedicine) have received a 101,150 Euro grant from Stichting StopHersentumoren to investigate if the efficacy of radiotherapy in glioma can be improved by pretreatment with cell cycle arresting compounds.

- Johan van der Vlag (Renal disorders) and Roland Brock (Nanomedicine) received a 100,000 Euro innovation grant from the Dutch Kidney Foundation. The project will investigate the targeted delivery of antisense oligonucleotides to treat inflamed glomerular endothelium.
- Margit Schraders (Sensory disorders) has received an international project grant (£110.000 for 2 years) from the Action on Hearing Loss foundation. The title of the project is "Deciphering the role of the known deafness genes in the aetiology of age-related hearing impairment".
- Jeroen JJP van den Beucken (Reconstructive and regenerative medicine), has received 100,000 Euro from the ZonMW program Translational Adult Stem Cell (TAS) Research, subprogram International Breakthrough projects, for pre-clinical research on intra-operative mesenchymal stem cell-monocyte constructs for bone regeneration.

RIMLS & Selected Awards

Selected Awards & Honours 2014

- To acknowledge their efforts for medical research, His Majesty honored John Jansen (Reconstructive and regenerative medicine) and Jelle Barentsz (Urological cancers) with the highly prestigious Knight of the Order of the Dutch Lion.
- Anneke den Hollander en Carel Hoyng (Sensory disorders), received the Radboud Science Award 2014. The award has been created by "het Wetenschapsknooppunt" Radboud University to allow researchers to translate their research into learning and teaching materials suitable for primary school pupils.
- The Royal Netherlands Academy for Arts and Sciences (KNAW) has elected new members, including John Jansen (Reconstructive and regenerative medicine) and Han van Krieken (Cancer development and immune defence).
- John Jansen (Reconstructive and regenerative medicine) received the Isaac Schour Memorial Award (International Association for Dental Research, IADR) for his significant and valuable contributions to tissue engineering, tissue regeneration, stem cell and biomaterials research.
- Han van Krieken (Cancer development and immune defence) has been invited to become an Honorary Fellow of the Royal College of Pathologists in recognition of his great efforts for the field of pathology. This is the highest possible award granted by the College.

- Joost Drenth (Renal disorders) has been elected as member of the Governing Council of the World Gastroenterology Organisation (WGO).
- Anneke den Hollander (Sensory disorders) received the 2015 Cogan Award from the Association for Research in Vision and Ophthalmology (ARVO), the largest vision research organization in the world with more than 12,000 international members.
- The Dutch Foundation for Post-Graduation Medical Courses in Indonesia has appointed Frans Cremers (Sensory disorders) as a visiting professor at the Faculty of Medicine Universitas Indonesia in Jakarta.
- Anna Simon (Inflammatory diseases) and Huib Croes (Nanomedicine) received the "Radboud Pluim" for their dedicated service to the Radboudumc.

- The NC3Rs, a UK-based scientific organisation dedicated to replacing, refining and reducing the use of animals in research and testing, awarded Martijn Wilmer, Roos Masereeuw and Tom Nieskens (Renal disorders) with the CRACK IT Challenge award for their NephroTube idea, a microfluidic device to screen for drug-induced nephrotoxicity.
- Monique van der Voet (Cancer development and immune defence) was selected as a promising young researcher for the Lindau Nobel Laureate Meeting, where Nobel laureates in medicine / physiology will network with young scientists during a week-long program.

- The Radboudumc team, consisting of Rutger Maas and Markus Loeven (Renal disorders), Joris Nas (Vascular damage), Rik Hansen (Vascular damage) and Jitske Jansen (Renal disorders), won the 'Battle of the Universities' in Eindhoven. Their presentation on improvement of vascular access for dialysis was considered the best solution.
- The Research Master Molecular Mechanisms of Disease (MMD, Director Roland Brock) of the Radboud University Medical Centre is the best Master's programme in the life sciences in the Netherlands according to the Dutch Master's programme information guide "Keuzegids Masters 2014". It is the second time in three years that MMD is ranked in the top and the first time that MMD is distinguished as a "Top Master". MMD is part of the graduate school of the Radboud Institute of Molecular Life Sciences (RIMLS).

Appointments

- Michiel Vermeulen (Cancer development and immune defence) has been appointed as Professor of proteomics and chromatin biology.
- Niels Riksen (Vascular damage) has been appointed Professor of Vascular Medicine.
- Anneke den Hollander (Sensory disorders) has been appointed Professor of Molecular Ophthalmology.
- Leo Joosten (Infectious diseases and host response) has been appointed Professor of Mechanisms of infectious diseases.

New Frontiers Symposium in Regenerative Medicine

Most people probably remember the infamous image of a mouse with an ear on its back. Prompting quite some debate in the 1990's, the Vacanti mouse, demonstrated the latest possibilities of tissue engineering. In this case cartilage. More than 15 years on state-of-the art tissue engineering and regenerative medicine is starting to look less science-fiction and more thought provoking. From potentially solving the problem of organ donation to wound healing, the implications in personalised healthcare and healthy aging are far reaching. Can we really construct working artificial organs? What are the ethical boundaries and considerations? In a symposium with the world's top researchers, New Frontiers in Regenerative Medicine looked at the latest research findings. A glimpse into the future.

Regenerative medicine takes full advantage of molecular life science developments in stem cell and molecular biology, epigenetics, genomics and proteomics and biomaterials and bioengineering, while seizing new opportunities as they emerge from advances in molecular diagnostics, imaging guided therapies for the minimally invasive treatments and novel drugs. True to New Frontiers, a top line-up of speakers provided high-quality presentations on current achievements and challenges ahead.

In front of an audience of more than 350 scientists - nearly half from outside Nijmegen, Prof. Paul Smits, Dean / vice-chairman Radboud University Medical Center, opened the symposium. The first speaker, Prof. Bob Langer, needed little introduction. By many regarded as the founding father of regenerative medicine with a CV that may sound a little like science fiction! With more than 1100 articles, 90,000 citations and 700 patents to his name, as well as being the only person to be elected to all four U.S. national academies, it was an incredible honour to host him in Nijmegen. Perhaps more a lesson in how to generate patents than hard-core science, the message was clear. Use your first publication draft as a basis for your patent application. Prof. Langer spoke about his many successes in launching new products from tumor-zapping nanoparticles to biosensors and blood tests, synthetic spinal cords, even anti-frizz hair products. Other topics included emerging biomaterial, supramolecular self-assembly, hydrogels, cell sheet engineering, epigenetics and ethics. The symposium was drawn to a close with an inspiring keynote lecture by Christine Mummery (Leiden University Medical Centre, Leiden) on utilizing derivatives of human pluripotent stem cells to model and understand the onset of many human diseases. The symposium was a huge success and paves the way for the next 'Radboud Frontiers' symposium on cilia in health and disease.

Bloemendal Medal 2014

The Hans Bloemendal Medal for 2014 is awarded to Professor Christine Mummery, in recognition of her groundbreaking studies in stem cell engineering and development. Christine Mummery studied Physics and has a PhD in Biophysics from the University of London. She received a postdoctoral fellowship from the Royal Society (UK) for research at the Hubrecht Institute where she became group leader and, in 2002, Professor of Developmental Biology. Her research focussed on development and differentiation of mouse and human embryonic stem cells (hES), in particular the role of growth factor signalling in directed differentiation. She has pioneered studies characterizing cardiomyocytes from hES cells and was among the first to inject them into mouse heart and assess their effect on myocardial infarction. Currently, her lab uses stem cell derived cardiomyocytes and vascular cells as disease models for drug discovery and cardiac repair.
She serves on the Medical and Ethical Councils of the Netherlands Ministry of Health (CCMO), providing specialized advice on human embryos and stem cell clinical trials. She is an elected member of the Royal Netherlands Academy of Arts and Sciences (KNAW, 2010), editor and editorial board member of journals that include Stem Cell Research, Cell Stem Cell, Stem Cells, elected board member of International Society for Stem Cell Research (ISSCR), and president of the International Society of Differentiation. In addition, she is on the boards of the Royal Netherlands Academy of Arts and Sciences (KNAW), Dutch Medical Research Council (ZonMW) and Netherlands Heart Institute (ICIN). She has written a popular book on stem cells “Stem Cells: scientific facts and fiction” (2011) intended as a semi-lay guide to stem cell biology and applications. Christine Mummery is a passionate and devoted researcher with over 300 publications and 12,000 citations.

Scientific Activities

PhD Retreat

In 2014, the 20th 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 Hof van Wageningen and was attended by 162 PhD students from RIMLS. Echoing the retreat in 2013, seven students from the Institute for Research in Biomedicine (Barcelona, Spain) were invited to join the retreat, to stimulate collaborations and promote international visibility of RIMLS. Traditionally, the retreat was opened by Bert van der Reijden, chairman of the PhD Program Committee. The program was divided in presentation session and poster sessions. Final-year students and several IRB students presented their data in 15 minutes talks, highlighting the broad background of the PhD students. All other participants had the opportunity to show 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 the traditional pubquiz. The pleasant atmosphere and the social interaction with other PhD-students, made this popular event a winner. Back in Hof van Wageningen, Prof. Ueli Schibler from the University of Geneva provided an interesting keynote lecture on *The daily rhythm of genes*, cells and organs. At the end of the retreat, the best oral presentation and poster presentations were awarded to Jeroen de Baaij and René Raavé, respectively (see page xx). For 2015 we are expecting more participants, due to the reorganisation of the Radboud research institutes, including fundamental, translational and clinical researchers. Therefore, in 2015, a bigger and even better PhD-retreat will be held at Conference Centre Koningshof, in Veldhoven (21st and 22nd May).

The Radboudumc Postdoc Initiative (RPI)

The RPI is an organisation that represents postdocs, research clinicians and final year PhD students. It's a diverse group of researchers with high individualised career choices and career needs. From careers in the clinic, to a career in or outside academia, the expectations of these early stage researchers is high. The RPI is a platform for this group of researchers to 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, three lunch seminars were organized with the topics: *Grant writing*, featuring successful awardees of prestigious national and international grants (Mangala Srinivas, Richarda de Voer and Dennis Vriens); *How to balance career and private life,* featuring a successful professor of the Radboudumc and the 2014 Valkhof Chair (Jolanda de Vries and Anna Moore, Harvard); and *Going abroad*, featuring young group leaders of the Radboudumc (Alessandra Cambi, Klaas Mulder, Jeroen van den Beucken). In addition, the RPI arranged a one-day retreat with the topic *How to communicate Science*. A new event introduced during 2014 is the *Pizza and beer event*, where postdocs from various disciplines can informally interact and socialize.
Since 2014, also newly arrived non-dutch speaking postdocs are offered an introduction day to the Radboudumc. There, the RPI is presented to the new employees, raising awareness of the above-mentioned activities. In addition, the RPI has been represented during major career development events at RU and Radboudumc, such as the *RU get inspired*. With the support of *the Research Board*, RPI actively lobbies issues concerning the postdoc community, with a focus on career development and work environment.

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 top researchers and clinicians. MMD is a unique and challenging programme. MMD meets the needs of talented students with the drive, motivation and ambition to push forward their scientific careers, and provides an excellent preparation for research in top institutions and to build an international research network. The small-scale and interactive nature of the MMD modules offers a challenging educational environment for both, students and lecturers at the crossroads between 'bench' and 'bedside' research activities. Following 2012, the Research Master MMD was again elected as the best Master's programme in the life sciences in the Netherlands according to the Dutch Master's programme information guide "Keuzegids Masters 2014". This time MMD was also distinguished as a "Top Master".

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. About 85% of them enter a PhD programme in Nijmegen or elsewhere in the world. Graduands have found PhD positions in for example Karolinska Institute (Sweden), Stanford University (USA), Institute for Research in Biomedicine Barcelona (Spain) and the RIMLS itself.

Students' comments on MMD:

Mireia Coll Tané: *It was one of those wonderful coincidences in life that brought me here; my group leader from back then in Barcelona suggested me to do my master abroad, and she proposed me to start searching in Nijmegen.*

I started my online search through all the masters offered by the Radboud University and between all, one stood out: the research master Molecular Mechanisms of Disease MSc. Besides from the excellence in the scientific field of the lectures, I was really attracted by the duration of the internships and the courses in scientific skills offered by the programme. I truly believe that those qualities are as important as the research itself, and training them is the only way to be an outstanding scientist in your field. In addition, another distinctive feature is the opportunity to talk and challenge international experts of various fields during the masterclasses; you have the chance not only to discuss with top-scientist about their high-impact papers but also to converse with them about the newest advances and future directions of their field. Moreover, during the first year of the programme we extensively practice grant writing, which becomes really useful already during the master for Ph.D. grants application. Indeed, I think that without the writing training I received, I would not have been able to win the Radboudumc Ph.D. fellowship. The international environment of the master together with the astonishing attitude of the Dutch students to integrate with their international colleagues makes you feel welcome and comfortable during and after the lectures. Furthermore, in order to tighten the relationship between first and second years, this year we started an MMD Introduction, and even had a weekend out together. I am certain that some of the people I met in the programme will be long-term friends. This combination between science and feeling embraced makes studying MMD one of the best decisions I have done in my life, career and personal.

Daniel Wesche: *After graduation from MMD I was admitted to the PhD program in Stem Cell Biology and Regenerative Medicine at Stanford University.*

The skills that MMD helped me develop played a major role in both, my enthusiasm for science and my ability to stand out as a scientist. The wide variety of lectures provided me with an overview of current frontiers in biomedical and translational research, and sparked my interest in the field that I chose to pursue later. In addition, I learned how to collaborate efficiently in small groups of people with vastly different backgrounds, a key skill in a globalized and interdisciplinary research environment. MMD also recognizes the importance of presenting oneself and one's research by developing excellence in communication skills, and trains in writing grants and research proposals.
Most importantly, the curriculum provided a unique opportunity for in-depth exposure to research through the two research internships. With its well-rounded structure, MMD was an invaluable stepping-stone for my career development in bridging the wide gap between a Bachelor-level degree and the high demands of a PhD programme.

Rosa Pascual: *After finishing my degree in Biotechnology at the Universitat Autònoma de Barcelona I was looking for a master programme abroad in order to focus my career on biomedical research;*

MMD master programme was much more than this! Besides being an amazing personal experience, MMD has been a cornerstone to successfully undertake a PhD afterwards. MMD has not only provided me with extensive theoretical and practical knowledge but also enlarged my critical thinking and my communication skills. Intensive training, enriching advice, great scientific atmosphere and motivation were crucial for getting an international and highly competitive grant for my PhD at the Institute for Research in Biomedicine (IRB Barcelona). I am currently working at the laboratory of Dr. Raúl Méndez, where my main interest is the regulation of mRNA processing and translation during stem cell renewal and differentiation.

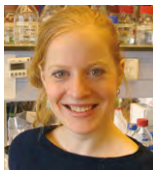
The RIMLS as Graduate School

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 clinical and fundamental researchers for students to explore the length of the molecule-to-man pipeline PhD students are offered an interdisciplinary training programme that can tailored to meet the individual interests of PhD students. In particular students are encourage to develop and refine their research competencies and transferable skills necessary for a successful independent scientific career. Students who complete the research and training requirements within the agreed research period are eligible for a RIMLS PhD Certificate and financial bonus.

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

"I believe that understanding the molecular mechanisms of diseases should not be achieved in an ivory tower, but rather should be done with the aim to impact the daily routine in the clinic". René Marke, Cancer development and immune defence.



"At the end of my PhD-programme, I hope to understand more about the role of glycosaminoglycans in ovarian cancer and its potential clinical applications". Sophieke van der Steen, Women's cancers.

"The focus of my research is to understand the natural disease course in a rare metabolic disease. Understanding mechanisms of disease is incremental for the development of future treatments for these patients". Paul de Laat, Mitochondrial diseases.

"To understand molecular mechanisms of disease. For me this means: 'going back to the basics". Jos Jansen, Renal disorders.

"I really enjoy finding out which mechanisms are at play during the host response against infections and finding out how these mechanisms work". Marloes Vissers, Infectious diseases and host response.

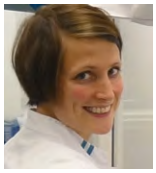
"I think the best way to understand disease is to study it in a molecular-mechanistic way". Duby Ballak, PhD student, Infectious diseases and host response.

The RIMLS as Graduate School

"For me, it took some time to realize that all the advancement in diagnosis and treatment of patients is only made possible by research on both clinical aspects and molecular mechanisms". Rahajeng Tunjungputri, Poverty-related diseases.

"As I have learned over the years, cells are very complex and regulation takes place at many different levels. Small mistakes in these regulatory processes can have large effects and cause disease". Jessie van Buggenum, PhD student, Neuro-developmental disorders.

"Understanding the molecular mechanisms of the immune system and its interaction with the cancer is in my opinion therefore the key to improving anti-cancer killer T cells". Florian Wimmers, Cancer development and immune defence.



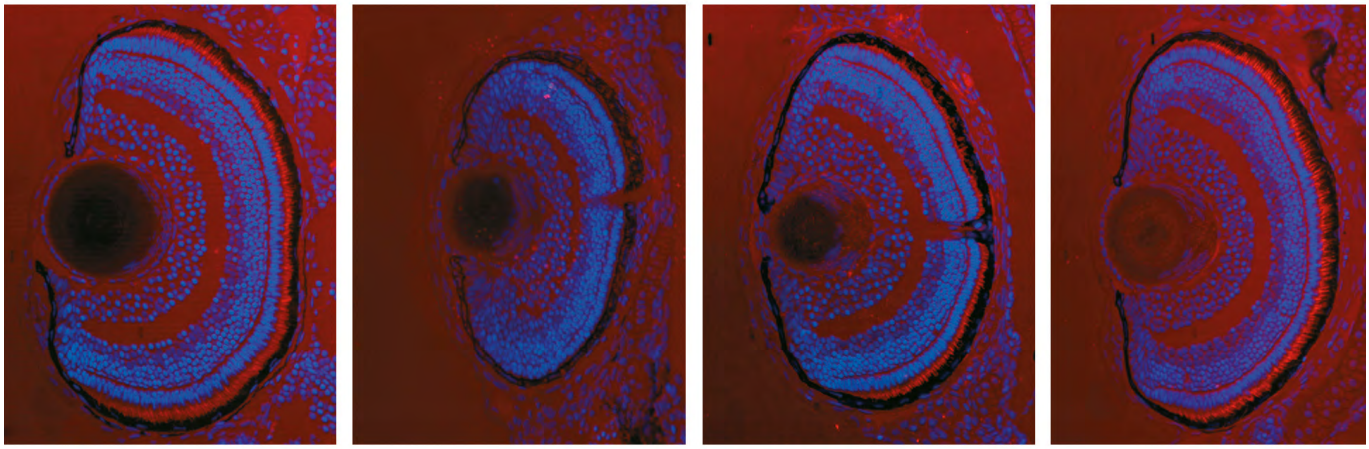
"If we can kill the 'hiding' cancer (stem)cells with natural killer cells, I could 'live happily ever after'". Janneke Hoogstad-Van Evert, Women's cancers.

"I enjoy the search on how to improve our vaccination, puzzling like a detective". Kalijn Bol, PhD student, Cancer development and immune defence.

"With respect to the development of an effective anti-malarial vaccine, I think it is essential to understand which immune responses play an important role in protection and which antigens are targeted by our immune cells". Marije Behet, Poverty-related diseases.

"Molecular mechanisms are involved in all steps during my project; from construction of implants to cellular interactions with the implant, and eventually the outcome of the experiments". Michiel Pot, Reconstructive and regenerative medicine.

"The importance of basic research tends to be neglected at the profit of "applied" or "translational" studies". Sarah Merkling, Infectious diseases and host response.



Selected Research Highlights

RIMLS 2014


Theme: Cancer development and immune defence

Sadia Saeed
Henk Stunnenberg

Science. 345:1251086, 2014.

Immune system and epigenetic programming: step forward to understand host defence and fight against disease

In the classical dichotomy of innate *versus* adaptive immunity, specialized white blood cells called monocytes and macrophages belong to the innate immune response. In individuals with an infection, activation of monocytes and differentiation into macrophages can differ depending on the type of pathogen and infection. During severe infections and sepsis, monocytes and macrophages undergo a period of reduced activity called *'tolerance'*, and in extreme cases immune paralysis. In contrast, during vaccinations e.g. Bacille Calmette-Guerin (BCG) or measles, they react more strongly to pathogens, a process termed '*trained immunity*'. Our study unravels for the first time distinct epigenetic programs executing immune tolerance and trained immunity, and describes novel pathways involved. We documented the importance of epigenetic regulation of immunological pathways underlying monocyte-to-macrophage differentiation and trained immunity providing invaluable resources to further understand and manipulate immune-mediated responses to fight against human diseases. Exploitation of these epigenetic regulators will have impact on potential pharmacological targets that modulate innate immunity.

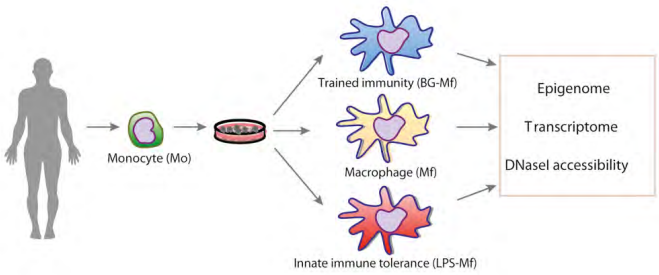


Figure 1: Epigenome, transcriptome and DNase I accessibility profiles characterizing the novel epigenetic signature of purified human circulating monocytes, in vitro differentiated naïve, tolerized (immunosuppression) and trained macrophages (innate immune memory).


Theme: Cancer development and immune defence

Davide Monteferrario
Bert van der Reijden

N Engl J Med. 370:245-53, 2014.

Inherited bleeding syndrome explained by GFI1B mutation

Gray Platelet Syndrome is a hereditary bleeding disorder characterised by reduced numbers of platelets, with a gray appearance caused by a shortage of alpha-granules (Figure 1). We studied a large family with autosomal dominant Gray Platelet Syndrome with unknown genetic cause. We observed that the platelet-producing megakaryocytes had severe dysplastic features, and they were abnormally distributed in the bone marrow. Megakaryocyte numbers were also significantly increased and showed high expression of the marker CD34, which is normally confined to blood stem cells. Genetic linkage analysis and targeted sequencing identified a nonsense mutation in the GFI1B gene to be causal to the disease. GFI1B functions as transcription factor. The GFI1B mutant protein inhibited non-mutant GFI1B transcriptional activity in a dominant-negative manner. Together, these studies show that GFI1B, in addition to being causally related to the Gray Platelet Syndrome, is key to megakaryocyte cell growth and development, alpha-granule synthesis, and platelet formation. These findings open new avenues to identify GFI1B-driven transcriptional programs that will enlarge our understanding of megakaryocyte development and platelet production.

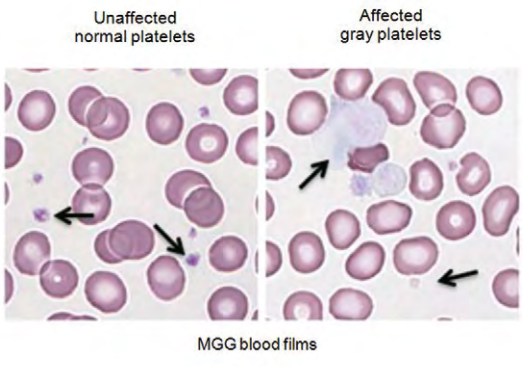


Figure 1: May–Grünwald-Giemsa (MGG) staining in left panel shows normal platelets (arrows) obtained from an unaffected family member. The staining in the right panel shows large gray platelets (arrows) obtained from an affected family member.


Theme: Disorders of movement

Monique van Scherpenzeel
Dirk Lefeber

N Engl J Med. 370:533-42, 2014.

Mechanism-based therapy for PGM1 deficiency, an exercise-induced myopathy

Congenital Disorders of Glycosylation consist of a heterogeneous group of genetic defects with abnormal glycosylation of proteins. Using a combination of mass-spectrometry based glycomics (Figure 1) and exome sequencing, we could identify a novel disease caused by deficient phosphoglucomutase (PGM1) activity. Patients showed a split uvula (Figure 2), exercise-induced muscle pain, rhabdomyolysis, liver disease with low blood sugar levels, heart failure and other symptoms. PGM1 is a key enzyme in energy metabolism, responsible for the conversion of glucose to glycogen and vice versa. In addition, we identified an important role in protein glycosylation by showing a lack of galactose and a loss of complete glycans in PGM1 patients. Studies in patient cells allowed us to partly understand the disease mechanism;addition of galactose restored protein glycosylation without affecting glycogen metabolism. Subsequent treatment of patients revealed normalised glycosylation of blood proteins after 2 weeks of galactose treatment (Figure 2B). Application of our novel high-resolution glycoprofiling method provides a unique glycosylation signature for early diagnosis, guided elucidation of the disease mechanism and allows establishment of a personalised therapeutic intervention.

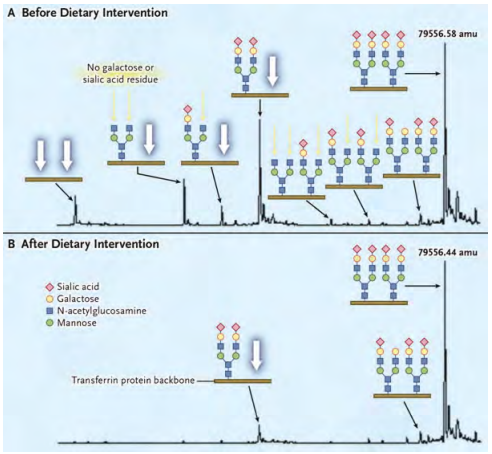


Figure 1: A) Characteristic PGM1 glycan profile; B) Normalization after dietary intervention

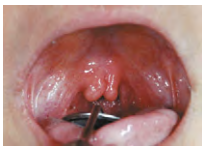


Figure 2: About 80% of patients presents with a cleft palate or bifid uvula (photograph)


Theme: Infectious diseases and host response

Shih-Chin Cheng
Mihai Netea

Science. 345:1250684, 2014.

Sugar energy-bar boosts the innate immune cell function

Trained immunity is the concept describing the memory characteristics of the innate immune system. The epigenetic programming through histone modifications was previously described by our group to be involved in the trained monocytes. Here we took a step further and reported that cellular metabolic rewiring underlines the trained immunity. The biochemical characterizations of the β-glucan trained monocytes revealed elevated aerobic glycolysis with reduced basal respiration rate, increased glucose consumption and lactate production, and higher intracellular NAD+/NADH ratio. The Dectin-1/Akt/mTOR/HIF1α pathway was responsible for the metabolic shift induced by β-glucan. Blocking mTOR/HIF1α pathway by chemical inhibitors inhibited trained immunity. Mice receiving metformin, an AMPK activator that subsequently inhibits mTOR, lost the trained immunity-induced protection against lethal *C. albicans* infection. The shift of central glucose metabolism from oxidative phosphorylation to aerobic glycolysis ('Warburg effect') meets the spiked need for energy and biological building blocks for rapid proliferation during carcinogenesis or clonal expansion in activated lymphocytes. Here we demonstrate that an elevated glycolysis is the metabolic basis for the trained immunity as well, providing the energy and metabolic substrates for the increased activation of trained immune cells. The identification of glycolysis as a fundamental process in trained immunity further highlights a key regulatory role for metabolism in innate host defense, and defines a potential therapeutic target in both infectious and inflammatory diseases.

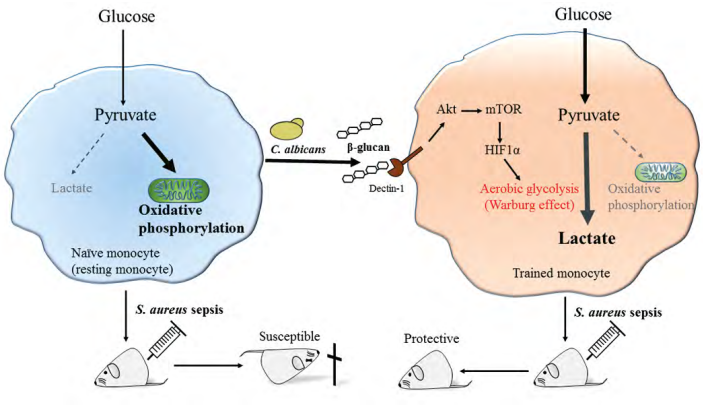


Figure 1: Schematic presentation of how metabolic shift underlined trained immunity.

Theme: Infectious diseases and host response

Sanne Smeekens
Frank van de Veerdonk

Proc Natl Acad Sci U S A. 111:3526-31, 2014.

Interleukin-1 blockade improves CGD colitis

Chronic granulomatous disease (CGD) is caused by a mutation in one of the genes of the NADPH complex, resulting in defective production of reactive oxygen species (ROS). Patients with CGD have an increased susceptibility to infections, like invasive *aspergillosis*. Paradoxically, ROS deficiency in CGD patients also results in a hyperinflammatory state, leading to granuloma formation and severe colitis. Autophagy is an evolutionary conserved process by which cells undergo partial self-digestion in order to secure homeostasis and organismal viability. Here we demonstrate autophagic dysfunction in humans and mice with CGD, resulting in increased interleukin (IL) 1β production. Blocking IL-1β with anakinra (an IL-1 receptor antagonist (Ra)) restores autophagy and results in protection against invasive aspergillosis in CGD mice and in improved clinical features of CGD patients with colitis. These results suggest that anakinra represents a new therapeutic drug that can modulate autophagy in clinically relevant settings and provides a rationale to perform clinical trials to investigate the efficacy of blocking IL-1 in CGD colitis.

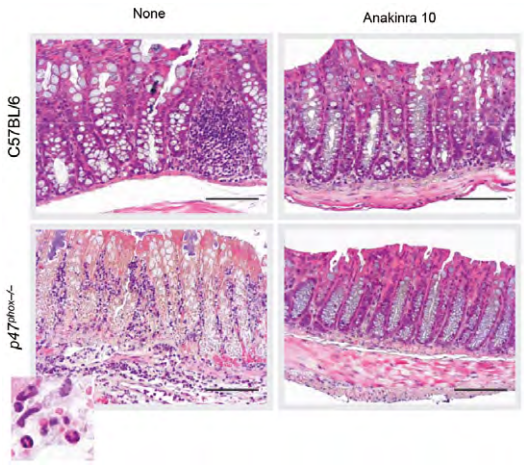


Figure 1: **Blocking IL-1 Is Beneficial in CGD Mice with Colitis**. Colonic sections from control (C57BL/6) or CGD ($p47^{phox-/-}$) mice mice with TNBS-induced colitis, who were treated i.p. with 50% ethanol (control) or anakinra (10 mg/kg) (IL-1 receptor blocker) for 5 days.

Theme: Inflammatory diseases

Lauranne Derikx
Frank Hoentjen

Gastroenterology. 146:119-28.e1, 2014.

Ulcerative colitis, towards endoscopic pouch surveillance guidelines

Ulcerative colitis, a form of inflammatory bowel disease, is a common disease in the Western world characterised by chronic mucosal inflammation of the colon. Approximately 30% of patients require removal of the colon during their life-time disease course. Subsequently, a new reservoir, also known as the ileo-anal pouch, can be constructed in order to avoid a long-term ileostomy (Figure 1).

Patients with ulcerative colitis bear an increased risk to develop colorectal cancer. In order to reduce colorectal cancer risk, endoscopic surveillance guidelines have been developed allowing detection and potential removal of precancerous lesions. Cancer may also arise in the ileo-anal pouch. Data regarding pouch cancer risk are scarce resulting in the absence of endoscopic pouch surveillance guidelines.

In this nationwide case-control study we determined a low cumulative pouch cancer risk of 3.3% after 20 years, which is even lower than the general lifetime colorectal cancer risk. Patients with prior colorectal dysplasia or cancer had an approximate 4- and 25-fold increase in risk, respectively. These findings may aid in developing personalised endoscopic pouch surveillance strategies.

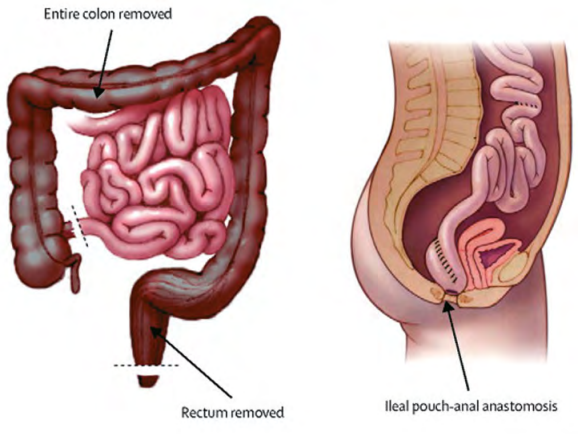


Figure 1: Proctocolectomy with ileoanal pouch formation.

Theme: Inflammatory diseases

Dennis Remst
Peter van der Kraan

Arthritis Rheumatol. 66:647-56, 2014.

Unraveling genes involved in osteoarthritis-related fibrosis

Osteoarthritis (OA) is the most common joint disease, causing joint stiffening and joint pain. Fibrosis of the synovium, one of the hallmarks of OA, is a major contributor to these symptoms.
TGFβ, the main driver of fibrosis induction, is elevated in OA, however blocking TGFβ, is not a therapeutic option. QUOTE We sought new targets downstream of TGFβ to prevent OA-related fibrosis. A comparison of gene expression in TGFβ-stimulated human OA synovial fibroblasts, synovium from mice with experimental OA, and synovium from humans with OA revealed that the genes PLOD2, LOX, COL1A1, COL5A1, and TIMP1 were up-regulated. Most of the up-regulated genes identified in this study would be poor targets for therapy development, due to their crucial functions in the joint. However, the highly up-regulated gene PLOD2, responsible for the formation of collagen crosslinks that make collagen less susceptible to enzymatic degradation, is an attractive and promising target for interference in OA-related fibrosis

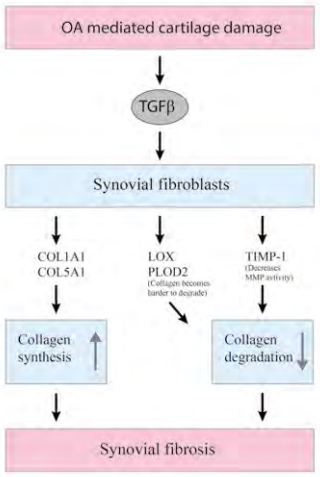


Figure 1: Schematic diagram showing the role of TGF-β in onset and maintenance of osteoarthritis–related fibrosis

Theme: Mitochondrial diseases

Richard Notebaart

Proc Natl Acad Sci U S A. 111:11762-7, 2014.

Underground metabolism drives evolutionary innovation at a network-level

A central unresolved issue in evolutionary biology is how metabolic innovations emerge. Low-level enzymatic side activities are frequent and can potentially be recruited for new biochemical functions. However, the role of such underground reactions in adaptation toward novel environments has remained largely unknown and out of reach of computational predictions, because it demands analyses at the level of the entire metabolic network. Here, we provide a comprehensive computational model of the underground metabolism in *Escherichia coli*. Many underground reactions are fully wired into the existing native network and form novel pathways that produce key precursors for cell growth. Together with a high-throughput experimental survey across hundreds of nutrient environments we predicted and confirmed new functional states of metabolism in which underground reactions allow growth when their activity is increased (Figure 1). Our results demonstrate that the genetic basis of evolutionary adaptations via underground metabolism is computationally predictable. The approach used here has potential for various application areas from bioengineering to medical genetics, such as understanding gain-of-function mutations in tumour development and antibiotic resistance evolution.

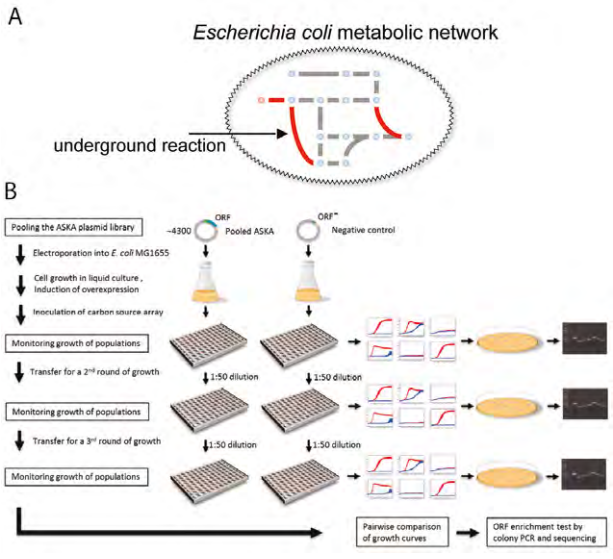


Figure 1: A) *E. coli* metabolic network including 262 underground activities predicts adaptation to novel nutrient environments via underground metabolism, which is B) highly consistent with gene over-expression screens across hundreds of environments.


Theme: Nanomedicine Cancer

Susanne Lütje
Otto Boerman

Cancer Research 74:6216-23, 2014.

A new tool for intra-operative imaging of prostate cancer

Despite advances in diagnostic procedures and clinical management, prostate cancer remains associated with significant morbidity and is the second leading cause of cancer-related deaths in men in the Western world. At present, extensive research is focused on the development of new molecular imaging techniques to improve detection and staging of this disease. In this regard, radiolabeled antibodies that target the prostate cancer–associated cell surface antigens seem to be particularly promising. We have developed a pretargeting strategy, using a bispecific monoclonal antibody and a dual-labeled diHSG peptide, for intra-operative imaging in prostate cancer by using specific tumour-targeted dual-modality probes that contain both a radiotracer and a fluorescent label. Improved intraoperative imaging techniques to help guide the surgeon in the detection of malignant tissue, should improve the outcome, reduce morbidity and treatment-related side effects.

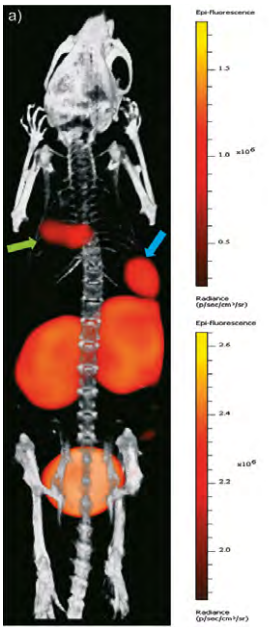
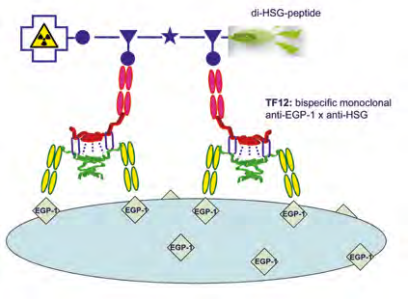


Figure 1: MicroSPECT/CT image of a mouse with two PC3 bone metastases in the ribs that were pretargeted with a bispecific antibody. Images were acquired 2 h after injection of the In-1111-labeled fluorescent peptide. The kidneys, bladder and two tumor manifestations (green and blue arrow) are visualized.

Figure 2:




Theme: Nanomedicine

Ruud Peters
Jan van Hest

Angew Chem Int Ed. 53:146-50, 2014.

Plastic cell with working organelles

The living cell contains smaller organelle subcompartments that are used to spatially organize and separate enzymes and reagents in order for the cell to function properly. To attain a model system to study the benefits of the natural compartmentalization process in more depth, a simple cell mimic was created based on polymer (plastic) building blocks. Several different types of small compartments containing enzymes (organelles) were encapsulated together with other reagents in a cell-sized polymeric vesicle and used to carry out a model enzymatic reaction sequence (Figure 1). Furthermore, by spatially separating incompatible enzymes in one of the organelle compartments, they were now able to work together in a reaction sequence without interfering with other enzymes. Further development of these concepts might lead to a better understanding of the structure and functioning of the living cell.

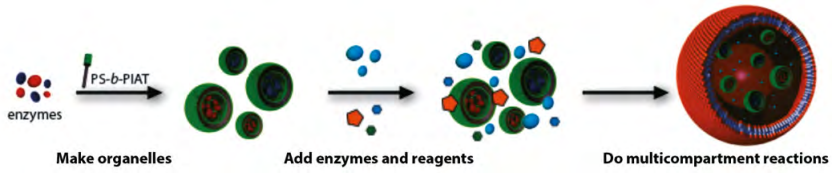


Figure 1: Concept of the plastic cell, where enzymes, reagents and enzyme-filled organelles are mixed together and encapsulated in a larger polymer vesicle to form a cell-like structure capable of spatially separating incompatible components and performing biochemical cascade reactions.

Theme: Poverty-related diseases

Anja Scholzen
Robert Sauerwein

J Infect Dis. 210:1981-90, 2014.

More than quantity alone matters for antibody mediated protection against malaria

Nearly half the world's population is at risk of infection with the malaria parasite *Plasmodium falciparum*. Despite major public health efforts, the mosquito-transmitted disease remains responsible for more than half a million death each year. A vaccine will be a crucial tool to combat this important infectious disease. In a setting of controlled human malaria infections, we have previously shown that healthy volunteers can be fully protected against a malaria challenge infection after serial exposure to bites from parasite-infected mosquitoes. Our aim is to unravel the immune responses responsible for this unprecedented protection against malaria. In the present study, we show that immunized volunteers have both antibodies and a robust memory B-cell response to several well-known parasite antigens. These immune responses are sensitive markers of malaria exposure during immunization. We also demonstrate, however, that more is not always better and the sheer magnitude of this response does not predict protection from challenge infection. To accelerate future malaria vaccine development, we are now further investigating the functionality and novel antigen targets of the induced antibody response.

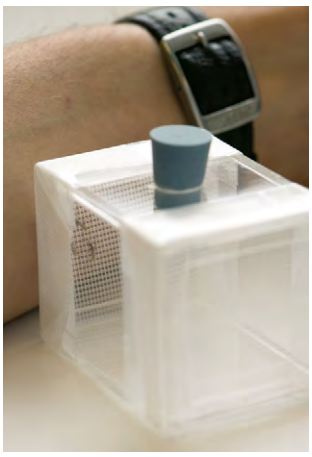


Figure 1: A volunteer is exposed to malaria-infected mosquito bites.

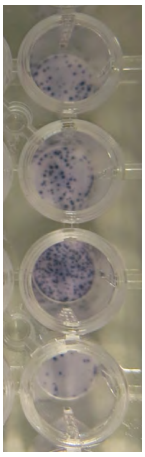


Figure 2: The ELISpot assay visualizes antibody secretion by individual activated memory-B cells.

Theme: Rare Cancers

Winette van der Graaf

Lancet Oncol. 15:415-23, 2014.

Is combination chemotherapy better than single agent chemotherapy in metastatic soft tissue sarcomas?

Soft tissue sarcomas (STS) are a rare and heterogeneous group of malignancies, which metastasize in almost half of the cases. There has been a long debate whether aggressive combination chemotherapy leads to a longer survival than single agent therapy. In a pan-European randomized phase 3 trial lead by the EORTC Soft Tissue and Bone Sarcoma Group combination therapy with doxorubicine and ifosfamide was compared with doxorubicin alone. Results of the study, in which 455 patients were included, show that combination therapy led to a higher response rate (26 versus 14%), which is important when subsequent surgical resection of metastases is considered, but the combination did not result in a significantly different improvement in overall survival (14.3 versus 12.8 months), while the combination induced considerably more toxicity. The results of the study underscore the advise for single agent therapy. Only in case a significant volume reduction of the tumor is required, combination therapy can be advised. The data of this study can be used in the discussion with the STS patient when making a personalized treatment plan.

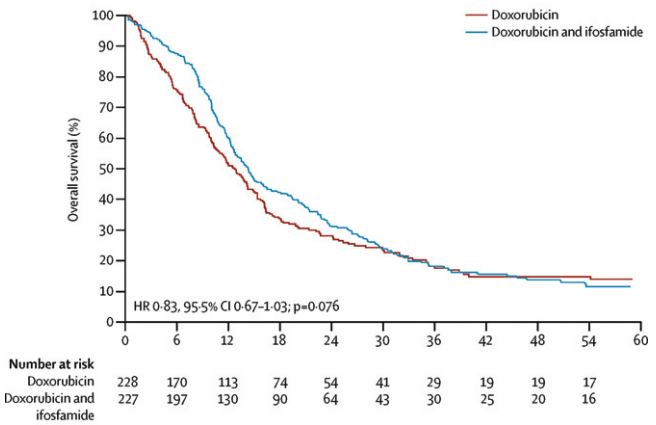


Figure 1: There was no significant difference between groups in terms of overall survival. The median overall survival was 12.8 months in the doxorubicin group versus 14.3 months in the doxorubicin and ifosfamide group.

Theme: Reconstructive and regenerative medicine

Reza Nejadnik
Sander Leeuwenburgh

Biomaterials. 35:6918-29, 2014.

Self-healing and mineral-adhesive nanocomposites for bone regeneration

Non-covalent interactions are often regarded as insufficient to construct macroscopic materials of substantial integrity and cohesion. However, the low binding energy of such reversible interactions can be compensated by increasing their number to work in concert to create remarkably strong materials. Reversible bonds are responsible for the outstanding structural properties of natural nanoscale composites such as nacre and bone. Inspired by nature, we have developed injectable, nanocomposite hydrogels based on reversible bonds between mineral calcium phosphate (CaP) nanoparticles and bisphosphonate-functionalized hyaluronan. These nanocomposites displayed unique properties including a remarkable self-healing capacity and adhesiveness to mineral surfaces such as enamel and hydroxyapatite. Most importantly, these physically cross-linked composites are surprisingly robust yet biodegradable upon extensive in vitro and in vivo testing, and show bone interactive capacity. These results indicate that adaptive, biocompatible biomaterials can be created without the need for covalent - and potential toxic - cross-linking, which will aid in the development of novel biomaterials for bone regeneration.

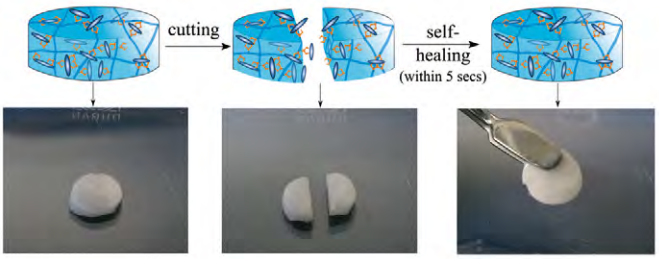


Figure 1: Self-healing behavior of physically cross-linked nanocomposites.

Theme: Renal disorders

Francisco Arjona Madueño
Jeroen de Baaij

PLoS Genet. 3;10:e1004267, 2014.

Magnesium handling in the kidney: a new gene discovered with clinical relevance

Hypomagnesemia is noted in ~15% of hospitalized patients, and the incidence may rise above 60% in intensive care unit patients. Usually, hypomagnesemia results from genetic and drug-induced renal disorders involving a variety of defects in filtration and tubular transport processes. Low plasma Mg^{2+} concentrations can cause a wide variety of features including serious cardiac and neurological manifestations. Early identification of the genetic causes of hypomagnesemia is of significant importance in the diagnosis of the disease, as predictor of the progress of the disease and for the determination of treatment. By combining genetic diagnosis with Mg^{2+} transport assays in cellular and zebrafish loss-of-function models, we identified CNNM2 mutations to be causative for hypomagnesemia due to disturbances in renal transcellular transport of Mg^{2+} (Figure). In addition, our findings demonstrated that dysfunctional CNNM2 results in aberrant brain development and motor-neurological impairments in addition to hypomagnesemia, explaining the complete physiological basis of this disease with this complex symptomatology. The screening of therapeutical options for CNNM2-patients is now entirely feasible using the models established in this study.

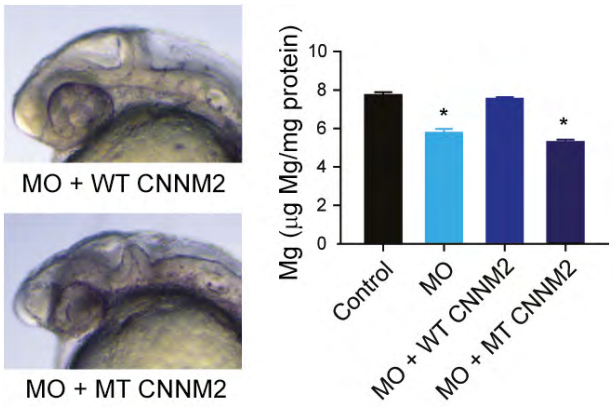


Figure 1: **CNNM2 function in health and disease**. Morpholino-knockdown (MO) in zebrafish of the orthologue Cnnm2a combined with overexpression-rescue experiments with mutant (MT) and wild-type (WT) CNNM2 mRNA, recognised (mutated) CNNM2 as a causal gene for hypomagnesemia of renal origin and aberrant brain development. Asterisks denote significant differences respective control means.


Theme: Renal disorders

Wybrich Cnossen
Joost Drenth

Proc Natl Acad Sci U S A. 111:5343-8, 2014.

Disease gene and pathway identification in polycystic liver disease families

Polycystic liver disease (PLD) is characterized by the presence of multiple benign, fluid-filled cysts spread throughout the liver. Enlarged liver volumes are common and result in massive abdominal distension. Patients have abdominal pain and other mechanical symptoms. Renal cysts without renal failure may be present in PLD and should be distinguished from polycystic kidney disease (ADPKD).
We identified a novel disease gene causing polycystic livers in PLD families. Gene identification directed us to a dysregulated canonical Wnt signaling pathway. Our results provide the first evidence of hepatic cystogenesis associated with this major signal transduction pathway. We aim for investigation of the functional consequences of the defective Wnt signaling in hepatic and renal cystogenesis. The search for more PLD genes continues to reveal the genetic interaction network.

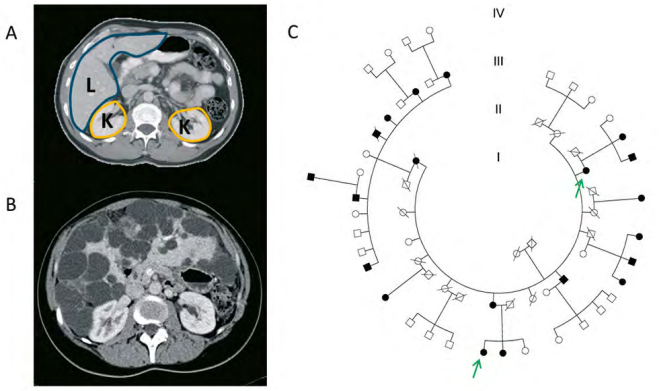


Figure 1: (A) A cross-sectional CT-scan slice of a healthy individual with normal kidneys and liver, and (B) a PLD patient with hepatomegaly. (C) Whole-exome sequencing of 2 affected individuals from an extended PLD family identified a pathogenic LRP5 variant.


Theme: Sensory disorders

Susanne Roosing
Frans Cremers

Am J Hum Genet. 95:131-142, 2014.

Genetic cause of inherited visual impairment discovered

In persons with cone-rod dystrophy, initially the cone photoreceptors of the retina break down which causes problems with seeing colors and details. Later on, the rods also break down, giving rise to severe visual impairment or even blindness. Using high-throughput DNA sequencing in two small families with recessively inherited cone-rod dystrophy, we identified mutations in POC1B gene. POC1B formerly had not been associated with inherited vision impairment. We suppressed the expression of POC1B in zebrafish which showed smaller eyes and absence of photoreceptors. Visual testing revealed that these zebrafish were blind. To provide convincing proof that the rare sequence variants identified in the POC1B gene were causative, protein-protein interaction studies were performed. We identified a protein interactor of POC1B, FAM161A, which previously was also found to be mutated in persons with rod-cone dystrophy. We also showed that the cone-rod dystrophy-associated mutations in POC1B disrupted the binding of POC1B with FAM161A. We hypothesize that the POC1B protein plays an important role in transport processes in rods and cones.

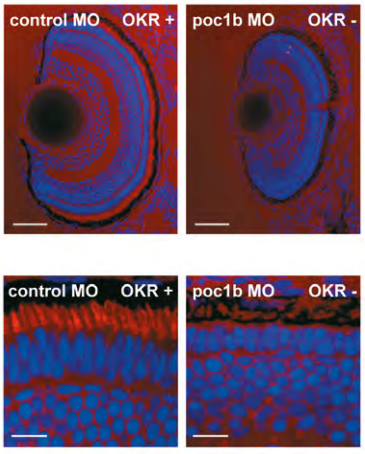


Figure 1: Suppression of POC1B in zebrafish results in small eyes (right upper panel) and absent photoreceptor outer segments (right lower panel). MO, morpholino-oligonucleotide; OKR, optokinetic response. Outer segments are in red; nuclei in blue.


Theme: Tumours of the digestive tract

Arjen Mensenkamp
Marjolijn Ligtenberg

Gastroenterology. 146:643-6.e8, 2014.

Better understanding of tumour genetics reduces the number of colonoscopies in relatives of patients suspected of Lynch syndrome

Lynch syndrome is the most frequent cause of hereditary colorectal cancer (CRC). This autosomal dominant disease is caused by germline mutations affecting the mismatch repair (MMR) genes *MLH1, MSH2, MSH6* and *PMS2*. Mutation carriers have a lifetime risk of up to 80% to develop CRC and other types of cancer. Inactivation of the MMR system results in aberrations in microsatellite repeat sequences known as microsatellite instability (MSI). Detection of MSI and absence of MMR protein staining in the tumor is an important indication for germline mutation analysis. In a subset of patients with these tumors no mutation in the MMR genes can be identified. First degree relatives of these patients are advised to undergo colonoscopy every two years, because they may have an as yet undetectable germline mutation. We identified an alternative explanation for the MSI and absence of MMR protein staining: biallelic acquired mutations in more than half of the tumors without underlying germline mutation (Figure 1). For relatives of patients with such tumors the frequency and starting age of colonoscopies are reduced.

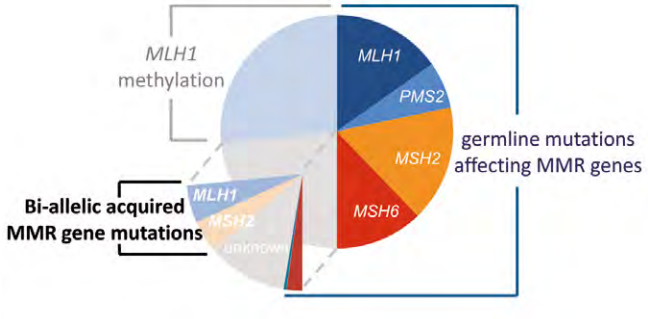


Figure 1: Underlying cause of MSI-high tumors (n=230, age at diagnosis 48 years on average). Half of the tumors in this group is explained by a germline mutation in one of the MMR genes, over 25% is caused by somatic hypermethylation of the *MLH1* promoter. Half of the tumors that were previously unexplained are caused by biallelic somatic mutations in *MLH1* or *MSH2*.


Theme: Urological cancers

William Leenders
Arend Heerschap

Cancer Res. 74:4898-907, 2014.

Non-invasive MR biomarker to identify and characterize a prognostic brain tumour mutation

Patients with a glioma brain tumour have an overall poor prognosis, but those with gliomas carrying a mutation in the IDH1 gene do better than the others. Since IDH1 is involved in the regulation of lipid synthesis we investigated the profile of phospholipids compounds of different human derived brain tumours with and without the IDH1 mutation, growing in the mouse brain, by *in vivo* phosphorus MR spectroscopic imaging (Figure 1). Mutant tumours display a distinct pattern of decreased levels of phosphoethanolamine and increased levels of glycerophosphocholine. This spectral profile was confirmed by *ex vivo* analysis of tumour extracts, and it was also observed in surgical biopsies of mutated gliomas in humans and in extracts of cells with and without the mutation. Our study involved the first *in vivo* localized analysis of phosphorus compounds in the mouse brain. It shows that *IDH1*-mutation alters phospholipid metabolism in gliomas and provides a new non-invasive clinical biomarker to assist in the identification of the mutation and in evaluation of existing and novel treatments for patients with IDH1-mutant glioma.
This study was performed together with the NTNU in Trondheim, Norway.

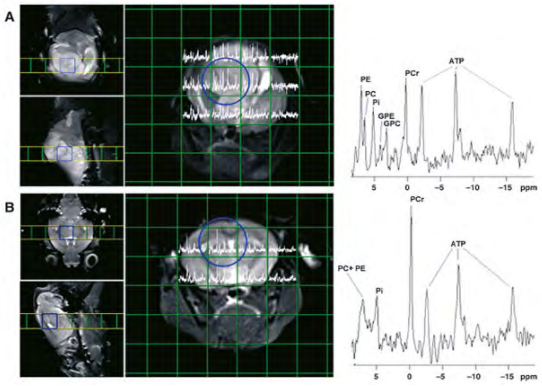


Figure 1: Phosphorus MR spectroscopy shows high energy phosphates and phospholipid compounds. (A) MRI of mouse brain with a human brain tumour and a ^{31}P MR spectrum from blue voxel in tumour. (B) Idem from healthy mouse brain. PE, PC are phospho-ethanolamine and choline; Pi, inorganic phosphate; GPE, GPC are glycerophospho- ethanolamine and choline: PCr, phosphocreatine and ATP. In tumour tissue phospholipid compounds are increased and PCr decreased. From Esmaeili M. et al. Cancer Res. 2014 (with permission).

Theme: Vascular damage

Anouk van Berkel
Henri Timmers

J Nucl Med. 55:1253-9, 2014.

Determinants of ^{18}F-FDG avidity in pheochromocytoma

Pheochromocytomas and paragangliomas (PPGLs) are rare catecholamine-producing neuroendocrine tumors that can be localized by ^{18}F-labeled fluorodeoxyglucose (FDG) PET imaging. Changes in tumor metabolism translate into genotype-specific differences in ^{18}F-FDG uptake, enabling functional tumor characterization of PPGLs by *in vivo* imaging. We found that the uptake of ^{18}F-FDG is particularly high in tumors with an underlying *succinate dehydrogenase (SDH)* mutation. *SDH* mutations result in compromised oxidative phosphorylation and a pseudo-hypoxic response which mediates an increase in aerobic glycolysis. This energy switch, also known as the Warburg effect, requires a much larger cellular influx of glucose. We found that activation of aerobic glycolysis in *SDHx*-related PPGLs is associated with increased ^{18}F-FDG accumulation due to accelerated glucose/^{18}F-FDG phosphorylation by hexokinases rather than increased expression of glucose transporters. Prompted by these findings, we are currently studying ^{18}F-FDG kinetics by dynamic PET scanning in patients with PPGL to better identify tumours of the *SDH* genotype that are prone to develop into metastatic disease.

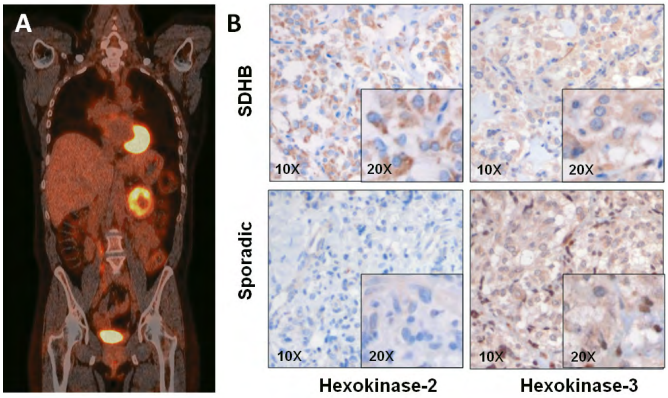


Figure 1: (A) ^{18}F-FDG PET scan in patient with sporadic PPGL located in left adrenal. (B) Immunohistochemical staining of PPGLs for hexokinase 2 and 3. Representative images of *SHDB*, and sporadic tumor.

Theme: Women's cancers

Remko Bosgraaf
Willem Melchers

Lancet Oncology. 15:315-22, 2014.

Molecular screening for cervical cancer

Worldwide 470,000 new cases of invasive cancer of the cervix are diagnosed annually. It is evident that human papillomaviruses (HPVs) are the causative agents in the development of cervical cancer (Figure 1), and HPV testing will be the primary screenings tool in the Dutch Cervical Cancer Screening Program from 2016 onwards. However, almost half of the cases of invasive cervical cancer are in the 30% of women who do not attend screening. Offering self-collection of cervicovaginal material for high-risk HPV (hrHPV) detection is highly effective in recruiting non-attendees into screening. However, women positive for hrHPV on self-sampled specimens require an additional triage as specificity of hrHPV is too low to justify direct referral to the gynecologist. Because cytology is not reliable on self-sampled material, direct molecular triage on HPV positive self-samples would be highly beneficial. In this randomised controlled non-inferiority trial, 12.819 women were included. We randomly allocated women who tested positive for hrHPV on a self-sample to either triage by cytology or direct triage on the self-sample by methylation analysis of *MAL* and *miR-124-2* genes. We found that DNA methylation analysis on HPV-test-positive self-samples is noninferior to cytology triage in the detection of cervical abnormalities, opening the way to a full molecular screening for cervical cancer in the near future.

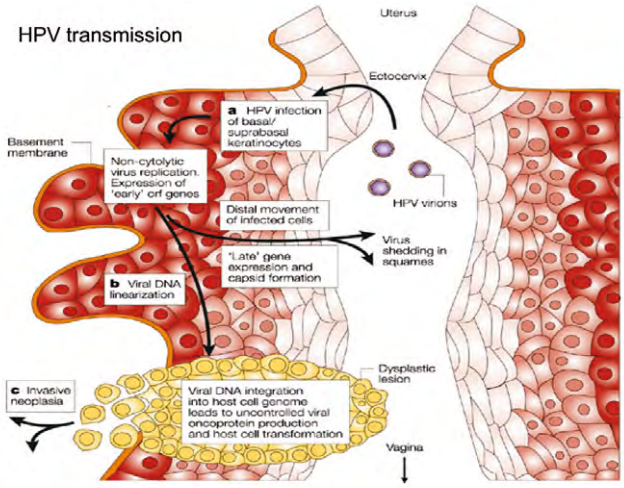


Figure 1: A. HPV infect basal cells of the cervical epithelium followed by limited viral replication and expression of 'early' proteins E1 and E2. During differentiation, the E4 protein, and the late capsid proteins L1 and L2, are expressed. Viral capsids are shed into the genital tract. B. Rarely, the HPV DNA integrates into the host cell genome. The break often occurs in the E2, resulting in the constitutive expression of the E6 and E7 oncogenes, predisposes infected cells to cellular transformation. C. Invasive tumour ruptures the basement membrane and invades the sub-epidermal tissue.

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 a multifaceted knowledge of normal and pathological processes. Findings are translated into clinical applications, into the development of diagnostics and into the treatment of patients within the general concept 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