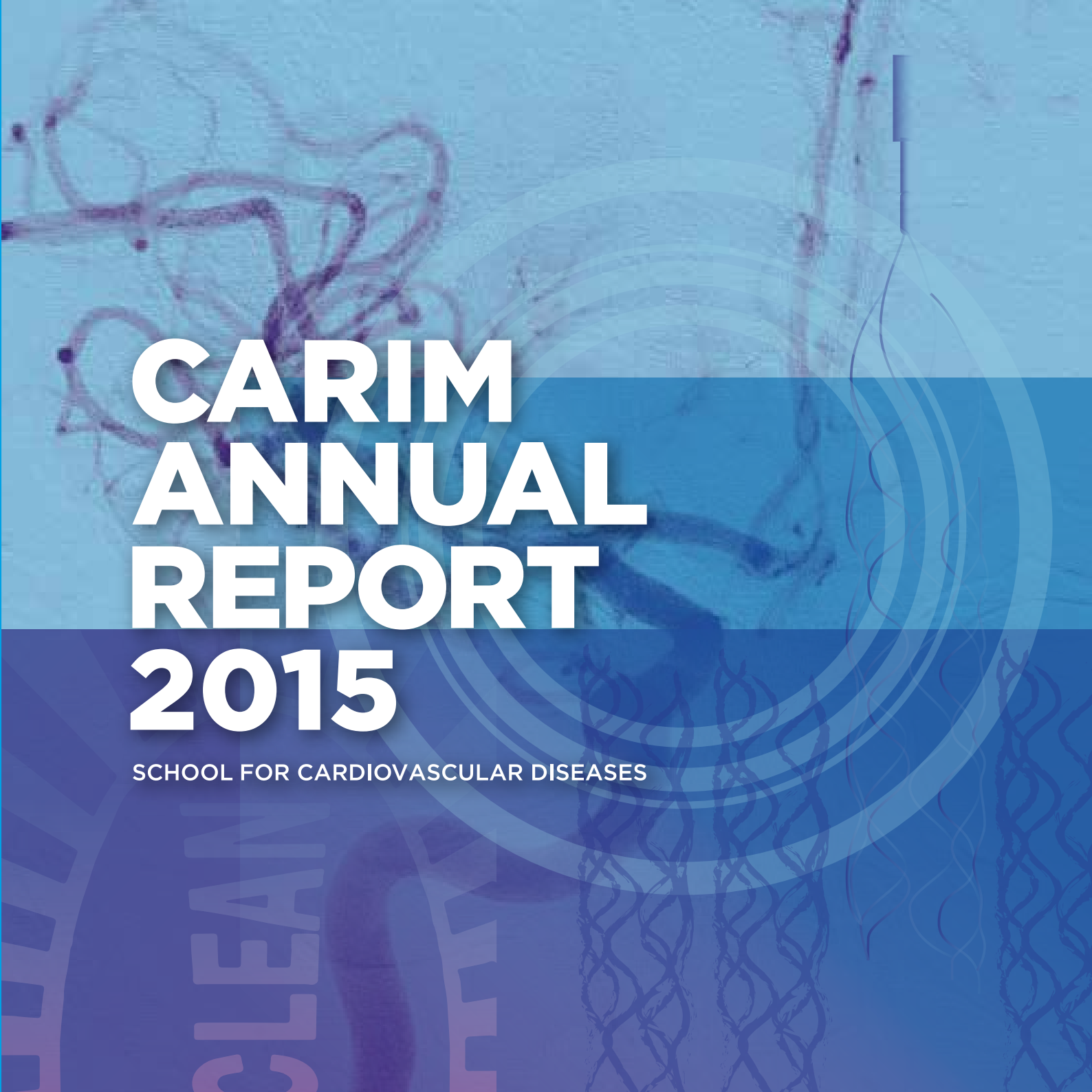


CARIM ANNUAL REPORT 2015

SCHOOL FOR CARDIOVASCULAR DISEASES

CARIM ANNUAL REPORT 2015

SCHOOL FOR CARDIOVASCULAR DISEASES

CONTENTS

PREFACE
CARIM IS DOING WELL!

Things are always on the move, especially in dynamic biomedical areas where cardiovascular research has its place. But after several eventful years, we at CARIM have achieved to quite an extent what I promised some years ago in the preface to the CARIM Annual Report 2011: "to look forward and to help the institute into a next phase, in which a more focused research strategy will help us to survive in the competitive field of cardiovascular research".

In June 2014, CARIM went through an on-site evaluation of an External Review Committee (ERC). The reviewers, while in principle being impressed by the scientific quality of the research done at CARIM, had several suggestions for further improvement. In line with the above mentioned idea of strengthening the focus of research within the three themes: 'Thrombosis and Haemostasis', 'Complex Arrhythmias and Structural Heart Disease' and 'Vascular Biology and Medicine', they also proposed to energise the fields of complex genetics and genetic epidemiology as well as systems biology, further to re-structure the vascular theme, intensify translational research together with the Heart + Vascular Centre (HVC) of the Maastricht University Hospital, build on the Maastricht Study, and readjust the number and scientific orientation of PI-ships.

Coinciding with the task of implementing the external reviewers' suggestions, CARIM was confronted in 2015 with two additional demands: First, to align the FTE (full-time equivalent) allocation of its researchers with the other schools (institutes) of FHML, i.e. from 0,7 to 0,5 FTE research affiliation, and second, to come up with solutions to balance part of the first money stream funding of the institute by FHML against the other schools on the basis of the number of PhD theses. Both issues turned out to be serious challenges. CARIM answered with a budgetary and structural plan which takes care of the various requirements and which, if everything goes well, will give the institute back its financial flexibility for innovations and incentives in the years to come.

Concerning genetics and systems biology, CARIM has made a decisive step in establishing a Maastricht University professorship in 'Genetic Epidemiology and Statistical Genetics' and to join forces with the newly founded MaCSBio (Maastricht Centre for Systems Biology), a joint initiative of the Faculty of Psychology & Neuroscience, Faculty of Health, Medicine & Life Sciences, and Faculty of Humanities and Sciences. Both new chairholders will give the male cohort of CARIM PIs a female touch. Apart from this, their appearance on the screen has already turned out to be extremely helpful for a substantial number of research projects in CARIM and will certainly be even more in the future.

With respect to the Maastricht Study, "...one of the most extensive phenotyping studies in both the general population and type-2 Diabetes mellitus participants world-wide..." [1], the time of harvest has begun; some papers have already appeared, and a flood of high quality publications are to be expected in the upcoming years.

In 2015, CARIM's researchers were in general highly successful in the acquisition of external research funding, e.g. a highly prestigious Vici grant as well as numerous other grants, awards and prizes by CARIM researchers (see page 54). External funding in 2015 was thus almost doubled compared to the year before. It is especially gratifying to see that CARIM turned out to be successful not only on national

1 The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. Schram MT1, Sep SJ, van der Kallen CJ, Dagnelie PC, Koster A, Schaper N, Henry RM, Stehouwer CD. Eur J Epidemiol. 2014 Jun;29(6):439-51.

grounds, but especially within the European 'Horizon 2020 framework'.

Funding is one side, the scientific output the other side of the coin. CARIM's scientific output, as measured by the so-called crown factor, published by the Dutch 'Centre for Science and Technology Studies', reflects the outstanding scientific achievements of our institute: Publications from CARIM were cited worldwide about two-times more than average[2] (see page 35).

Yes, we can be proud: CARIM with all its assets is on the international screen and is considered there as an innovative, solid, reliable and highly esteemed member of the scientific community. This is an achievement that can't be regarded high enough and certainly only to a very minor degree the merit of CARIM's Scientific Director. The scientists with their technical assistants, the students, the financial and logistic administration, the leaders and co-workers in faculty and academic hospital, they are the ones responsible for heaven or hell, and they deserve my deep respect because we are much closer to the first than to the latter. I sincerely hope that this condition will prevail.

With this, I wish you much pleasure browsing through CARIM's Annual Report 2015.

Professor Thomas Unger
Scientific Director CARIM
School for Cardiovascular Diseases

2 Bibliometric study on Dutch academic medical centers 1998-2012/2013 – Center for Science & Technology Studies (CWTS) and Dutch Federation of University Medical Centers (NFU)

SOME THOUGHTS ABOUT TRANSLATIONAL RESEARCH

THOMAS UNGER

'Translational research' is a buzzword of the day, but what does it mean? Let's approach the question in two different ways:

Educated in the traditional German *Bildungssystem* – the German word *Bildung* cannot be literally translated (there is that word again) into the English *education*; it goes beyond, sometimes defined as "what remains when you have forgotten everything that you have learned" - I would start with the etymological approach. The Latin verb *transferre* means that you carry something from one side to the other of, for instance, the Alps (cf. *Gallia trans-alpina*) or another obstacle. In doing this, there may be an advantage: you may conquer a new territory, you may learn something you have never heard of, you may combine your ancient, traditional knowledge with new insights and reach a higher level of wisdom. In order to achieve this, however, there must be something already in existence to be transferred, 'a thing'.

The second approach to 'translation' is, of course, the one that most of us use: Wikipedia. What does the oracle say with respect to translational research?

"Translational research (TR) - often used interchangeably with translational medicine - is a highly interdisciplinary field, the primary goal of which is to coalesce assets of various natures within the individual pillars in order to improve the global healthcare system significantly. The goal of translational medicine is to combine disciplines, resources, expertise, and techniques within these pillars to promote enhancements in prevention, diagnosis, and therapies."[1]

The citation refers to a 2014 article by Cohrs et al.

1 Source: https://en.wikipedia.org/wiki/Translational_research

'Translational Medicine definition by the European Society for Translational Medicine (EUSTIM)'. EUSTIM further defines translational medicine as "an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside and community."[2]

This gives us enough material to chew on for a few minutes.

Forget for a moment whether 'translational research' is interchangeable with 'translational medicine'; this is clearly not always the case, since both (bio)medical research and medicine are still distinct, although sometimes overlapping, areas. Let's concentrate on the interdisciplinarity of translational research. What this means is not only that scientists from different fields of basic research, e.g. a molecular biologist and a pharmacologist working together to develop a new therapeutic molecule, as this needs to be done anyway to be successful these days, but, rather, the interdisciplinary approach refers to the aforementioned pillars: first, from bench to bedside and then, maybe, to the community.

From bench to bedside: something, 'a thing' that has been developed, an idea, a technique, a methodological approach, is *transferred* (here is the word again) to the clinic, is subsequently investigated in patients, and, if successful, further disseminated to the community. The first step, from bench to bedside, certainly makes sense. Biomedical research draws its justification, to a large extent, from the principle of developing applications in order to help sick people or to prevent disease. We strive to invent; to develop new diagnostic, prognostic and therapeutic approaches;

2 Cohrs, Randall J.; Martin, Tyler; Ghahramani, Parviz; Bidaut, Luc; Higgins, Paul J.; Shahzad, Aamir. „Translational Medicine definition by the European Society for Translational Medicine". New Horizons in Translational Medicine. 2 (3): 86–88. doi:10.1016/j.nhtm.2014.12.002

to drive the medical field forward and to benefit patients. Undoubtedly, there are beautiful examples of such direct translation here in Maastricht, *inter alia* one supplied by eminent physiologist, Frits Prinzen, in his narrative 'Societal impact of research on Electro-Mechanics of the Heart' on page 45. In this impressive illustration, translational research indeed converts into translational medicine. Do not forget: the indispensable electrophysiological experiments, which allowed the direct transfer of his results into a live-saving clinical application in the catheter laboratory, were performed in animal experiments, notably in dogs.

In November 2015, the traditional annual CARIM Day was devoted to the topic of 'Translational Research'. Several duo-presentations, each delivered jointly by a basic and a clinical scientist, provided further examples of translational research at CARIM. These presentations spawned full-length publications, which will soon appear in a special issue of the journal *Cardiovascular Drugs and Therapeutics*, edited by H. Crijns, U. Schotten and Th. Unger.

These were the themes:

- *Non-invasive Imaging of Atherosclerosis – from Bench to Bedside* by J Bucerius, I Dijkgraaf, FM Mottaghy and LJ Schurgers: "*Our review describes biological, chemical and medical expertise to support a translational approach that will enable better risk prediction and will benefit patients by identifying vulnerable atherosclerotic plaques using imaging."*

- *The glycation pathway: on the road to precision medicine* by NMJ Hanssen, CDA Stehouwer and CG Schalkwijk: *"...we highlight recent efforts to translate findings from glycation research toward clinical applications."*

- *Go places with pacing, the role of translational science"* by K Vernooy, WYR Vanagt, MM Rad and FW Prinzen: *"...we highlight the road from animal studies to clinical studies that leads and led to better pacemaker therapies."*

- *A Disintegrin And Metalloproteases (ADAMs) in cardiovascular, metabolic and inflammatory diseases: aspects for theranostic approaches"* by EPC van der Vorst, C Weber and MMPC Donners: *"...we describe the role and association of A Disintegrin And Metalloproteases (ADAMs) in various human cardiovascular, metabolic and inflammatory diseases...additionally, an overview will be given concerning ADAM-based therapeutic and diagnostic (theranostic) opportunities."*

- *Mathematical upper extremity vessel modeling: can we support vascular surgery access planning in hemodialysis patients?"* by W Huberts, N Zonnebeld, AS Bode and JHM Tordoir: *"...we highlight recent efforts to develop and apply a cardiovascular (computer) model for supporting*

clinical decision-making for vascular access creation in hemodialysis patients."

- *Post-thrombotic inflammation: a key to understanding pathology of deep venous thrombosis"* by C Wittens, M de Geus and EA Biessen: "*...we highlight recent advances in our understanding of the role of inflammation in deep venous thrombosis (DVT) and the high promise of targeting inflammation as therapeutic measure for DVT."*

This wide variety of themes, along with many others dedicated to the three scientific foci of CARIM ('Thrombosis and Haemostasis', 'Complex Arrhythmias and Structural Heart Disease', and 'Vascular Biology and Medicine'), demonstrates the deep involvement of CARIM's scientists in translational issues, and, additionally, gives an impression of the great potential that the translational approach represents in cardiovascular research and medicine.

The second step, translating the clinical application of a new drug or a new procedure or method to the community, is less straightforward. Indeed, current members of the 'educated' community claim their right to receive all of the information available on biomedical progress, since, in the end, it is they, the taxpayers, who fund most of that research, at least to the extent that academia is involved. The societal impact, however, is not always as obvious as in the previously mentioned narrative by Frits Prinzen. In this translational step, the sender and the receiver are often not well attuned to each other, which opens the door for misunderstandings and false expectations, since the community (receiver) cannot be expected to command the same knowledge and expertise as the information–providing scientists (sender), despite Wikipedia and the like. Good examples are the hope-raising monthly reports of novel treatments for Alzheimer's disease that seldom survive the drying of the ink on the paper on which they are printed (if printing is still used for such messages).

Therefore, while I agree that scientists need to open their Pandora's boxes to the scrutiny of the tax-paying community, I acknowledge that this pillar (here translational research has really turned into translational medicine) is quite a delicate issue, requiring serious efforts from both sides to synchronize sender and receiver.

In view of all of the arguments speaking in favour of going translational, shouldn't an institution like CARIM, which strives to be among the best of its kind, become fully translational to satisfy all of the present demands of the public, of governments, of official and industrial grant giving agencies? Don't we have to write longer and longer paragraphs in our grant submissions and research reports on 'societal impact'? Doesn't societal impact in medical research automatically imply translational research? Don't we have the obligation to quench the unslakeable thirst of the media for constant, and sensational, steps in the progress of diagnosis and therapy?

Yes, we have this obligation, to a certain extent, but there is something else in the world of science, something which is entirely un-translational: the conduct of research driven solely by curiosity.

Curiosity-driven research is not primarily application-oriented. It springs from what is engraved in stone above the portal of Heidelberg University: *Dem lebendigen Geist* ("to the living spirit", where 'living' does not mean 'just alive' but rather 'attentive' and 'creative'). The zest to discover what is holding the world together, in a first approach, without

respecting boundaries or considering consequences. In my view, scientists need to be given the chance to follow their curiosity, sometimes even serendipity, to think the hitherto unthinkable, to bind together thoughts and approaches previously separated, to have never-heard-of, fantastic ideas under the morning shower or while shaving, and try them out.

When the great scientific discoveries and achievements of the past are evaluated, many, if not all, were born out of a combination of the knowledge of the time with one or more unconventional ideas, resulting in the creation of a new paradigm, a new 'thing'.

One example, which I witnessed myself, may serve to illustrate this: the venom of the Brazilian snake *Bothrops jararaca* contains certain peptides. Brazilian researchers found out that one or more of these peptides inhibit, among other things, the enzymatic degradation of another peptide present in our body, bradykinin, thus potentiating the actions of the latter. This was an interesting finding, but in and of itself, not sensational. The 'living spirit' entered the game when somebody thought of linking the bradykinin degradation to another well-known peptide system, the renin-angiotensin system (RAS), by demonstrating that the bradykinin degrading enzyme, kininase II, was identical to the angiotensin converting enzyme (ACE), which splits off the blood pressure increasing peptide, angiotensin II, from its precursor. With this intellectual bridge to the RAS, the ground was paved for the development of non-peptide small molecules, ACE-inhibitors, which inhibit the formation of angiotensin II (and potentiate kinins). ACE inhibitors were subsequently introduced into the clinic with tremendous success for all kinds of cardiovascular indications and, even, beyond. What is important in this story, however, is this: years of research passed within a curiosity-driven period without translational moves, until the time and the 'thing' were ready for drug development, i.e. the translational, application-oriented phase.

The above example, and many others, tells us that there seems to be a pre-phase driven by curiosity and creativity until the product of this phase finally enters the translational path. Is this curiosity-driven first step a prerequisite for translation? I would say, in most cases, yes: you need to create the 'thing', a (drug) target or a novel method or procedure, first and then shape it into an object of translation and render it clinically applicable. On the other hand, does the product of curiosity driven research always end up in translation? Not necessarily, but it happens quite often. To sharpen the argument: does curiosity-driven research inevitably have to end in translation because researchers have a responsibility towards official funding sources or society at large? My answer to this is a definite no.

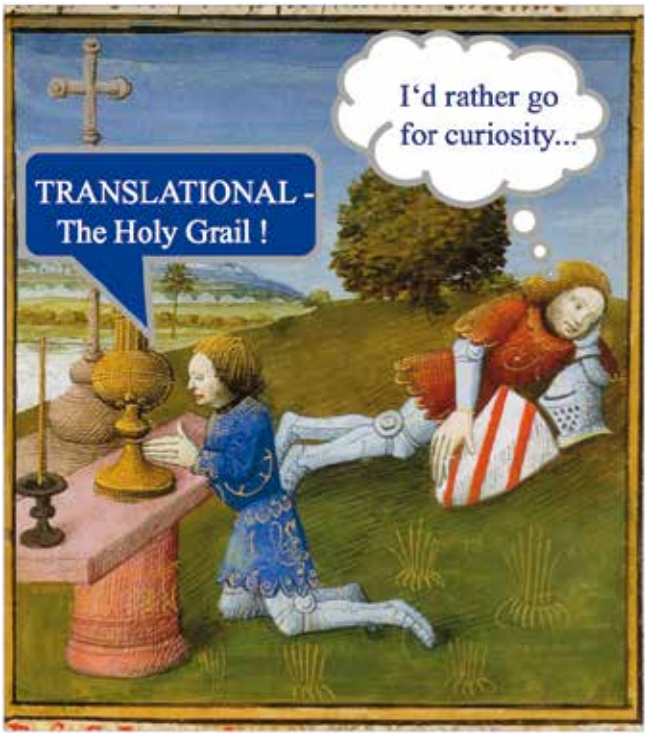
Curiosity-driven research needs to exist in its own right, not merely because it's the predecessor of the translational. It exists as an expression of the irrepressible human drive to deepen our knowledge about the world, as an expression of the living human spirit. It may even possess an intrinsic aesthetic value. Similarly, the results of our scientific curiosity have their own value, whether or not they will, in the short or long term, engender translational exercises or

even give rise to ethical concerns with which scientists and the community will have to deal. These results serve what is called 'gain of knowledge' and are regarded as inherently valuable in our culture.

Perhaps not coincidentally, the landmark publications in the leading scientific journals, such as *Nature, Science*, *Cell* and the like, usually deal with topics in the 'curiosity-driven' category.

If this argument is accepted, how should an institution devoted to cardiovascular research, like CARIM, which is privileged to host basic and clinical researchers under one roof, act or react between the poles of curiosity and translation? Should it lean entirely towards the side from which the money and societal pressure comes or should it insist on providing a playground for the free development of the living spirit, even if the products of these spiritual endeavours are lost in (or for) translation?

A question posed like this is, of course, a rhetorical one. It is my deep conviction that both approaches need to live together in an institution like ours, and that a preeminent objective of CARIM leadership is to provide the basis for this co-existence and to make it as harmonious and fruitful as possible. Thus, the call is out: copiously water all of the flowers growing in the field of creative cardiovascular research; watch them carefully, but let them bloom in their own right; don't be disappointed if not all of them can be picked and bound together, but, simultaneously, help those selected on their way to become part of the rich bouquet of translational medicine.



PROFILE

01

PROFILE

Founded in 1988, the Cardiovascular Research Institute Maastricht (CARIM), School for Cardiovascular Diseases, has established itself over the last two decades as a leading research institute in the field of cardiovascular disease. At CARIM, basic mechanisms as well as early diagnosis and individual risk stratification of cardiovascular diseases are studied, allowing faster translation of new research concepts to clinical practice. New findings, products and techniques which can be applied in healthcare are evaluated, often in collaboration with private companies, and the results of scientific research are published in high-ranking international journals. Master's students, PhD students and MD students are trained to become independent researchers, and post-docs are trained to become leading scientists in the field of cardiovascular disease.

CARIM is built around three broader research themes, each led by a program leader: I) Thrombosis and Haemostasis, II) Complex Arrhythmias and Structural Heart Disease and III) Vascular Biology and Medicine. These three themes comprise 27 basic and clinical programs, each led by a Principal Investigator (PI). The PIs are responsible for the scientific progress of their program, for linking activities and seeking collaborations between PIs and themes, for mentoring of PhD students and post-docs and, finally, for the financial basis of the program. All three themes involve basic and clinical programs. Cardiovascular scientists from around the world join CARIM because it values open communication, close cooperation, high ambitions, good facilities and a critical learning. CARIM is one of the six research schools of the Faculty of Health, Medicine and Life Sciences (FHML) of Maastricht University and is embedded within the Maastricht University Medical Centre+ (Maastricht UMC+). CARIM is recognised by the KNAW as a research school and as an international training site for Early Stage Researchers in the framework of the Marie Curie Program.

CARIM plays an important role in public-private research partnerships as main author and project manager of three transition grant projects of the Centre for Translational Molecular Medicine (CTMM) in the Netherlands. CTMM is a public-private consortium that comprises universities, academic medical centres, medical technology enterprises and chemical and pharmaceutical companies. In addition, CARIM is a member of several national and international networks; NHF CVON, Horizon 2020, Leducq Transatlantic Network. Especially the new European Horizon 2020 program has given rise to a great number of scientific co-operation networks spanning all over Europe, and CARIM is participating in more than twenty of them with increasing tendency and a relatively high success rate

To translate research into clinical practice, CARIM, in close collaboration with the HVC of the Academic Hospital Maastricht, under the name of the Cardiovascular Centre Maastricht (CVC) is aiming to develop into a unique internationally recognised centre of excellence in cardiovascular medicine in research (including translational research and medical care).

KEY FIGURES 2015

ANNUAL BUDGET: **22.397** K€

NEW CONTRACTS AND GRANTS: **16.523** K€

RESEARCHERS: **162** FTE

TECHNICAL AND SUPPORTING STAFF: **56** FTE

DEPARTMENTS/DISCIPLINES: **13**

SCIENTIFIC ARTICLES: **586** (Wi-1: 522)

PHD THESES: **43**

PATENTS: **4**

INTERVIEW

HENRI SPRONK
HARRY CRIJNS

People suffering from atrial fibrillation (AF) are at risk not so much from the arrhythmia itself, but from its vascular complications: myocardial infarctions, cerebral infarctions and heart failure. "We should do something about that", was the idea of a multi-disciplinary group of researchers working at three university medical centres in the Netherlands. In 2015, the group, which included a considerable share of representatives from Maastricht, received a CVON grant worth 5 million euros. In five years from now, the researchers hope to have a much better understanding of the roles of coagulation (thrombin) and scar tissue formation (fibrosis) in atrial fibrillation.

The acronym CVON stands for Cardiovasculair Onderzoek Nederland (cardiovascular research in the Netherlands), in which the Netherlands Heart Foundation, the Netherlands Federation of University Medical Centres (NFU), the Royal Netherlands Academy of Arts and Sciences (KNAW) and the Netherlands Organisation for Health Research and Development (ZonMw) are collaborating. Its main aim is to get the best medical researchers in the Netherlands (whether preclinical or clinical) to meet and collaborate.

The project is led by Uli Schotten, a physiologist at CARIM, and Isabelle van Gelder, a cardiologist at Groningen University Medical Centre. In addition to these two centres, the AF group also includes researchers from Leiden University Medical Centre, as well as the cardiology departments of a large number of Netherlands hospitals. The three centres contribute essential knowledge and expertise on all aspects of AF, that is, what *they* consider to be essential knowledge, as their hypothesis, which says that people whose blood coagulates more easily have a higher risk of AF, is fairly revolutionary.

Two of the founding fathers of the project were from Maastricht: Henri Spronk (a biochemist investigating coagulation) and Harry Crijns (head of the Cardiology department). They had previously done animal experiments to substantiate their hypothesis. Spronk: "We're actually reversing the conventional theory that AF causes more coagulation, by claiming that more coagulation leads to AF. So then you wait anxiously to see what international colleagues will think of that. That's why we did quite a lot of preparatory work before sending off our grant proposal. We did a study based on animal experiments, which led to a publication in the *European Heart Journal*." The study used goats to show that giving them anticoagulants reduces AF, and also showed that AF can be more easily induced in mice whose blood has a higher tendency to coagulate.

COAGULATION CASCADE

Crijns: "In effect, our proposal centres around thrombin, the protein that initiates the blood coagulation. We will be undertaking human, cellular and animal experiments to examine the molecular pathways in the coagulation cascade in which these proteins play a role. And how this can lead to AF and hence to things like stroke." To which Spronk adds: "For a long time we thought that thrombin only caused the formation of clots and activation of platelets. But in recent years we've been finding that coagulation factors that cause blood clotting can also activate other cells than platelets. And these cellular processes in turn play a role in scar tissue formation, for instance in the atrial wall. Our theory is that if you inhibit the coagulation, you not only reduce the risk of thrombosis, but also that of AF." Crijns: "And the ultimate goal is of course to improve the diagnostics, to enable us to make a distinction between people who are at increased risk of AF complications like stroke and cardiac infarction and those who aren't. Lead molecules, which allow personalised medicine: that's our dream."

A GREAT BOOST

The researchers have been working to realise their dream for some time now. "But this grant really is a great boost", says Crijns. "We're very happy that this heavyweight international committee which assesses all grant applications has acknowledged our hypothesis. When the email confirmation came in, we put out the flag and opened bottles of champagne at the three centres." Whereas 'Maastricht' contributes a lot of expertise on the physiology of the heart and blood coagulation, 'Leiden' is strong on scar formation and 'Groningen' on clinical epidemiology and biomarking. In

Spronk's view, the strength of their grant proposal lay not only in the published animal study, but especially in the concerted effort. "The project is divided into eight work packages, and everyone has their own task within each of these subsidiary projects. That makes it a truly multidisciplinary project."

MATCHSTICK

Spronk is the leader of Work Package 2, which investigates in detail how the coagulation factors contribute to scar formation at cellular level. Crijns heads Work Package 6, which involves a study including 750 patients with recent self-terminating AF. They will be followed for at least a year, examined thoroughly and fitted with a 'LinQ' device implanted under the skin of the chest, above the heart. This device, about the size of a thick matchstick, is able to monitor the cardiac rhythm, as well as the body's reaction to AF, for three years. "This way we hope to get a grip on the relationship between the number of cardiac arrhythmias and the changes in the blood", explains Crijns. Besides the three participating university centres, seven hospitals around the country are helping to find the patients to be included within 2.5 years.

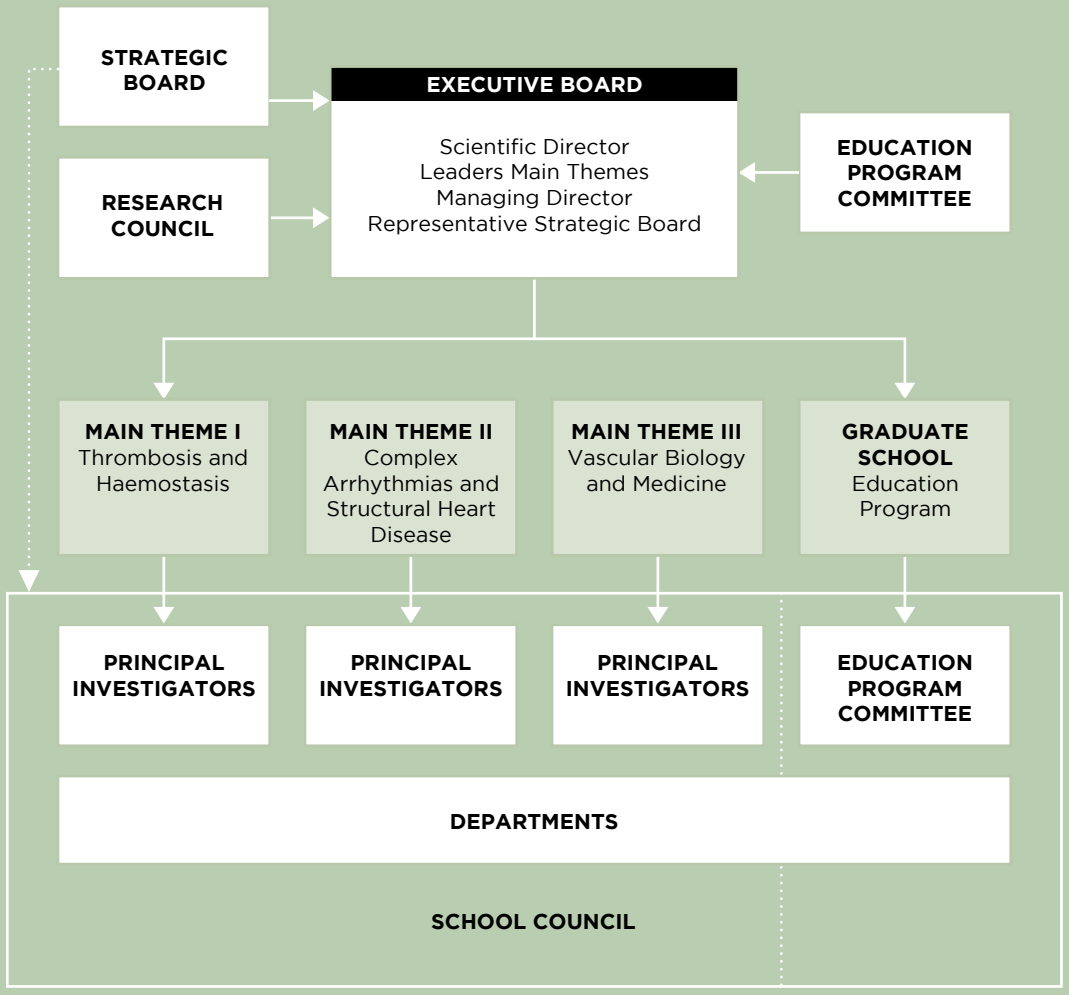
Once the grant has been fully spent, after five years, it may be extended. Crijns, who also chairs the Heart Foundation's Scientific Council, says: "I thinks it's very good that CVON thus brings together researchers and grant providers in order to find a common field of interest. And CVON also has a Young Talent programme, offering a platform where young researchers involved in such projects can meet and discuss their research questions. After all, they're the ones who are going to succeed the current generation of researchers."

"OUR PROPOSAL CENTRES AROUND THROMBIN, THE PROTEIN THAT INITIATES THE BLOOD COAGULATION"

ORGANISATION

02

ORGANISATION



CARIM's Scientific Director, Professor Thomas Unger, has the final responsibility for the research institute, including the organisation and management of the research program, the scientific output, the training of Master's and graduate students and post-doctoral fellows, and the financial management and the public relations of the institute. At the end of 2012, the Strategic Board (SB) was formed to advise and support the Scientific Director in managing long term policy. The board is also a discussion forum and generates written visions of the future of CARIM and its survival in an increasingly competitive European scientific environment. The SB meets regularly to discuss issues such as grant applications, national and international collaboration networks, interdisciplinary communication and CARIM's visibility in the national and international cardiovascular fields.

The Scientific Director is assisted by the Managing Director, Rob van der Zander, who takes care of the financial and human resource management. Together with the three leaders of the main themes and a representative from the Strategic Board, the Scientific and Managing directors make up the Executive Board (EB) of the institute. The EB meets monthly to discuss and decide upon issues at strategic and operational level. The EB is advised by three councils/committees: the SB, the Education Program Committee and the CARIM Research Council. The Educational Committee coordinates both the PhD- and Master's training programs and consists of the PhD Program Coordinator, the Master Program coordinator, 4 CARIM staff members (of which 2 clinical) and 4 PhD students. The committee advises the EB on all issues regarding the PhD and Master's programs. At the end of 2009 the EB established the Research Council (RC). The RC advises the EB and PIs on the quality of all research proposals and meets regularly to discuss grant applications.
Finally, the School Council consists of the Principle Investigators and department heads and meets four times a year.

EXECUTIVE BOARD

- Professor Thomas Unger, Scientific Director
- Professor Tilman Hackeng, Vice Director & Leader Main Theme I
- Professor Harry Crijns, Leader Main Theme II
- Professor Harry Struijker Boudier, Leader Main Theme III
- Professor Coen Stehouwer
- Professor Uli Schotten, representative Strategic Board
- Rob van der Zander, Managing Director

STRATEGIC BOARD

- Professor Uli Schotten, Chairman
- Professor Hugo ten Cate
- Professor Leon de Windt
- Professor Chris Reutelingsperger
- Professor Robert van Oostenbrugge
- Dr Judith Sluimer
- Rob van der Zander

PRINCIPAL INVESTIGATORS

- Professor Erik Biessen, Dept. of Pathology
- Professor Matthijs Blankesteijn, Dept. of Pharmacology & Toxicology
- Professor Hans Peter Brunner-La Rocca, Dept. of Cardiology
- Professor Harry Crijns, Dept. of Cardiology
- Professor Hugo ten Cate, Dept. of Biochemistry
- Professor Tammo Delhaas, Dept. of Biochemistry
- Professor Tilman Hackeng, Dept. of Biochemistry
- Professor Johan Heemskerk, Dept. of Biochemistry
- Professor Stephane Heymans, Dept. of Cardiology
- Professor Jan Glatz, Dept. of Genetics and Cell Biology
- Professor Peter de Leeuw, Dept. of Internal Medicine
- Professor Jos Maessen, Dept. of Cardiothoracic Surgery
- Professor Robert van Oostenbrugge, Dept. of Neurology
- Professor Mark Post, Dept. of Physiology

- Professor Frits Prinzen, Dept. of Physiology
- Professor Chris Reutelingsperger, Dept. of Biochemistry
- Professor Harald Schmidt, Dept. of Pharmacology & Toxicology
- Professor Uli Schotten, Dept. of Physiology
- Professor Bert Smeets, Dept. of Genetics and Cell Biology
- Professor Coen Stehouwer, Dept. of Internal Medicine
- Professor Monika Stoll, Dept. of Biochemistry
- Professor Harry Struijker Boudier, Dept. of Pharmacology & Toxicology
- Professor Hans Vink, Dept. of Physiology
- Professor Paul Volders, Dept. of Cardiology
- Professor Christian Weber, Dept. of Biochemistry
- Professor Joachim Wildberger, Dept. of Radiology
- Professor Leon de Windt, Dept. of Cardiology

RESEARCH COUNCIL

- Professor Frits Prinzen, chairman
- Dr Kristiaan Wouters, secretary
- Professor Erik Biessen
- Dr Matthijs Blankesteijn
- Professor Jan Glatz
- Professor Chris Reutelingsperger
- Dr Henri Spronk
- Professor Thomas Unger

EDUCATION PROGRAM COMMITTEE

- Dr Marc van Bilsen, chairman, PhD Coordinator
- Dr Adriaan Duijvestijn, Coordinator Biomedical Sciences Master
- Dr Matthijs Blankesteijn, staff member
- Dr Eline Kooi, staff member
- Dr Hans Vink, staff member
- Dr Simone Sep, staff member
- Yvonne Olischläger, PhD student
- Tom Mastenbroek, PhD student
- Elke Marsch, PhD student
- Armand Jaminon, PhD student

CARIM OFFICE

The CARIM office consists of Riet Daamen, Tara de Koster and Esther Willigers. The controller is Sietske Satijn.

HR-SUPPORT

Patrick Janssen and Dennis Aarts of the Human Resources Department of Maastricht University are related to CARIM.

ADMINISTRATIVE SUPPORT

The Finance Department of Maastricht University provides support on accounting the CARIM research projects on a part-time basis. At this moment the Finance employees are Henny Kerckhoffs, Esther van Heel and Mark van Gisteren.

PARTICIPATING DEPARTMENTS AND DISCIPLINES

The research in the three main themes involves the research activities of people working in several basic and clinical departments/disciplines of Maastricht UMC+.

BASIC RESEARCH DEPARTMENTS

- BIOCHEMISTRY
- BIOMEDICAL ENGINEERING
- GENETICS & CELL BIOLOGY
- PHARMACOLOGY & TOXICOLOGY
- PHYSIOLOGY

CLINICAL DEPARTMENTS

- CARDIOLOGY
- CARDIO-THORACIC SURGERY
- CLINICAL CHEMISTRY
- INTERNAL MEDICINE
- NEUROLOGY
- PATHOLOGY
- RADIOLOGY
- SURGERY

HIGHLIGHT THEME I

CHRISTIAN WEBER

DEPARTMENT OF BIOCHEMISTRY

Chemokine interactome mapping enables tailored intervention in acute and chronic inflammation

The role of chemokines and their receptors in health and disease continues to be under intense scientific scrutiny and is receiving much attention, owing to their fundamental role in homeostasis, immune surveillance and inflammation. This is exemplified by the newly established nomenclature for atypical receptors, and by recent advances and insights into their structural characterisation. The complexity of chemokine biology and receptor interactions, however, presents significant barriers to translational developments towards therapeutically applicable approaches targeting the chemokine system. It is particularly receptor blocking strategies which have been hampered by side-effects or lack of efficacy.

Our interdisciplinary work has aimed to thoroughly elucidate a much underappreciated and emerging feature of chemokines, i.e. their propensity to engage in heterophilic interactions. The chemokine interactome derived from all possible pairwise heteromeric interactions would represent an entirely new systematic concept to explain the combinatorial and functional plasticity of these molecules. A functional 'interactome' could integrate a multitude of migratory signals to amplify, inhibit or fine-tune the overall cellular response. At the same time, this regulatory principle could be useful to model the pathogenesis of inflammatory diseases, and hence to develop more specific and tailored strategies for therapeutic targeting.

SUMMARY

Chemokines are integral regulators directing leukocyte traffic and function. The concept of interactome proposes that heterophilic interactions of chemokines can provide combinatorial control to amplify or fine-tune their activity; however, systematic screening of chemokine interactions and their functional relevance has proved elusive. We used ligand blotting and surface plasmon resonance to obtain a validated comprehensive map of chemokine interactions. Structure–function analysis by nuclear magnetic resonance (NMR) spectroscopy, chemotaxis and arrest assays revealed a distinct pattern of mixed chemokine pairs whose activity was enhanced by CC-type heterodimers but inhibited by CXC-type heterodimers. Synergy was ascribed to increased receptor heteromerisation and affinity or to auxiliary proteoglycan binding. Obligate CC-type heterodimers showed improved synergy and were active in inducing

acute lung injury and atherosclerosis. These were reduced by chemokine-derived peptide inhibitors specifically disrupting heterodimers or by knocking in interaction-deficient variants in mice. Inhibitory effects were mimicked by a-helical chemokine peptides, e.g. in thrombus formation, and explained by structural changes affecting receptor activation. Overall, our data establish that formation of specific chemokine heterodimers dictates functional activity, a finding applicable in therapeutic targeting.

COMPREHENSIVE STRUCTURE–FUNCTION ANALYSIS

In an unbiased, bidirectional immunoblot chemokine screen, where one partner was immobilised with the other in solution, we identified heteromeric interactions of all pairwise combinations of known human chemokines. The resulting interactome matrix revealed hotspots of heteromeric interactions mostly for inflammatory chemokines, as well as large areas devoid of interactions, e.g. for transmembrane and non-mucosal homeostatic chemokines.

Interactions were validated by surface plasmon resonance (SPR) and refined by kinetics analysis of saturation binding. The results confirmed high affinity interactions (e.g. for CCL5-CCL17, CCL5-CXCL4) and helped to identify variants and mutants deficient in or retaining heteromeric interactions, as well as regions, motifs and individual residues critical for different types of heteromeric interaction.

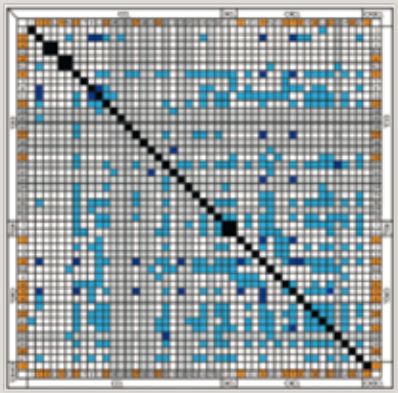
Subsequent NMR structural studies focused on CCL5 and its interactions with relevant chemokines. Spectral changes in resonance intensity and chemical shift (Dδ) indicated that heteromer formation occurs between chemokine monomers. Moreover, perturbations in characteristic residues unveiled the specific localisation of the heterodimer interface and gave rise to the conclusion that interactions occur in a preferred CC-type (e.g. for CCL5-CCL17) or CXC-type (e.g. for CCL5-CXCL12) heterodimer, as confirmed by *in silico* modelling of pre-constructed CC- and CXC-type chemokine heterodimers.

Based on these models, we generated CCL5-derived peptides (CKEY, CAN, and VREY) forming part of CCL5 heterodimer interfaces with CXCL4, CCL17, and CXCL12, respectively. Specific perturbations at the interface with CKEY and CAN reflected disruption of CCL5-CXCL4 and CCL5-CCL17 CC-type hetero-dimers, whereas VREY mimicked CCL5 helix interactions with CXCL12 in the CXC-type heterodimer. SPR confirmed that chemokine heterodimers can be targeted by specific CCL5-derived peptides.

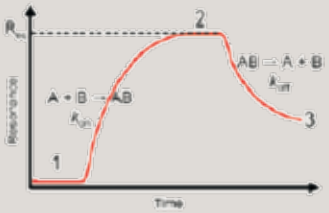
In line with our structural analysis, functional assays using primary T-cell chemotaxis and monocyte arrest on endothelial cells indicated that different types of heterodimeric interactions can result in opposite functional consequences, namely in that CC-type heterodimers mediate synergy, whereas CXC-type heterodimers cause inhibition. In contrast, chemokine combinations lacking a specific type of interaction were functionally neutral. As novel underlying mechanisms, functional synergy involved the N-termini and could be ascribed either to increased receptor heteromerisation or affinity to enhance potency (for CCL5-CCL17), or to auxiliary proteoglycan binding preventing receptor internalisation to enhance efficacy (for CCL5-CXCL4). A synthetic covalently-linked CC-type heterodimer (CCL5-CXCL4) with flexible but not tethered N-termini displayed improved synergy. Proximity ligation assays indicated that chemokine heteromerisation can occur *in vivo* and promotes functional receptor heteromers, which can be targeted by receptor peptides. All functional effects

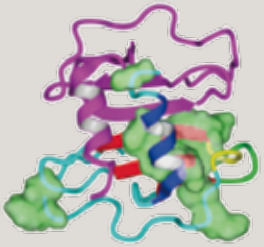
SYNOPTIC SCHEME

interactome mapping



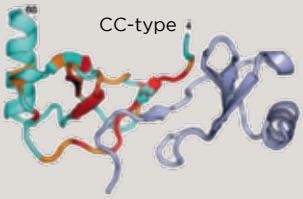
binding characteristics





CXC-type

mechanism
structural changes caused by
reduced receptor activation



CC-type

mechanism
increasedreceptor affinity
and heteromerisation
decreased internationalisation
by proteoglycan binding

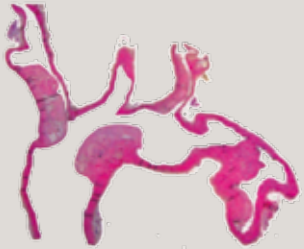
structure by NMR

function

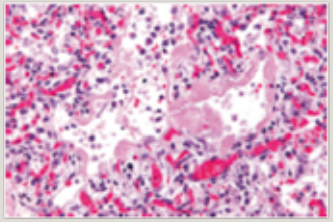
synergy | **inhibition**

specific peptide inhibito | **specific peptide mimetic**

heterodimers as targets in disease models



atherosclerosis acute lung injury



thrombus formation

of chemokine heterodimers could be specifically targeted or mimicked by the respective CCL5 peptides.

EVIDENCE FOR EFFICIENT TARGETING *IN VIVO*

Ultimate evidence for the *in vivo* relevance of chemokine heterodimer formation was provided in a model of LPS-induced acute lung injury. Disease activity, as assessed by neutrophil recruitment, was promoted by the obligate CCL5-CXCL4 heterodimer and inhibited by the peptide inhibitor CKEY, but not by variants with substitutions in residues critical for heterodimer formation.

In an apolipoprotein E-deficient genetic background, mice with a knock-out of CXCL4 and knock-in of the human variant CXCL4L1 not interacting with CCL5 showed reduced atherosclerotic lesion formation, similar to CXCL4-deficient mice. In contrast, atherosclerosis was exacerbated by treatment with the obligate CCL5-CXCL4 heterodimer in apolipoprotein E-deficient mice carrying the non-interactive CXCL4L1 variant or reconstituted with bone marrow genetically deficient in both CCL5 and CXCL4. Atheroprotective effects of CCL17 deficiency, which increases the levels of regulatory T cells, could be phenocopied by the CCL5-derived peptide CAN, specifically disrupting CCL5-CCL17 heterodimers.

Finally, inhibitory effects of a CXC-type interaction (for CCL5-CXCL12) were mimicked by the α-helical CCL5 peptide VREY, which inhibited CXCL12-driven human platelet aggregation and mouse platelet activation and thrombus formation scores *ex vivo*, in a similar way as did CXCL12 deficiency. These effects could be ascribed to structural changes in CXCL12, which likely affect CXCR4 receptor activation.

Taken together, our comprehensive mapping of the chemokine interactom provides a highly valuable resource for many other scientists assessing potential effects and interactions of multiple chemokines in different contexts and microenvironments of health and disease. Further validation and analysis of the structure–function relationship revealed a striking dichotomy between different types of heterodimers, mediating opposite effects. In addition, it allowed specific peptide inhibitors and mimetics to be designed to selectively target or exploit the chemokine heterodimer activities in models of acute and chronic inflammation. Genetic tools and synthetic chemistry helped to unequivocally prove the *in vivo* relevance of chemokine heterodimers. Eventually, our findings could pave the way to a renaissance of peptide therapeutics and the emergence of new options, based on endogenous sequences that are highly selective in modulating only synergistic or inhibitory effects of chemokine heterodimers and not primary chemokine-receptor interactions, and are thus devoid of many side and adverse effects associated with direct inhibition or receptor antagonism.

YOUR ANIMAL EXPERIMENTS ARE IN GOOD HANDS AT THE MUROIDEAN FACILITY

MF STEERING GROUP

All researchers within Maastricht University using small animals have access to the Muroidean Facility, or 'MF'. Muroidea refers to the superfamily of rodents, which include mice and rats (and hamsters, voles, lemmings, gerbils etc.). The zoological technicians in this core facility have extensive experience and expertise in micro-surgery and in phenotyping mice and rats. We work in a client-oriented manner, offering custom solutions with flexibility and efficiency, and can act as a sparring partner in experimental design. As a core facility, we deliver innovative, high quality services.

THE EXPERIMENTAL CYCLE

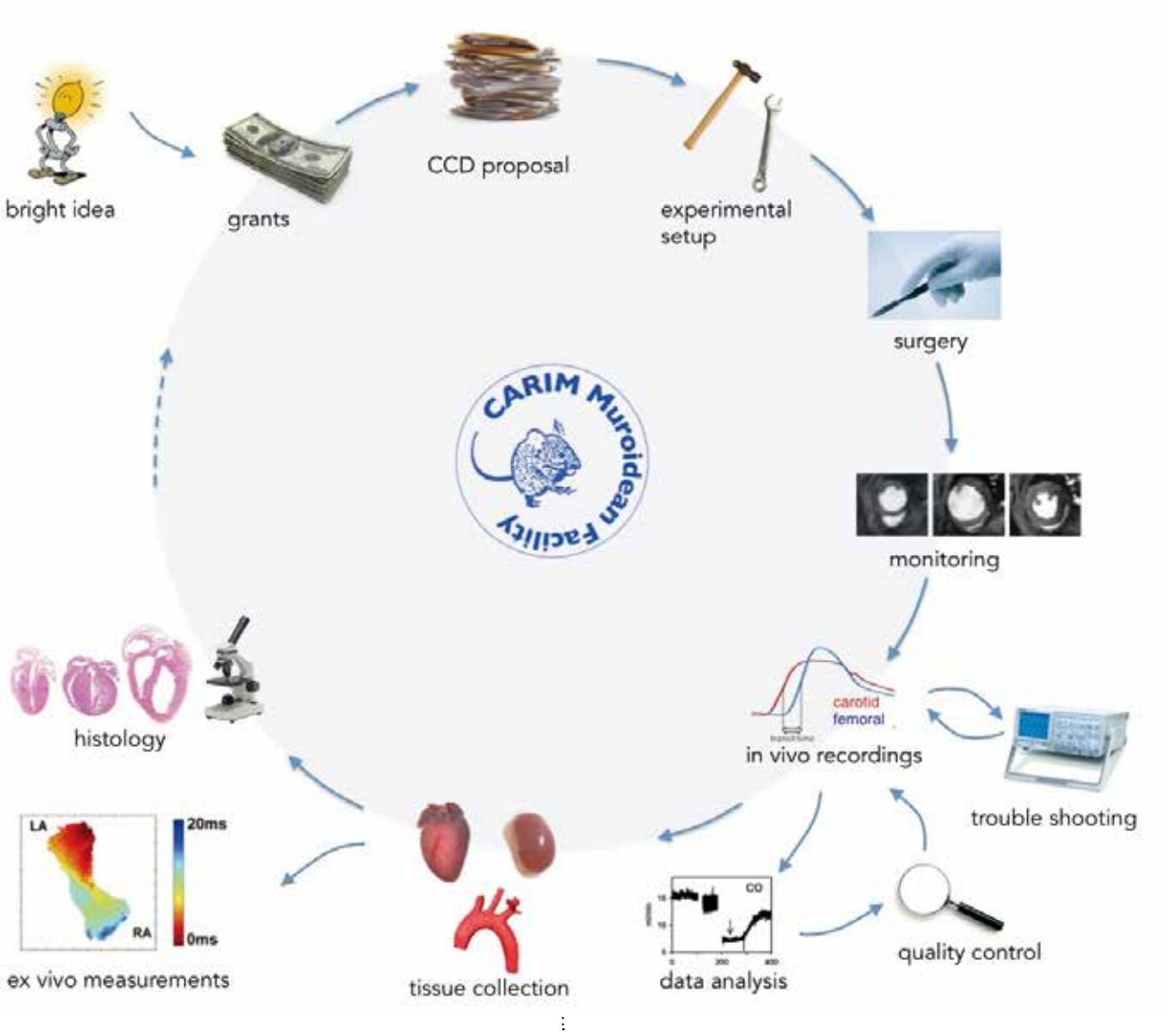
Of course, you will still have to provide the initial bright idea, but the MF can assist in every further step of the experimental cycle (see figure). We can be involved in all aspects from the description of animal experiments in grant proposals, advising on experimental design and animal numbers in CCD (*Centrale Commissie Dierproeven*) protocols, developing or customising experimental setups, surgical procedures to animal monitoring, in vivo recordings, tissue procurement, histology and data analysis.

To complement this range of services, the MF develops new animal models for various kinds of diseases and disorders. To quote one of our technicians: "In addition to cardiovascular disease models such as transverse aortic constriction and myocardial infarction, we also have experience with creating and analysing tumor models and performing bone-marrow transplantation. And now, we are further developing genotyping and histological analyses, to support and streamline the phenotyping aspects of studies. Over the years, researchers have been really impressed by our micro-surgical skills, for instance on small blood vessels in mice. One cannot expect a PhD student to, alongside doing experiments and writing papers, also master complex surgical procedures without compromising the quality or rigor of the work. This is not to say that the student shouldn't receive proper basic training and can't contribute to experiments. However, with our extensive experience and skills we are able to perform the surgery and instrumentation in shorter amount of time, which benefits the animals' well-being and therefore the quality of the experiment and reliability of its outcome. In the end, this really helps to perform high-quality, efficient studies."

COST EFFECTIVENESS

With support of the FHML faculty, our core facility is able to offer rates well below those of commercial companies, comparable to a hourly cost of a PhD student. These low internal rates apply to all researchers within the FHML faculty; other clients pay a higher external rate. Even at the internal rates, it may still appear tempting to have a PhD or postdoc to do basic training in animal work, acquire surgical skills, and carry out animal experiments. However, often such an approach in the end requires more time, money and animals. Moreover, the acquired expertise often disappears again when the PhD student leaves the group, leading to a loss of continuity.

Using a core facility, as opposed to the traditional 'in kind' *quid pro quo* approach, takes some getting used to for many users. For example, it is important to factor in all costs associated with animal experimentation in grant proposals. To this end, we can help at an early stage to discuss experimental design and to provide cost estimates. To facilitate reimbursement by funding organisations, we use an 'audit-proof' time registration system.


bright idea
grants
CCD proposal
experimental setup
surgery
monitoring
in vivo recordings
carotid
femoral
trouble shooting
quality control
data analysis
CO
tissue collection
ex vivo measurements
LA
RA
20ms
0ms
histology
CARIM Muroid Cadan Facility

INNOVATION

Our core facility employs 5 expert zoological technicians, and is guided by a steering group of 5 researchers from different groups within CARIM. The wide range of disciplines covered by the steering group members facilitates innovation with the core facility. In addition to our traditional strength in hemodynamic measurements, we are actively developing new techniques to expand our repertoire. For example, we have recently built an experimental tonometry set up to measure pulse wave velocities in vivo, equivalent to state-of-the-art human arterial stiffness studies. As another novel development, characterisation of cardiac electrophysiology and testing for vulnerability to arrhythmias can be carried out in any transgenic or disease model. We have also started offering tissue embedding, sectioning, staining and histological analysis at competitive prices.

Altogether, we offer precious and promising research tools and approaches and therefore, we expect our services will be valuable to many of our fellow researchers. Don't hesitate to contact us!

More information available at:
www.carimmaastricht.nl/carim-muroidean-facility
Contact us by e-mail: CARIM-MF@maastrichtuniversity.nl

FACTS AND FIGURES

03

FUNDING AND EXPENDITURE AT INSTITUTIONAL LEVEL 2010-2015

	2010	2011	2012	2013	2014	2015
	K€	K€	K€	K€	K€	K€
FUNDING						
Direct Funding structural	8.411	8.242	7.391	7.419	7.500	7.443
Direct Funding specific programs	3.603	2.830	2.717	2.272	1.309	1.492
Total Direct Funding (1)	**12.014**	**11.072**	**10.108**	**9.691**	**8.809**	**8.935**
Research grants (2)	2.140	1.284	1.566	1.730	1.481	1.850
Contract research (3)	9.900	13.202	13.464	13.456	11.117	11.612
	12.040	**14.486**	**15.030**	**15.186**	**12.598**	**13.462**
Total funding	**24.054**	**25.558**	**25.138**	**24.877**	**21.407**	**22.397**
EXPENDITURE						
Personnel costs	15.024	15.984	16.492	17.501	16.343	15.039
Other costs	7.474	7.855	8.475	8.379	6.392	5.986
Total Expenditure	**22.498**	**23.839**	**24.967**	**25.880**	**22.736**	**21.025**
RESULT	**1.556**	**1.719**	**171**	**-1.003**	**-1.328**	**1.372**

(1) Direct funding originating from the University as provided by the Dutch government

(2) Research funds received in competition from national science foundations and governmental organisations e.g. NWO, ZonMW, STW, KNAW

(3) Third party funding received in competition from European Union, Netherlands Heart Foundation, Dutch Kidney Foundation, Industry

RESEARCH OUTPUT IN 2010-2015

	2010	2011	2012	2013	2014	2015
SCHOOL LEVEL						
Scientific publications	544	571	635	605	584	586
Other publications	37	53	80	50	70	48
PhD theses	35	39	50	34	35	43
Total* (I)	**616**	**666**	**765**	**689**	**689**	**677**
Academic staff** (II)	38,3	34,3	33,1	32,4	33,4	32,6
Ratio I and II	16,1	19,4	23,1	21,3	20,6	20,8
THEME I						
Scientific publications	95	107	108	111	109	125
Other publications	6	12	12	13	19	8
PhD theses	5	8	8	7	10	10
Total	**106**	**127**	**128**	**131**	**138**	**143**
THEME II						
Scientific publications	190	214	246	240	239	249
Other publications	6	13	25	20	34	13
PhD theses	9	14	20	17	10	21
Total	**205**	**241**	**291**	**277**	**283**	**283**
THEME III						
Scientific publications	312	309	353	331	313	301
Other publications	25	28	45	22	32	31
PhD theses	21	17	22	12	17	12
Total	**358**	**354**	**420**	**365**	**362**	**344**

* Please note that the sum of the publications in Themes I, II and III exceeds the total number of publications at School level, due to a double counting of publications with authors from different themes ** Academic staff: PhD students and post-docs not included

PhD theses: including PhD theses externally prepared

Scientific publications: Wi-1 publications in refereed SCI-SSCI indexed journal, excluding abstracts, Wi-2 publications in refereed non SCI-SSCI indexed journals, and Letters to the Editor

Other publications: Wn (publications in national journals), Wb (book, or contribution to book, conference papers/proceedings), Vp (professional publications in national or international periodical)

NEW CONTRACTS AND GRANTS CONCLUDED IN 2015

FUNDING	THEME I	THEME II	THEME III	TOTAL SUPPORT
	K€	K€	K€	K€
Type 2	320	2.457	6	2.783
Type 3	647	3.654	1.953	6.254
Type 4	354	1.152	431	1.937
Type 5	250	250	5.050	5.550
Total	**1.571**	**7.513**	**7.439**	**16.523**

Type 2 Grants received in competition from national and international science foundations (NWO/ZonMw, STW, KNAW)

Type 3 Grants received from third parties for specific research activities and from charities (NHS, EU Framework, CTMM, BMM, etc.)

Type 4 Industry, excl. CTCM (turn over in 2015: 2.247 K€)

Type 5 Annual support MUMC+ (750 k€) Cardiovascular Center-CARIM “Pieken in de Breedte” and Maastricht Study Phase 2 (4,8 mln€)

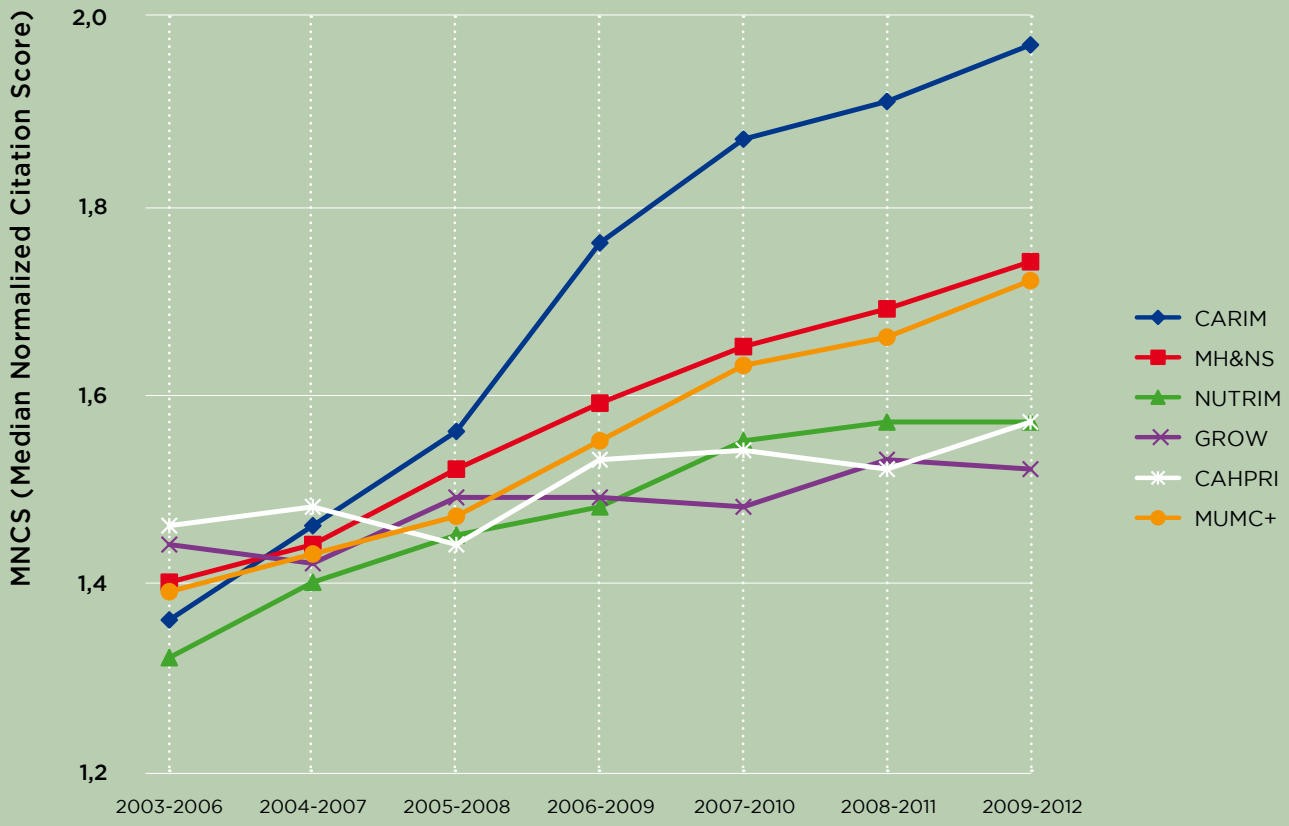
SUMMARY OF SCIENTIFIC AND TECHNICAL STAFF CARIM 2015 (IN FTE)

RESEARCH AREA	WP1			WP2			WP3			WP4			azM	TOTAL
	Faculty	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	FTE
Thrombosis and Haemostasis	7,5	3,1	-	1,0	2,9	2,9	-	8,4	2,9	-	3,8	3,4	1,8	38,5
Complex Arrhythmias and Structural Heart Disease	13,5	4,4	1,1	1,3	5,8	2,4	-	19,3	8,7	1,0	2,6	1,7	5,3	66,0
Vascular Biology and Medicine	11,6	2,9	1,1	0,4	1,7	2,4	0,2	18,9	11,7	-	0,9	1,0	5,2	57,9
TOTAL	**32,6**	**10,3**	**2,2**	**2,6**	**10,3**	**7,7**	**0,2**	**46,6**	**23,3**	**1,0**	**7,3**	**6,1**	**12,3**	**162,3**

RESEARCH AREA	OBP 1	OBP 2	OBP 3	OBP 4	azM	TOTAL
Thrombosis and Haemostasis	4,8	1,0	1,5	1,5	2,2	10,9
Complex Arrhythmias and Structural Heart Disease	14,5	0,5	3,3	-	-	18,3
Vacular Biology and Medicine	11,2	0,2	11,1	2,8	1,9	27,2
TOTAL	**30,5**	**1,7**	**15,9**	**4,3**	**4,1**	**56,4**

WP scientific staff
OBP technical staff
1 University
2 NWO/KNAW
3 non-profit organisations
4 industry
azM University Hospital Maastricht

LOCAL PERFORMANCE CARIM



Source: Bibliometric study on Dutch academic medical centers 1998-2012/2013 – Center for Science & Technology Studies (CWTS) and Dutch Federation of University Medical Centers (NFU)

INTERVIEW
BRAM KROON

When he was taken on at Maastricht by Peter de Leeuw as a young internal medicine specialist some twenty years ago, he probably could not have suspected that he would have become his successor by 2016. “But”, says Bram Kroon, Professor of Vascular Damage in Hypertension “I’m not De Leeuw Mark 2.0. I try to add new aspects to the hypertension research that I initiated partly together with him.” The theme that runs through his entire career is that of helping people. “Even when I was ten I already knew that’s why I wanted to become a doctor. Being able to help even one patient gives me just as much satisfaction as publishing a research paper.”

In recent years, the research into hypertension at the Department of Internal Medicine was led by Peter de Leeuw, and Bram Kroon was his right-hand man. As such, Kroon really misses his mentor now that the latter has formally retired. “The idea is to appoint someone to help me lead the research effort here. We do need that, as the combination of organising and doing scientific research and patient care is very demanding.”

Kroon’s decision to add scientific research to patient care only came after he had completed his internal medicine training. “You can do more for patient care by studying something in-depth. In my case, that was a PhD project investigating lipid metabolism disorders.” He completed the project in 1996, after having worked at Maastricht for just a year. There he helped Peter de Leeuw to set up the Cardiovascular Centre. As De Leeuw’s retirement began to approach, Kroon took over the training of vascular medicine students, and in 2013 he also took over his position (as a temporary appointment at first, and permanently this year) as Principal Investigator (PI) for CARIM. The close bond that developed between them over the years transcends De Leeuw’s retirement. They still see each other regularly, and he also continues to frequent De Leeuw’s holiday cottage in France, where they often used to go with PhD students for some time out to write. “I learned so much from De Leeuw. Such as writing concisely, though I can still learn a lot from him in that respect. But also the way to revitalise a study that has stalled. He’ll then say: ‘We’ve now shone a light on all the data from this side, and now we’re going to do it from the other side.’ In the end, he’s much more than just a colleague, and we still regularly meet up.”

VASCULAR STIFFNESS

On the basis of his great respect and appreciation for the work done by De Leeuw, Kroon intends to expand the research work. The chair he holds is called ‘Vascular Damage in Hypertension’, and he is particularly interested in vascular stiffness. “When you reduce blood pressure, the blood vessels don’t always recover proportionally. We don’t yet have effective medication to tackle the stiffening of the vessel wall.” High blood pressure changes the structure of the blood vessel, resulting in an altered perfusion pattern and other effects in very small vessels, for instance those in the kidney. Even at an early stage this leads to an irrevocable decline of the renal function. “So I think we should focus on preventing vascular stiffness and microvascular damage.”

High blood pressure, the central issue, results in vascular damage, which in turn causes end organ damage (in the

“YOU CAN DO MORE FOR PATIENT CARE BY STUDYING SOMETHING IN-DEPTH”

brain, the kidneys and the heart). Kroon's research covers this entire chain of events. "A nice broad scope, as you might expect in internal medicine", he smiles. CARIM's cardiovascular focus, providing an essential link between the various disciplines, is very helpful. "I mostly do studies on patients, and I think the available patient cohorts can be used for research even more than is now the case. Not just for me but for all CARIM researchers. And I would also like to add more animal experiments to the ones we're already doing together with Leon Schurgers at the Biochemistry department, to study calcium deposits in blood vessels in greater detail."

BUILDING BRIDGES

As a physician, he recognises the value of linking clinical and preclinical work, and by coordinating the "Hypertension and Vascular Damage" research line together with Maastricht University researcher Koen Reesink (from the Biomedical Technology department), he hopes to strengthen this link. But he also regards building bridges between primary and secondary care (i.e. general practice and peripheral hospitals) and between secondary and tertiary care (university hospitals) as an important mission. "Our university hospital also functions as a regional hospital for the city, which I think makes it unique. For a number of years, I've been trying to offer patients something in between primary and secondary care. Working together with GPs enables patients with low-complexity problems to be treated in general practice. And by collaborating with peripheral hospitals we can achieve that some of the more complex cases are treated there, and only the really complex treatments take place here."

These complex treatments include implanting a *baropacer* to lower blood pressure through electrical stimulation (baroreflex activation therapy). De Leeuw and Kroon recognised the potential value of this technique in 2003, and now, after many further studies, care insurers are on the verge of reimbursing this therapy as part of regular care. Kroon now has the rewarding task of enabling more university hospitals around the country to start implanting this device. "But it's also possible to reduce blood pressure mechanically, by means of a stent in the carotid artery. We have just contributed to the first human studies into this option. Half of the thirty participating patients were operated upon in the Netherlands, placing us in the vanguard of this field. We're also very interested in ablation of the nerves in the wall of the renal arteries, which is known as renal denervation. These kinds of new techniques always have to be linked to clinical studies."

SATISFACTION

The research group Kroon is currently coordinating consists of five PhD students, three of whom are full-time researchers and the other two are clinicians. He also enjoys doing the outpatient clinical hours: "I wouldn't want to miss that. You get so much satisfaction out of helping just one patient with therapy-resistant hypertension. To me, that's just as valuable as getting a research paper published. Even as a youngster I knew I wanted to help people. And it may sound simplistic, but that's still what I want. You hope to achieve that on a large scale by means of scientific research of course, but I find the contact with patients very gratifying."

At the end of a working day he often dons his running shoes to make his way home, a distance of twelve kilometres. And each year he runs one or two marathons, like the one in Valencia this autumn. It completely clears his head: just what he needs to keep up the marathon at work.

HIGHLIGHT THEME II

KEVIN VERNOOY

DEPARTMENT OF CARDIOLOGY

Improving device therapy in heart failure patients

Up to one-third of patients with heart failure have concomitant ventricular conduction disturbances, evidenced by a wide QRS complex on ECG. In recent decades, cardiac resynchronisation therapy has been shown to be one of the most effective treatments for patients with heart failure and ventricular conduction disturbances, especially left bundle branch block (LBBB). Large trials have shown that CRT improves prognosis and reduces symptoms and the number of hospitalisations due to heart failure. CRT involves implanting a device with two ventricular pacing leads that aims to restore the dyssynchronous ventricular activation by biventricular stimulation (figure 1). At present, approximately 3000 CRT devices are being implanted in the Netherlands each year. However, the clinical response to CRT varies considerably. Factors that are held responsible for this variation are the selection of patients and the positioning of the left ventricular (LV) pacing lead.

An important issue in selecting patients for CRT is that the criteria used to define LBBB differ between European and American guidelines, and between various large clinical trials or studies that have investigated LBBB as a predictor of CRT response. As a consequence, it is currently not clear whether QRS duration or morphology should be preferred as the primary marker to select which patients will benefit from CRT. QRS duration may not be specific, but LBBB criteria may be too complex. In order to try and solve these issues, we returned to the basic physiology of ventricular dyssynchrony and the mechanism of CRT.

Delayed LV activation is considered to be the underlying substrate amenable to ventricular resynchronisation. Paced pre-excitation of the delayed activated LV free wall aims to restore a synchronous ventricular electrical activation and contraction. In animal experimental studies we have confirmed that CRT creates a more synchronous contraction pattern in hearts with delayed LV activation due to LBBB, resulting in marked hemodynamic improvement. The clinical importance of delayed LV activation has become evident in studies showing that a greater delay between the onset of the QRS complex and the local activation at the LV pacing site is associated with a greater likelihood of benefit from CRT. This has supported the notion that an electrical substrate, consisting of a sufficient amount of LV activation delay, needs to be present for CRT to be effective.

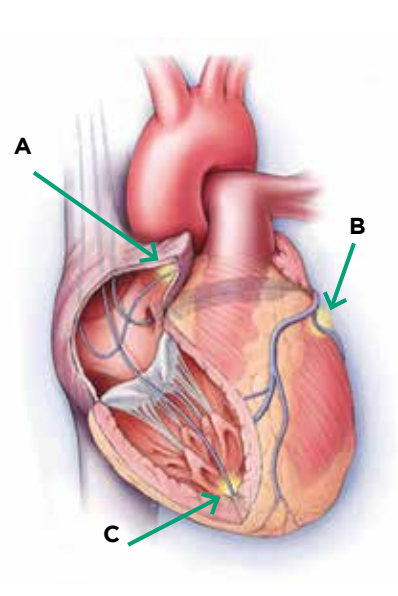


FIGURE 1

Positioning of pacing leads in cardiac resynchronisation therapy. Conventional pacemakers are equipped with two pacing leads, i.e. the right atrial (A) and right ventricular leads (C). In CRT, a third lead is placed at the left ventricular free wall (B). Combining all three leads aims to create a synchronised contraction of the ventricles.

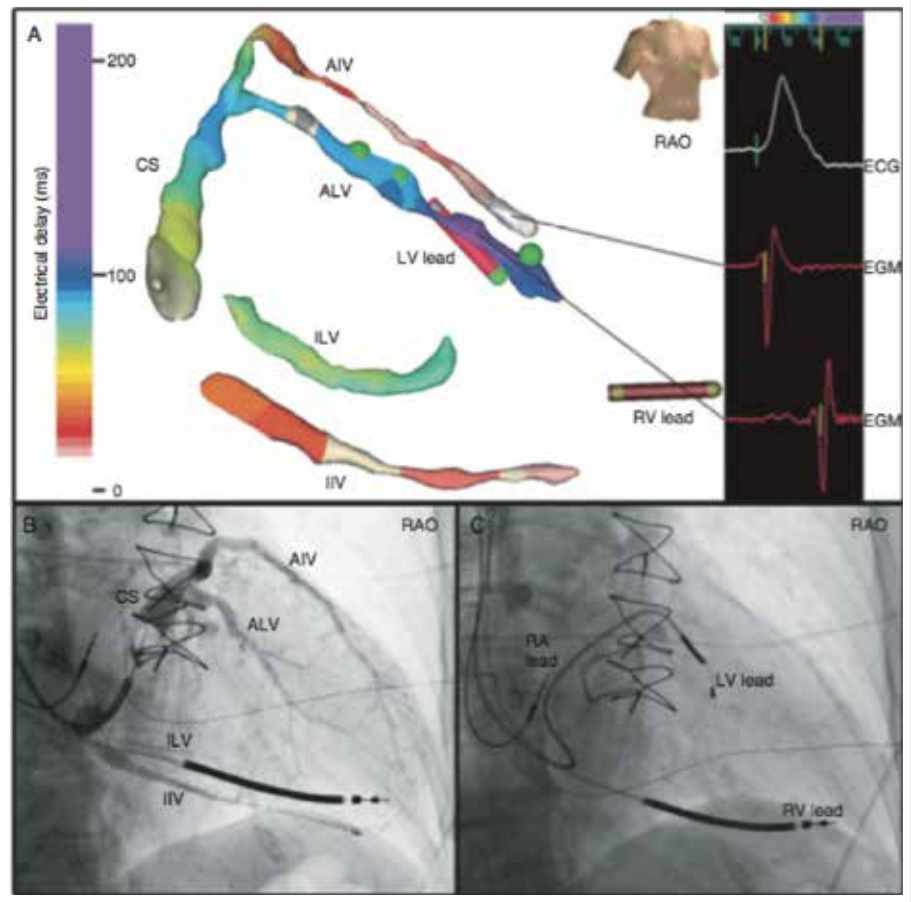


FIGURE 2

Coronary venous electro-anatomic mapping of the ventricular activation in a patient with left bundle branch block, together with the corresponding unipolar electrograms collected from the regions of earliest and latest ventricular activation. The coronary vein and all side branches have been mapped in this example. The bottom images show the angiogram of the coronary venous system (left) with the final lead positions (right).

HIGHLIGHT THEME II

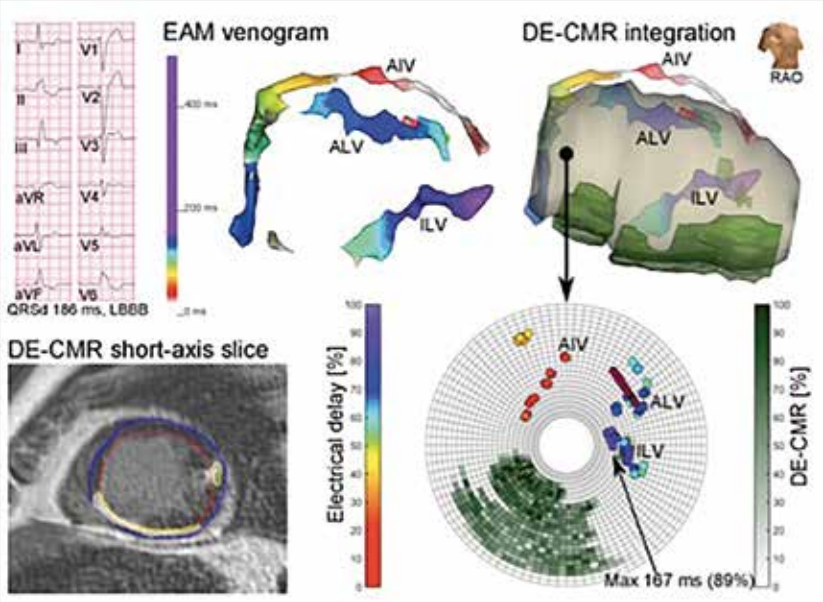


FIGURE 3
An example of image integration of delayed enhanced cardiac MR (DE-CMR) with electro-anatomic mapping (EAM) in a 65-year old man with left bundle branch block (LBBB). The inferolateral vein (ILV) was activated latest, but was shown to be located in scar by DE-CMR integration (96-segment/slice bullseye). The LV lead was therefore positioned in the anterolateral vein (ALV) outside scar.

Although different methods are available to determine delayed LV contraction (ECG, echocardiography, cardiac MRI, etc.), the most accurate way to evaluate this is by invasive electrical mapping. In our center, we have started to apply a new approach by using 3D electro-anatomic mapping during the CRT implantation procedure, in such a way that the procedure time is hardly prolonged, without increasing the invasiveness of the procedure. A guidewire that allows for unipolar sensing and pacing is connected to an EnSite NavX system (St. Jude Medical) and manipulated through the various coronary veins to create an anatomic map along with local electrical activation times (Figure 2). In this mapping study of 60 patients at MUMC we were able to show that both QRS duration and QRS morphology were inadequate in identifying patients with delayed LV activation.

Another issue in CRT is that pacing in or near scar has been shown to diminish the effectiveness of the therapy. Since coronary heart disease is a major cause of heart failure, the presence of scar in CRT candidates is an important issue. Previous studies have shown that the best hemodynamic effect of CRT is achieved when the LV lead is located as far as possible from both scar and septum. We therefore tried to incorporate scar imaging by delayed enhanced Cardiac MRI with electro-anatomic coronary venous mapping, and were the first to show that this is feasible during CRT implantation (figure 3).

While electro-anatomic mapping certainly improves the characterisation of the 'electrical substrate' for CRT, and can improve the positioning of the LV lead, this can only be applied after the decision to use CRT implantation has been

made. There is therefore a need for better predictors that can be assessed before CRT implantation, as QRS duration and morphology seem to be inadequate. Recently, we have explored the value of the reconstructed vectorcardiogram (VCG) for characterising the electrical substrate and predicting CRT response. VCG contains 3D information about the electrical forces within the heart, which might provide more valuable information than the ECG (figure 4). We hypothesised that electrical dyssynchrony would lead to large unopposed electrical forces during ventricular depolarisation, and that ventricular dyssynchrony may be well represented by the QRS_{AREA}, the area of the QRS complex in three directions. We showed that the QRS_{AREA} was associated with the CRT response in a prospective group of 80 CRT patients at our centre, and this is currently being investigated in a large Dutch multicentre study. Moreover, QRS_{AREA} predicted CRT response better than QRS duration or LBBB QRS morphology. We also showed that a large QRS_{AREA} was highly predictive of the presence of delayed LV activation as determined by coronary venous electro-anatomic mapping.

The great practical benefit of QRS_{AREA} is that this parameter is measured in an objective manner and quantified as continuous variables, as opposed to LBBB, which is a dichotomous measurement that is subject to the use of different definitions and subjective interpretations. Another practical benefit of QRS_{AREA} is that it can easily be derived from the standard 12-lead ECG. The next step in our research is thus to confirm the predictive value of the QRS_{AREA} in a large multicenter CRT trial. We think that if that study yields positive results, QRS_{AREA} is ready to be adopted in routine clinical practice.

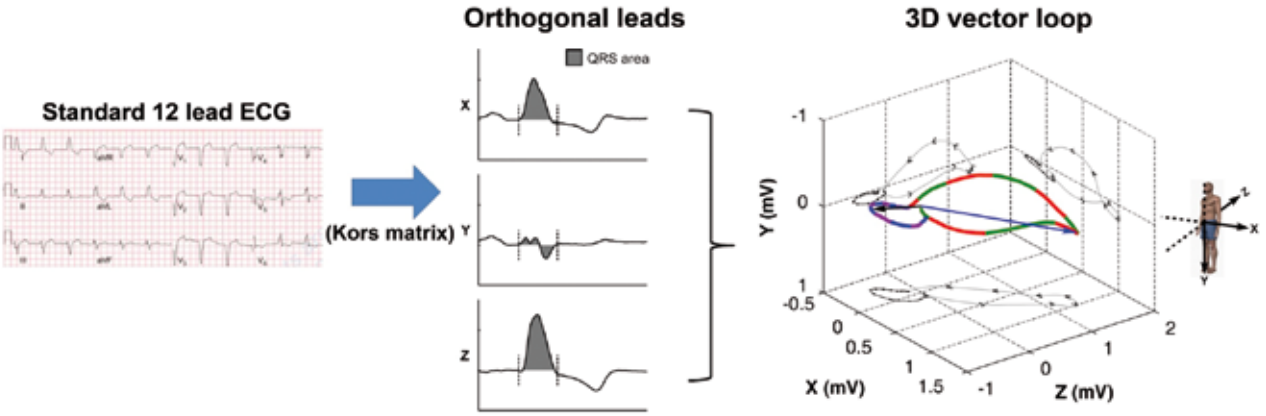


FIGURE 4 Example of a vectorcardiogram consisting of the three orthogonal leads X, Y and Z (middle) derived from the standard 12-lead ECG (left), which together form a 3D vector loop (right). The green/red loop represents the QRS vector loop, and the blue/purple loop the T vector loop. The QRSAREA is calculated using the integral between the ventricular deflection curve and the baseline from beginning to end of QRS in leads X, Y, and Z.

SOCIETAL IMPACT OF RESEARCH ON ELECTRO-MECHANICS OF THE HEART

FRITS PRINZEN, DEPARTMENT OF PHYSIOLOGY

When within a short period of time

1 animal activists protest against your experiments,
2 the university forces you to stop those experiments,
3 the local newspaper spends a 2-page interview about your work and
4 you get a phone call from the grandmother of the first patient benefiting from 'your' therapy to thank you.....
... you know that your research has societal impact,
... albeit not always in the way you like.

An important phase in this research line was my sabbatical leave at the Johns Hopkins University, 20 years ago, where for the first time MRI tagging studies were performed in the paced (animal) heart. We were able to determine the enormous regional differences in mechanical loading within a paced heart. This resulted in a still frequently cited article in *JACC*[1].

In subsequent years we continued to contribute to the evidence that the conventional pacemakers create abnormal contraction patterns and, while correcting heart rate, created a loss of pump function. And we sought for better sites for ventricular pacing, in order to avoid these problems. In 2003 we published the first evidence in animal experiments that pacing at the apex (=tip) of the left ventricle (LV) or at the left side of the interventricular septum provides the best pump function[2]. In 2007 we published in the *New England Journal of Medicine* how LV apex pacing cured one child[3] and this was confirmed five years later in a large clinical trial, published in *Circulation*[4]. Currently, proper positioning of the pacemaker electrode in children is almost routine around the world, as shown for example by an article from Cuba[5].

Together with the Bakken Research Center Medtronic we developed (and patented) a novel pacemaker electrode that can be implanted chronically at the LV septum in a very easy way. We demonstrated feasibility and functional excellence in chronic animals in 2009. It took a few years to achieve sufficient permission to move to a first-in-man study. When the permission was granted in 2012, the study was performed by Dr Kevin Vernooy and colleagues in the MUMC+ and was completed in 2015. The article, in *Circulation Arrhythmia and Electrophysiology*, was selected as the 'editor's pick' in the issue where it appeared[6]. Currently we are preparing further continuation of the development of LV septal pacing in patients.
Another aspect of research is that sometimes the results

1 Prinzen FW, Hunter WC, Wyman BT and McVeigh ER. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using Magnetic Resonance Imaging tagging. J Am Coll Cardiol. 1999;33:1735-1742.

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3 Vanagt WY, Prinzen FW and Delhaas T. Reversal of pacing-induced heart failure by left ventricular apical pacing. N Engl J Med. 2007 357:2637-8.

4 Janoušek J, van Geldorp IE, Krupičková S, Rosenthal E, Nugent K, Tomaske M, Früh A, Elders J, Hiippala A, Kerst G, Gebauer RA, Kubuš P, Frias P, Gabbarini F, Clur SA, Nagel B, Ganame J, Papagiannis J, Marek J, Tisma-Dupanovic S, Tsao S, Nürnberg JH, Wren C, Friedberg M, de Guillebon M, Volaufova J, Prinzen FW, Delhaas T and Cardiology. WGfCDaEotAfEP. Permanent cardiac pacing in children: choosing the optimal pacing site: a multicenter study. Circulation. 2013;127:613-23.

5 Cabrera Ortega M, Morejón AEG and Ricardo GS. Left Ventricular Synchrony and Function in Pediatric Patients with Definitive Pacemakers. Arq Bras Cardiol. 2013;101:410-417.

6 Mafi-Rad M, Luermans JG, Blaauw Y, Janssen M, Crijns HJ, Prinzen FW and Vernooy K. Feasibility and Acute Hemodynamic Effect of Left Ventricular Septal Pacing by Transvenous Approach Through the Interventricular Septum. Circ Arrhythm Electrophysiol. 2016;9:e003344. doi: 10.1161/CIRCEP.115.003344.

open up an entirely new and previously unexpected field. The animal research on ventricular pacing increased the awareness that any abnormal ventricular conduction has an adverse effect on function of the heart. Clinical studies showed that this is particularly true in patients with heart failure. A novel pacemaker therapy (cardiac resynchronisation therapy, CRT) evolved in the late 1990's. In a selected subgroup of heart failure patients CRT significantly improves quality of life and prolongs life expectancy. Our research group contributed significantly to this field[7,8].

One of the interesting achievements during the last years is the finding that the 3-dimensional vectorcardiogram (VCG) can be calculated from the regular 12-lead ECG and that this VCG provides better clues for application of CRT than the regular ECG. Because such VCG measurements are non-invasive and can be performed in every center, these findings will have major clinical impact. Due to this experience, we are currently the core-lab ECG and VCG for two clinical trials. We also achieved a valorisation grant from the 'Center for Translational Molecular Medicine' for further development of concepts derived from our understanding of the VCG.

Moreover, close collaboration with the Department of Biomedical Engineering resulted in the use and rapid further development of the CircAdapt computer program for CRT research, solving questions like how to optimize CRT and development of a new echocardiographic parameter for better selection of candidates for CRT (collaboration with Prof. Tammo Delhaas and Dr Joost Lumens). Several publications[9,10] describe studies that are close to clinical trials and approach the goals described in the Avicenna document on "how computer simulations will transform the biomedical industry". The CircAdapt program is also currently adopted and coupled to programs of other computer scientists. A simplified version is publically available and frequently used for teaching (bio)medical students (www.circadapt.org).

With all the experience in the field of CRT, Prof. Prinzen participated in the committee writing the '2012 Expert Consensus Statement for CRT', of EHRA/HRS, the European and American organisations for cardiac arrhythmia. This statement supports the guidelines for professionals in the field. As of 2014 he is the chairman of the EHRA Innovation Committee.

Dr Lumens is member of the working group on eCardiology of the ESC. In this working group all novel digital technologies, for therapies and training in cardiology, are discussed and stimulated, ranging from information provided by smart phones to computer models.

The extensive international network also leads to close scientific collaboration with, among others, the Universities of Lugano and Bordeaux, resulting in many

7 Prinzen FW, Vernooy K and Auricchio A. Cardiac resynchronization therapy: state-of-the-art of current applications, guidelines, ongoing trials, and areas of controversy. Circulation. 2013;128:2407-2418.

8 Vernooy K, van Deursen CJ, Strik M and Prinzen FW. Strategies to improve cardiac resynchronization therapy. Nat Rev Cardiol 2014;doi: 10.1038/nrcardio.2014.67.

9 Leenders GE, Lumens J, Cramer MJ, De Boeck BWL, Doevendans PA, Delhaas T and Prinzen FW. Septal deformation patterns delineate mechanical dyssynchrony and regional differences in contractility: analysis of patient data using a computer model. Circulation: Heart Failure. 2012;5:87-96.

10 Lumens J, Ploux S, Strik M, Gorcsan Jr, Cochet H, Derval N, Strom M, Ramanathan C, Ritter P, Haïssaguerre M, Jaïs P, Arts T, Delhaas T, Prinzen FW and Bordachar P. Comparative electromechanical and hemodynamic effects of left ventricular and biventricular pacing in dyssynchronous heart failure: electrical resynchronization versus left-right ventricular interaction. J Am Coll Cardiol 2013.

joint publications, exchange of young investigators and visiting professorships. The broader societal impact of the research group is also expressed by a large number of scientific grants and industry contracts, as well as the five personal ('Dekker') grants provided by the 'Netherlands Heart Foundation'. Finally, members of the team frequently give talks for health care professionals, including allied professionals, and for organizations of heart failure patients.

The abovementioned history of research on pacing therapies may be characteristic for many medical discoveries: starting in experimental animals and continuing on to patients. Even though in this particular case the line was fairly straightforward, it took more than a decade to come from animal research to clinical application. Nevertheless, these important medical developments would not have been possible without animal experiments. Notably, these studies were performed in a species of which the heart is most similar to man, being the dog.

Experiments in dogs are a sensitive topic to the general public, related to the strokability of these animals. However, there was considerable literature and experience from the own laboratory that effects of ventricular pacing were significantly different when testing in other large animals, like pigs and goats. Therefore, doing the studies in dogs was the only way to reach the goal of a better treatment for pacemaker patients.

The ethical question raises whether it ethically acceptable to take a dog's life to save a human life. A university employee, commenting on the discussions about the dog experiments, addressed this question impressively: "I have a dog and I have been diagnosed with heart failure. I really love my dog, but if I have to choose between his life or mine, I chose mine." Of course, it is the heavy responsibility of the investigator to perform the experiments in the most ethical way, more specifically respecting the three 'R's': replacement (if possible), reduction and refinement. In addition, it is the joint responsibility of the investigator and the university to be pro-active and inform the public sufficiently and preferably ahead of time, to explain why such studies are performed. Here clearly some work is to be done.

EVENTS AND HIGHLIGHTS

04

SCIENTIFIC HIGHLIGHTS

In 2015, the hard work of our researchers paid off in 586 scientific publications in peer refereed journals (522 WI-1 publications, excluding abstracts and 29 letters to the editor, 43 PhD theses, 4 patents and 2.8 million Euros funding received in competition from national and international science foundations and 8.2 million Euros funding from third money parties, charities, EU-framework programs, industry, etc. In 2015, the overall average Impact Factor is 4.9.

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RESEARCHERS GRANTS AWARDED TO INDIVIDUALS

In this part we present most of the CARIM researchers that were successful in obtaining projects and personal grants.

NWO TALENT SCHEME

Prof. **Leon de Windt** (Dept. of Cardiology) received a **Vici grant** of 1.5 million Euros from NWO for his research. The funding will enable him to perform his research for the next five years and to build up his own research group.

In his Vici proposal 'EXPERT: EXploiting non-coding RNA Pathways for novel diagnostics and thERapeuTics in heart failure', Leon de Windt and coworkers will first establish the cause-effect relationship between biological mechanisms underlying one specific subtype of heart failure, discover new diagnostic tools in defined clinical cohorts and use antisense oligonucleotide technology to design fundamentally new classes of drugs aimed to ameliorate this subtype of heart failure. For the execution of his Vici grant, Leon de Windt will closely collaborate with high profile research groups in Germany and Italy, as well as scientists in MERLN Institute for Technology-Inspired Regenerative Medicine and Maastricht Centre for Systems Biology. Leon de Windt previously received a Veni grant (2001) and a Vidi grant (2007), making the Veni-Vidi-Vici Talent scheme cycle complete with the award of this most recent Vici grant.

Dr **Jordi Heijman** (Dept. of Cardiology) received one of the 23 **Veni grants** awarded in the field of medicine by the Netherlands Organisation for Scientific Research (NWO) for his proposal 'Understanding the rhythms of the heart: integrative computational modeling of cardiac arrhythmogenesis'. Cardiomyocyte Ca^{2+} handling has emerged as a critical determinant of cardiac electrophysiology, contractility, development and remodeling. Through all these processes, Ca^{2+} also modulates the likelihood of various arrhythmias. However, it remains unclear exactly which Ca^{2+}-dependent processes are harmful. The goal of Jordi's project is therefore to develop an integrative computational analysis of the various roles Ca^{2+} plays in the initiation, maintenance, and progression of cardiac arrhythmias. These models will be based on new experimental confocal Ca^{2+}-imaging and patch-clamp data. Insights obtained from this analysis may facilitate the development of improved therapeutic options for patients with heart rhythm disorders. (See page 82 for a full interview with Jordi Heijman).

NWO ASPASIA

Dr **Ingrid Dijkgraaf** (Dept. of Biochemistry) and Dr **Blanche Schroen** (Dept. of Cardiology) both received a NWO Aspasia grant following their Vidi fellowships. Aspasia provides grants (100.000 Euros) to help more female scientists progress to associate and full professorships. Aspasia is

linked to the Vidi and Vici competitions of the NWO Talent Scheme.

NHS DR E. DEKKER PROGRAM

All 2015 NHS Dr E Dekker Senior Postdoc grants and the Established Investigator grant have been awarded to CARIM researchers. Dr **Joost Lumens** (Dept. of Biomedical Engineering), Dr **Judith Cosemans** (Dept. of Biochemistry) and Dr **Anna Papageorgiou** (Dept. of Cardiology) were awarded a Senior Postdoc grant, while the Established Investigator grant has been awarded to Dr **Paula da Costa Martins** (Dept. of Cardiology). Earlier in 2015, Dr **Marc Strik** (Dept. of Physiology) and Dr **Martijn Brouwers** (Dept. Internal Medicine) received a Cardiologist in Training Dekker grant and Junior Specialist Dekker grant.
See page 62 for information on the individual research projects and a full interview with the laureates.

KOOTSTRA FELLOWSHIPS

During the first round of the Kootstra Talent Fellowships 2015, **Andrea Raso** (Dept. of Cardiology) was granted a fellowship, followed by a fellowship for **Job Verdonschot** (Dept. of Cardiology) during the second round. The Kootstra Talent Fellowships are granted to young scientific talents by the Board of Maastricht UMC+ with the aim to support developing their scientific career. The fellowship is meant to provide financial support for young researchers to bridge the time between graduation in Medicine, Health or Life Sciences and the start of a PhD, between the graduation of the PhD student and the start of an official contract as a postdoc or enable them to combine their studies in Medicine, Health or Life Sciences with an active involvement in scientific research.

MARIE CURIE FELLOWSHIP

Martina Calore (Dept. of Cardiology) received a Marie Sklodowska-Curie fellowship for her project 'MicroRNAs as therapeutic targets for ARVC (MIRAGE)'. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a hereditary disease mainly characterised by the progressive substitution of the myocardium with fatty or fibro-fatty tissue involving predominantly the right ventricle. Clinically, ARVC shows wide variation between individuals. Together with modifier genes, common sequence variants, and environmental as well as endogenous factors, epigenetic modifiers such as microRNAs are hypothesized to be potential targets for disadvantageous environmental stimuli and may lead to the onset of complex and heterogeneous diseases such as ARVC. The main research objective is to assess and validate the relevance of disease mechanisms underlying the development of ARVC and to identify novel RNA-based targets in mouse models and ARVC patients.

OTHER AWARDS, PRIZES AND GRANTS

In 2015, many CARIM researchers were awarded with other grants, prizes and awards. Below, some of them are highlighted.

CVON GRANT RACE V FUNDED

The Dutch Heart Foundation invests 5 million Euros (CVON grant) in a research project on atrial fibrillation 'Reappraisal of Atrial Fibrillation: Interaction between hypercoagulability, Electrical Remodeling, and Vascular Destabilisation in the Progression of AF (RACE V)'. The research project is supervised by Prof. **Uli Schotten** (CARIM, Dept. of Physiology) and Prof. Isabelle van Gelder (UMC Groningen,

Dept. of Cardiology). A group of people from Leiden University is also involved. In Maastricht, the following people are engaged in the project: Prof. **Harry Crijns** (Dept. of Cardiology), Prof. **Hugo ten Cate** and Dr **Henri Spronk** (Dept. of Biochemistry), Prof. **Martin Prins** (Dept. of Epidemiology) and Prof. **Monika Stoll** (Cardiovascular Systems Medicine). (See page 14 for a full interview with Harry Crijns and Henri Spronk).

STEPHANE HEYMANS RECEIVES ESC OUTSTANDING ACHIEVEMENT AWARD

On August 30, Prof. **Stephane Heymans** (Dept. of Cardiology) received the Outstanding Achievement Award 2015 from the European Society of Cardiology (ESC) Council on Basic Cardiovascular Science. This prize is given by the ESC

to researchers with an outstanding achievement in the early stage of their career. The award is presented during the yearly ESC Congress in London.

EU HORIZON 2020 PROJECT ROBERT VAN OOSTENBRUGGE AND JULIE STAALS FUNDED

The project of which Prof. **Robert van Oostenbrugge** and Dr **Julie Staals** (Dept. of Neurology) are collaborators is funded by EU-HORIZON 2020. Both are part of a consortium led by the Ludwig Maximilian Universiy in Munich that applied for funding of their project 'SVDs@target (SVDs-at-target) – cerebral small vessel diseases in a mechanistic perspective: Targets for Intervention'.

Cerebral small vessel diseases (SVDs) are a major cause of stroke and dementia, and yet there is no targeted treatment. Progress in understanding the mechanisms that drive microvascular dysfunction and brain damage in SVDs has been elusive, until now. SVDs@target proposes a coordinated programme to elucidate key mechanisms common to different SVDs, and determine how these mechanisms contribute to individual SVDs. The overall aim is to identify novel targets for prevention and therapy where none currently exist.

At CARIM, clinical studies with patients with manifest cerebral small vessel disease as well as animal studies into the role of inflammation in the development and progression of cerebral small vessel disease are performed.

SERVIER RESEARCH GRANT SÉBASTIEN FOULQUIER

Dr **Sébastien Foulquier** (Dept. of Pathology) has received the 2015 Servier Research Grant in Hypertension during the ESH meeting in Milan. The Award Committee of the European Society of Hypertension has found the research proposal most interesting and has classified Sébastien first among the applicants to the 2015 Servier Research Grant.

LEDUCQ TRANSATLANTIC NETWORK AND ZONMW MEER KENNIS MINDER DIEREN JUDITH SLUIMER

The Leducq Foundation has awarded 6 million US dollar for a transatlantic network of excellence entitled 'Modulating autophagy to treat cardiovascular disease'. Dr **Judith Sluimer** (Dept. of Pathology) is one of eight European and American core members, including world-class investigators Dr Beth Levine, Dr Ana Maria Cuervo and Dr Guido Kroemer. Autophagy is an intracellular process to recycle nutrients and macromolecules. The goal of this network is to delineate the role and therapeutic potential to modulate macroautophagy, mitophagy and chaperone-mediated autophagy in cardiovascular disease. Judith will receive 350.000$ to study autophagy in atherosclerosis.

Furthermore, ZonMW has awarded Dr Judith Sluimer 5.570€ in the framework of the program 'Meer kennis met minder dieren' (more knowledge using fewer animals). The goal of this program is to stimulate open-access publication of negative or neutral animal experiments.

ATVB AWARD JUDITH COSEMANS

Dr **Judith Cosemans** (Dept. of Biochemistry) is the 2015 recipient of the Karl Link Early Career Investigator Award in Thrombosis, for her article 'Factor XII Regulates the Pathological Process of Thrombus Formation on Ruptured Plaques' (Arterioscler Thromb Vasc Biol. 2014;34:1674–1680). The *ATVB* Awards recognised articles published in *ATVB* in 2014 that were submitted by new investigators and judged to be the most outstanding in the Atherosclerosis/ Lipoprotein, Thrombosis, and Vascular Biology sections of the journal.

ISTH-EHA JOINT FELLOWSHIP PAOLA VAN DER MEIJDEN

Dr **Paola van der Meijden** (Dept. of Biochemistry) has been awarded an ISTH-EHA Joint Fellowship. The EHA-ISTH Joint Fellowship is a collaborative program between EHA and the International Society of Thrombosis and Haemostasis. It

provided a grant of 50.000 Euros per year for a maximum of two years to fellows who are pursuing projects in studying the physiology of coagulation, bleeding or thrombosis. Paola focusses on translational research in the field of thrombosis and haemostasis, bridging cellular aspects (particularly platelets) with clinical aspects and patient care. With the Fellowship she hopes to gain new insights into the determinants of bleeding in patients with thrombocytopenia due to hematological malignancies and chemotherapy. By developing new animal models and translating the animal work to patient diagnosis and treatment, she would be able to acquire expert knowledge on the risk assessment of bleeding and transfusion strategy in acquired thrombocytopenia. Furthermore, this fellowship supports her in her pursuit to become an independent researcher within the institute and to further extend her own line of research.

1.6 MLN EU GRANT FOR CLINICAL TRIALS OF 5 MINUTE HEART ATTACK TEST FOR FABPULOUS

The European Union awarded FABPulous BV a 1.6 million Euros Phase 2 grant to fund two clinical trials in the UK and Belgium/Netherlands and automate the manufacture of its 5 minute, patented H-FABP True Rapid Test®, which helps emergency medical workers quickly distinguish whether a patient with chest pain is at risk of a heart attack.

GERT VAN MONTFRANSPRIJS BART SPRONCK

The evening before the National Hypertension Congress**,** **Bart Spronck** (Dept. of Biomedical Engineering) won the Gert van Montfansprijs for best paper on hypertension (*Journal of Hypertension*) by a young researcher: ‘Pressure-dependence of arterial stiffness: potential clinical implications’. Authors: Bart Spronck, Maarten Heusinkveld, Floris Vanmolkot, Jos Op ’t Roodt, Evelien Hermeling, Tammo Delhaas, Bram Kroon and Koen Reesink.

12TH ANNUAL EDWARD JAMES OLMOS AWARD FOR ADVOCACY IN AMPUTATION NICOLAAS SCHAPER

Dr **Nicolaas Schaper** (Dept. of Internal Medicine) has won the Edward James Olmos Award for Advocacy in Amputation Prevention during the 13th Annual Diabetic Foot Global Conference (DFCon) in Los Angeles. The award is named in honor of the celebrated actor and director Edward James Olmos, who has been active in raising awareness of the ravages of diabetes and the importance of limb preservation in the Latino community. “Dr Schaper’s work demonstrates both the dedication to patient-oriented research and clinical care and the national and international scope of leadership that the Edward James Olmos award was created to honor,” said Dr Andros. “He has made a direct impact in the care and treatment of the diabetic foot, with the ultimate result being to give hope to patients who thought they were out of options.”

MARJO DONNERS RECEIVES BAYER SUPPORT GRANT

Within the Grants4Targets Initiative, Bayer HealthCare allocates grants for the exploration of attractive, novel drug targets and biomarkers. Dr **Marjo Donners** (Dept. of Pathology) has received a Support grant of 10.000 Euros for a phage display approach to select ADAM10 antibodies for therapeutic intervention in cardiovascular diseases.

Monika Rech, **Kristiaan Wouters**, **Ana Casas** and others have received YOUNG INVESTIGATOR AWARDS from several organisations.

Ana Casas - Young Investigator Award 7th International Conference ‘Cyclic GMP: Sources, Targets and Therapeutic Implications’

Monika Rech – Bill Stanley young investigator award at the 13th annual meeting of the Society for heart and vascular metabolism in New York

Kristiaan Wouters – Terpstra Young Investigator Award during annual meeting of the NVDO

OTHER HIGHLIGHTS

NEW START-UP FOR THE DEVELOPMENT OF MICRORNA THERAPIES FOR CARDIOVASCULAR AND METABOLIC DISORDERS

Mirabilis Therapeutics BV (Mirabilis) is a Maastricht based start-up biotechnology company that is dedicated to the early development of microRNA-based therapies for cardiovascular and metabolic disorders. The main objective of Mirabilis is the development of new molecules to silence or enhance microRNAs based upon antisense oligonucleotide (ASO) technology or viral delivery, respectively.

In the laboratory of Prof. **Leon de Windt** and Dr **Paula Da Costa Martins** (Dept. of Cardiology), unique and patented drug candidates have already shown great potential in animal models. These innovative and fundamentally new treatments are deployed by Mirabilis to counter cardiovascular and metabolic diseases. It was recently shown that cardiovascular and metabolic disorders are driven by changes in the expression of a collection of specific microRNAs. The founding of Mirabilis validates those observations, expands the number of potential targets for therapeutic intervention and ensures benefits of the group's academic endeavours.

MARIEKE RIENKS IN FACES OF SCIENCE PROJECT KNAW

As from 2015, Dr **Marieke Rienks** (Dept. of Cardiology) is one of the participants in the Faces of Science project of the Young Academy of the KNAW. The website Facesofscience.nl informs young scientists who are working on their doctoral research about their lives, research and passions. Marieke Rienks is a physician-researcher in experimental cardiology.

She studies heart damage. Damage can lead to inflammation and ultimately to heart failure. Marieke tries to find her study answers the questions how the immune system works and how it can be that the immune system can heal the heart, but sometimes it also makes sicker. Previously she examines proteins responsible for inflammation. Faces of Science is a project of the Academy and the Young Academy in collaboration with Kennislink.

APPOINTMENTS PROF. MONIKA STOLL AND PROF. PAUL VOLDERS

As of July 1, 2015, Prof. **Paul Volders** has been appointed extraordinary Professor of Genetic Cardiology, based in the Department of Cardiology. Paul Volders, Cardiologist and

CARIM Principal Investigator, coordinates the cardiogenetic care of patients with inherited arrhythmias and cardiomyopathies at Maastricht University Medical Centre. Within this clinical-experimental environment there is an active research program to gain novel pathogenetic insights in arrhythmias and sudden cardiac death. The Volders team has a long-standing focus on the electrophysiological characterisation of arrhythmia substrates in inherited cardiomyopathies and acquired cardiac overload. While these studies continue at the cellular, intact-animal and patient level, increasing research activities are directed to: 1) intracellular signaling pathways that determine ion-channel function; 2) the genetic and genomic basis of cardiac arrhythmias; 3) complex genetics and heart disease; 4) systems approaches to integrate the basic molecular and functional determinants of arrhythmia syndromes with the clinical characteristics of individual patients, in order to provide better risk management and treatment.

As of July 1, 2015, Prof. **Monika Stoll** (Münster) has been appointed extraordinary Professor of Genetic Epidemiology and Statistical Genetics, based in the Department of Biochemistry. It is a part time appointment of 0.2 FTE. Her research focusses on the dissection of the genetic architecture underlying complex trais, in particular of cardiovascular and inflammatory diseases.

CARIM COMMITMENT AWARD ROB VAN DER ZANDER

During CARIM Symposium 2015 that took place on November 4, the first CARIM award was presented to **Rob van der Zander**. The CARIM Commitment Award is intended for any CARIM member who has devoted his/her heart and soul to CARIM in an exceptional way, be it on an academic, managerial, service or community level. The award consists of a bronze coin of the sculptor Marina van der Kooi.

"Since the very beginning of CARIM he is the help and stay of the scientific staff and as such he has been and still is an important silent force behind the success of CARIM. We all are acquainted with administrative officers that stress their personal importance by finding a difficulty to every solution. In fact it is one of the hardships of scientific life to cope with the hurdles that are put on our way by administration. The mind-set of Rob is precisely the opposite: He feels that he is there to make life easier for those who are to produce the result that CARIM thrives on: Good research. This commitment he knows to enact on the whole staff that he is in charge of."

THOMAS UNGER LECTURER OF THE YEAR BELGIAN HYPERTENSION COMMITTEE

Prof. **Thomas Unger** has been honoured with the title 'Lecturer of the Year' by the Belgian Hypertension Committee. A lecture tour through Belgium with lectures at 7 universities was organised in the beginning of March. Distinguished speakers over the past years are: M. Azizi, P. Verdecchia, G. Bakris, M. Burnier, P. Palatini, J. Redon, T. Heagerty, K. Narkiewicz, P.F. Plouin, G. Parati, A. Dominiczak, E. Ritz, S. Laurent, S. Julius, C. Bulpitt, J. Reid, P Corvol, O' Brien, G Mancia.

INTERVIEW

DR DEKKER LAUREATES

Judith Cosemans, Anna Papageorgiou, Paula da Costa Martins, Martijn Brouwers, Joost Lumens and Marc Strik

Half of the Dekker grants, annually awarded by the Dutch Heart Foundation, went to Maastricht in 2015. Six of CARIM's 'top researchers' got the opportunity to further develop their research with this personal grant, which comes in different forms, aimed at different career stages. We put the six laureates around a table, poured some coffee and threw in some provocative propositions. Do they think obtaining a large personal grant is largely a matter of luck? Are publications in high impact journals the best measure of the quality of a researcher? And is translational research anything more than a sound bite?

At Maastricht, teaching is more important than research.

Joost Lumens: "It depends on who you talk to. For CARIM the priority is research, but for the Faculty of Health, Medicine and Life Sciences education is relatively more important."
Judith Cosemans: "I know that ever since the university was started, the initial idea was to have a strong emphasis on education and it was a battle to implant research here. At the moment, the 70% research time most of us have is being reduced by the faculty to 50%. If we have grant money we can invest that in keeping the extra 20% research time, if not, we'll have to teach more or come up with other alternatives. Thus in a way history is repeating itself."
Joost: "Indeed this is a crucial change that may reduce the chances for CARIM talents to obtain Dekker grants in the future. If you have to compete with other researchers, at institutes offering more time for research, that's a serious difference."
Judith: "I think some people will leave Maastricht because of this. It's a threat."
Anna Papageorgiou: "But leaving the environment where you started your career is really hard work, I know from experience. The glory days of being Marie Curie and just doing your thing are gone nowadays. Things change."

Earning a Dekker grant is a matter of 50% quality and 50% luck.

Marc Strik: "I agree. When people are deciding if they're going to give you the grant or not, there are always many factors at work, not just quality."
Judith: "I wouldn't say luck, I would say environmental factors, such as the number and quality of the other applications."
Joost: "I agree."
Marc: "Still everything I hear is luck. It's also what the committee had for breakfast, if it's sunny outside…"
Anna: "50% is maybe a bit high, but there is certainly a degree of luck involved. But when you receive a grant you've made a long journey and done a lot of hard work to get there."
Martijn Brouwers: "In my case, I may have been lucky to get this grant, but if I manage to get a second and a third one, it's not just luck."

The Matthew effect in science, where the rich researchers get richer, is a good thing.

Martijn: "It would be good if you all had equal opportunities when you start, and once the talented people get recognised

"QUALITY IS MORE THAN THE DISCOVERY THAT YOU'RE PURSUING"

I think it would be OK that they get more and more. Because it's a waste of money to reward someone just because he was unfortunate last year. We live in a competitive world and it's money paid by society, so we should spend it in a good way. Give it to the best people."
Paula da Costa Martins: "There's nothing wrong with promoting the best people."
Joost: "Statistically it may be true that if you get a first grant, it's easier to get a second one, but it's not as simple as that. I believe it also greatly depends on the scientific quality achieved during the first grant period whether you'll get a second one."
Anna: "One item of feedback I got from the reviewers for this grant was that I hadn't received a prestigious personal grant so far. That doesn't mean that you haven't done good science up to that point. I guess people see it as a certificate of quality. But there's an element of luck in there as well, so do you want your selection criteria to be based on something like luck? I don't think so. I believe your evaluation should be based on your work over the last five to six years, not what you've done in your whole career."
Joost: "I think that the definition of quality has changed over the years. Visibility, at conferences for example, is a crucial factor in getting grants as a young researcher nowadays. So we have to teach our PhD students to actively promote themselves. Quality is more than the discovery that you achieve or are pursuing."
Paula: "Also because you have to combine different types of expertise, build a network, find the right people that will help you."
Judith: "I think you have to persevere. I've now obtained a Vidi and a Dekker, but I applied for six other grants that I didn't receive. You only see what I got."

Writing a grant proposal is the least fun part of scientific research.

Marc: "It's a really good way to get your story straight, but I was surprised how much time, effort and convincing other people is involved in grant writing. I'm the least experienced in this room, but working on several grant proposals every night for six months, that amount of work surprised me. And I don't look forward to a life full of grant application writing. And every year they come up with more things to make it 'better', or more complicated. So an equilibrium should be found. I don't think anybody enjoys applying for grants."
Joost: "Except when you end up getting the grant."
Marc: "But you don't know that yet when you're writing."
Joost: "There's nothing more difficult than applying and taking a bird's eye view of your work. That's what writing a grant proposal forces you to do. It's crucial, which may be something different than it being fun."
Anna: "It's probably the moment where you do the most thinking, because you have to structure your ideas, check how it fits in with other theories. Personally I don't enjoy the bureaucracy surrounding it and the pressure to try and get it, but thinking about ideas, a hypothesis, that's where you're defining what you're going to do in the next three or four years. That's also quite exciting."
Paula: "I do enjoy going to interviews. You learn a lot, like how to deal with different people with different expertise, who are very critical towards you. Sometimes you see your research from a different point of view. It's very intense."
Judith: "I like the interviews too, it's a challenge. I don't think there are that many true challenges for a researcher, where you have to perform in twenty minutes. I learned a lot from that. How to deal with disappointment is an example. In the end you regain your motivation, rewrite your grant proposal and try again next year.

Marc: "Every grant asks things in a different way. Sometimes you even have to discuss how Catholic you are."
Joost: "Yes! I applied for the same grant: Niels Stenson. I was an acolyte in church for seven years but sadly I didn't put that in my CV. It might have changed my chances if I had done so."

My presentation for the CARIM Research Council was the key to my success with this grant.

Marc: "It's a good idea to rehearse."
Judith: "The people who were there gave me quite useful feedback."
Anna: "I agree with that. I found it really helpful."
Martijn: "As a clinician it was really helpful to receive feedback from basic scientists."
Judith: "But for me the key to success is to talk to people who have already obtained the grant. I really think that if colleagues from Maastricht apply for a Dutch Heart Foundation grant, and get invited, the Research Council should consider inviting one of us to talk to them. We can tell them for instance that the atmosphere at the Dutch Heart Foundation is often quite informal. At NWO it's more formal. There they try to challenge you and make you doubt your own proposal. You have to stand your ground. And I was prepared for that. I knew the question would come up, because four other people had told me."
Martijn: "I had the same experience with my Veni interview: I already knew then they were going to reject my proposal."
Joost: "I think it really depends on who is chairing the session. I once had a very hostile interview for the Junior Postdoc Dekker grant, while the interview for the present round was very friendly. During that first interview, the chair was trying to catch me out on something, asking the same question several times but in different words. Afterwards I realised that it was a big theatre. There was an epidemiologist who said: 'I don't know anything about this, this is way too difficult for me.' And the chair was just watching me. I realised afterwards that it was a test. So this time I prepared for these kind of questions, but I didn't get them."
Paula: "I had the same experience. The only expert in my field told me: 'I like your proposal, but the whole concept is wrong.'"
Judith: "That's what they always say!"
Paula: "This was the person with the most authority in my field. So I took a step back, tried to think and then said: 'I disagree with you' and gave my arguments. I have the feeling that was the point where they approved my proposal."

Publishing in scientific journals with a high impact factor is the most relevant measure of the quality of a researcher.

Anna: "That's one of the evaluation criteria that are easy to measure, but I don't believe it reflects the best science."
Joost: "But every alternative has its weaknesses too."
Anna: "There are journals that are completely run by publishing houses and have a different interest in maintaining their impact factor. That's the downside of academia."
Marc: "It also depends on what field you're publishing in. Cardiology inherently has quite a high impact factor. I don't know if you guys use Research Gate, but they just add up all the impact points you've earned with your papers and that gives you a score and this is like your quality. That's really too extreme for me."
Paula: "People always want to measure quality. It does help to get you an interview."
Judith: "That's what I experienced too. My personal opinion is that if you have a high impact paper that nobody reads,

it's of little use. I would rather have a paper with a medium impact factor that is being read by people and where they make use of it in their own work."
Joost: "The impact factor refers to the average number of citations of a journal's papers, so on average there is a correlation between the factor and the way it's used. But sometimes people just get lucky to get some irrelevant stuff in a high impact journal."
Martijn: "So on average you say: high impact factor is higher quality?"
Joost: "No, it's more often cited."
Martijn: "And that makes it better quality or more relevant? Or both? I think a paper in *Science* or *Nature* is good quality."
Judith: "Not always. There are quite a few mistakes in *Cell* papers, it's unbelievable."
Joost: "Yes, but the same holds for lower impact journals. The volume of publications is simply too high. I don't regard my highest impact paper as my best paper, and I think that holds for most of us."
Judith: "Sometimes the big journals have a wider scope and then the reviewers are not always true experts in the field of the article that is being submitted for review. That's why you get errors sometimes. With a journal specialising in your field, the reviewers are often more experienced in that specific field. That makes for better papers, but the impact factor is not the highest you could have gotten elsewhere."
Paula: "You always have to balance: who and what do you want to reach? A more general community of biologists and more citations, or a very specialised journal? In our group we tend to try and go for the more general ones, because that gives you more visibility, also outside the field of cardiology. The mechanistic part is not only related to cardiovascular disease, so other disciplines can use our output as well."

Translational research is nothing more than a sound bite.

Anna: "I think it's a very important element for a lot of academic research these days. I got into this sector because I wanted to learn, but also to help people. Translation is the bridge between the two, but I do think it's overemphasised. The value of all research is not only in its translational value."
Paula: "We are being bombarded with translational requests, but we are basic researchers. We don't have to find applications for our research, that's not our main goal. This word, translation, everyone can interpret it in a different way … We try to develop something that can grow further, all the way to a clinical study, but that's how far we can go. Of course that's translation, but the word is also used differently."
Joost: "For my part, I really want to change something at clinical level and I choose my clinical partners in order to actually reach the patients. You can call that translational or applied research. I'm fine with both."
Paula: "But you can also 'just' identify genes and mechanisms that are important in cardiovascular systems, which other people can then pursue as future targets, and keep it at that, very fundamental. Do good, valuable research."
Judith: "I visualise it as a chain from basic science to patients and it's good to have people in the entire chain. Let people do what they do best. Joost is interested in making a larger step, so please facilitate the way he's doing that. Paula is more interested in fundamental research, so please facilitate her in doing what she does best. Also, the emphasis on valorisation creates false hope sometimes, because not every basic finding is important for patients and it's just not realistic to create that hope. But it's good to make people aware of valorisation opportunities. I attended a workshop on this topic by the Dutch Heart Foundation and that was very helpful to me. Sometimes you're inside your own box, and you get inspired to think outside of that. And it's good to

talk to people who are further down the chain."
Martijn: "I attended the same workshop and I asked the question whether it's my duty to inform patients and lay people about my research results, or if it's the Heart Foundation's. In the end one of the workshop leaders suggested that I should spend my time more efficiently. I still haven't figured out how. In the past you were a basic or clinical scientist and that was just it, and now you have to do translational science, and education, and you have to talk to lay people. These are all good aspects, but if you have to focus on them all, you may lose focus."
Joost: "So is the talent of the future then someone who is a little bit good at everything?"
Judith: "I don't agree. If we made the chain here, Paula, Joost and Martijn would work on one problem, everyone would be doing what they're really good at and together you reach the patients."
Anna: "I'm also at the start of the chain. There can be great research that has no translational value, and it also needs to be funded."

Without CARIM I wouldn't have been where I am now.

Joost: "I do think that CARIM has been crucial for my development. I've found myself in such a critical scientific environment, with my mentors who all originate from the 'Rob Reneman school'. Their guidance shaped me to a large extent as regards my self-confidence, my ability to refute arguments, to focus on scientific discussions. I see that as a CARIM heritage and crucial for my career. It's still that atmosphere that makes me happy to come here every day."
Paula: "Scientifically I could have been where I am now, but careerwise I think CARIM gave me the right opportunities at the right time. For that I'm very grateful."
Marc: "I have limited experience with CARIM, but what they did very well was arrange my transfer to Bordeaux within one month. That was very efficient and nice."
Martijn: "For me CARIM provides the network which in the end is essential to do your work. But to be honest, since my work also has metabolic aspects, there is also a connection with NUTRIM. I really feel affiliated with CARIM, but I don't want to restrict myself to this institute. It is important to be surrounded by people who share your scientific interest. It should not depend on a CARIM label to collaborate across disciplines."
Anna: "CARIM is a very good cardiovascular research environment and it's always stimulating to be around other researchers who do complementary work. But it's a tough environment to break through in as a young researcher. I think there's room for improvement, to create a pathway to keep talented people at CARIM."
Joost: "I think the institute is in an extremely difficult situation at the moment. We all need to cope with the current lack of money to invest."
Paula: "I'm not always sure about that. Priorities seem to have changed."
Joost: "What we all want is to see, for example, is that CARIM does everything in its power to prevent the extra educational tasks for researchers. I'm not saying CARIM will be able to prevent the faculty from going through with this change, but they should be seen to be trying."
Judith: "I think it's all about communication. As a young researcher, I used to have the feeling that I didn't get all the relevant information. As of recently we get to be invited to important school and planning and control meetings. For me that's important: if I want to build my career here, I want to be informed. This way I heard that CARIM is working very hard to make up for the 20% loss of research time. So I think the institute is on the right track."

Martijn Brouwers (1978) received a Junior Specialist Dekker grant of approximately 200.000 Euros. He completed his training as an internist/endocrinologist in 2013 and is trying to combine research with his work at the Maastricht clinic and teaching.
"My project is about non-alcoholic fatty liver disease as a new risk factor for cardiovascular disease. My hypothesis is that it's not the liver fat itself that causes the risk, but the pathway leading to the fat. The fat synthesized from glucose is the bad pathway, I believe. This grant was just enough for a PhD student, so I worked hard over the last year to obtain more smaller grants to finance the experiments as well."

Judith Cosemans (1980) received a Senior Post Doc Dekker grant worth 400.000 Euros. In 2011 she received the Junior Post Doc Dekker grant and in the summer of 2016 she was awarded a Vidi grant by NWO. In addition she also obtained several grants in the past for her research on alternatives to animal experiments.
"My project is about those patients who have experienced a myocardial infarction, and who in spite of treatment suffer a recurrent thrombotic event. Platelets, which are cell fragments in the blood and essential components of an arterial thrombus, are the focus of my research. I found that platelet-thrombi can remain active for a long time after a thrombotic event, thereby negatively influencing adaptations in the vessel wall. Current antiplatelet medication insufficiently addresses this. The aim of my project is to reveal underlying mechanisms for the role of platelets in long-lasting thrombus activities and to find effective ways to inhibit these activities."

Paula da Costa Martins (1976) received an Established Investigator Dekker grant, worth 600.000 Euros. In 2010 she also received a personal grant from the Dutch Heart Foundation and in 2012 both the NWO Meervoud grant and the Fondation LeDucq Career Development Award. In the summer of 2015 she was awarded a grant from the Portuguese government to enable her to fund a student exchange between Portugal and Maastricht.
"My research proposal focuses on the microvasculature of the heart, in particular the little capillaries that surround the cardiac muscle cells, as they become less abundant once the heart is stressed by either chronic hypertension or a myocardial infarction. We try to find genes that regulate the formation of these small capillaries, in particular microRNAs. We have identified a few that can decrease or increase capillary formation and we are trying to see whether by modulating their expression we can improve cardiac function and adaptation to stress."

Joost Lumens (1982) received a Senior Post Doc Dekker grant, worth 400.000 Euros. In 2012 he received the Junior Post Doc Dekker grant.
"My research is on computer modelling of cardiac function, specifically focussing on the electromechanical properties of the tissue. I concentrate my project on the treatment of heart failure with a special pacemaker therapy, called cardiac resynchronization therapy (CRT). Many people treated with CRT do not respond as well as expected to this invasive and expensive therapy. My idea is that by combining electrical and mechanical information in a mechanistic way, so by using models that describe the underlying relation between the two, one can significantly improve patient selection for CRT and even use simulations to tailor the treatment to a specific patient's underlying pathology. I really hope to reach the patient, the clinic, at the end of the project, in four years."

Anna Papageorgiou (1978) received a Senior Post Doc Dekker grant, worth just under 400.000 Euros. It is her first personal grant, after being involved in several grant projects with European consortia before.
"My project is looking at heart failure with preserved ejection fraction, also called diastolic dysfunction. I study how a particular protein, osteoglycin, behaves in the heart in this disease. This protein can take on different forms that are more specific for particular aspects of the disease. I hope to uncover which form does something good or bad, and I hope to be able to use it to improve disease outcome. It's very basic research, but still it comprises all elements of cardiovascular research, from cell to the patient situation."

Marc Strik (1984) received a Cardiologist in Training Dekker grant, worth approximately 150.000 Euros. Marc competed his pretraining in internal medicine and started four years of clinical training in September 2016.
"My project concerns heart failure patients who need pacemaker therapy to resynchronize their heart. To see if we can find something to increase the efficacy of this therapy, I just returned from one year of research in Bordeaux, where they have a special non-invasive electrical mapping system. It's like a vest you wear and we tested different parameters to check if patients respond in six months or not. That works, we know that now. But we also want to know if you can use this vest to predict the best pacing site in the heart, and that doesn't work at all. The rest of the grant money will be spent to pay for a PhD student, whom I will supervise."

HIGHLIGHT THEME III

ROBERT VAN OOSTENBRUGGE

DEPARTMENT OF NEUROLOGY

WIM VAN ZWAM

DEPARTMENT OF RADIOLOGY

The endovascular treatment of acute ischemic stroke

Vascular neurology has a long-standing research tradition in cerebral small vessel disease, which is an umbrella term covering all pathological processes related to the small vessels of the brain. In the last few years, a novel area of research has opened up: the treatment of acute stroke. Now is a good moment to look back and see how this new line of research has developed and to look at its future prospects.

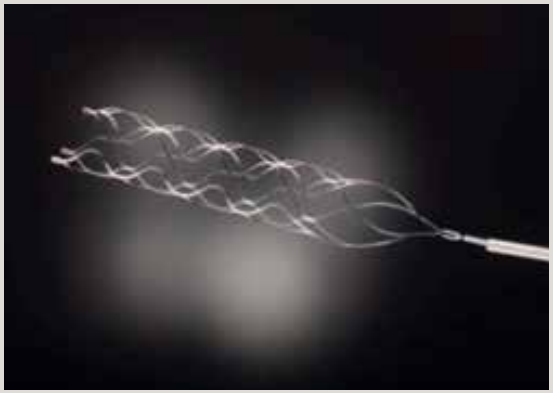
Stroke is one of the major causes of death, and the main cause of dependency in the western world. Intravenous thrombolysis to achieve early recanalization has proved effective for acute ischemic stroke patients treated within 4.5 hours after stroke onset. However, despite the overall beneficial effect of this treatment, its effect in acute ischemic stroke patients with intracranial large-vessel occlusion is limited, with intravenous thrombolysis leading to recanalisation in only 33% of treated patients. Furthermore, the small time window of intravenous thrombolysis is a major drawback, as many patients arrive at the emergency department outside this time window.

For more than 20 years, studies (non-randomised as well as randomised) have suggested a benefit of endovascular treatment of acute ischemic stroke due to intracranial large-vessel occlusion. However, although likely, it remained unproven whether this treatment in an unselected sample of patients is indeed beneficial. This was the reason to set up MR CLEAN, a multicentre randomised clinical trial of endovascular treatment of acute ischemic stroke in the Netherlands, in collaboration with Erasmus Medical Center (Rotterdam) and the Academic Medical Center (Amsterdam). MR CLEAN has received funding from the Dutch Heart Foundation.

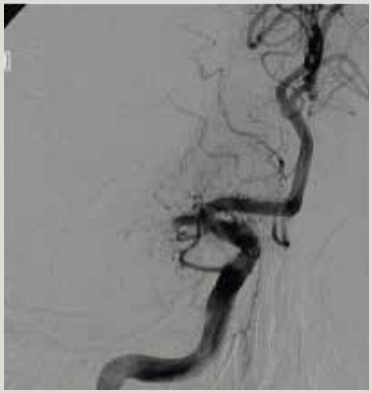
MR CLEAN

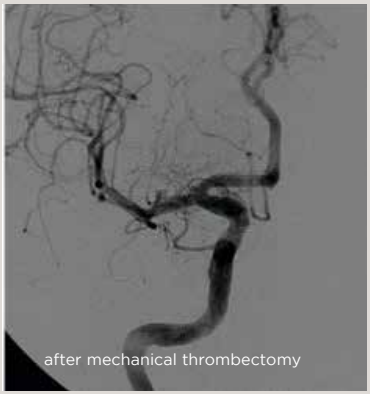
The primary objective of MR CLEAN was to estimate the effect of endovascular treatment on overall functional outcome after acute ischemic stroke due to proven intracranial large-vessel occlusion of less than six hours' duration. The treatment contrast was endovascular treatment versus no endovascular treatment and the primary outcome was functionality at 3 months, estimated by the modified Rankin scale, a 7-point scale ranging from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence.

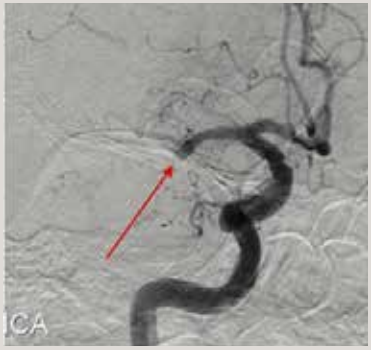
HIGHLIGHT THEME III



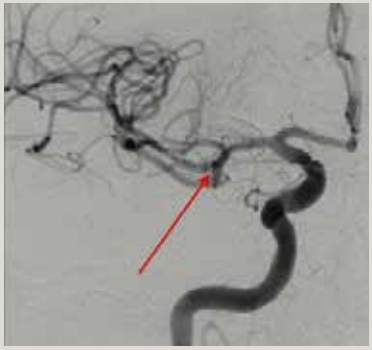
Example of a stent retriever used for mechanical thrombectomy







Digital subtraction angiography of two patients showing occlusion of the main stem of the middel cerebral artery



Digital subtraction angiograpghy showing complete recanalisation of the middle cerebral artery after mechanical thrombectomy

HIGHLIGHT THEME III

In December 2010, the first patient was included in MR CLEAN, which runs at 16 sites in the Netherlands. Patient accrual was faster than expected, largely as a result of the decision of the Dutch government to make reimbursement of the treatment costs conditional on participation in the trial. The last patient was included in the trial in March 2014.

Results were first presented at the World Stroke Congress in Istanbul in October 2014, and were published in the *New England Journal of Medicine* on 1 January 2015 (New Engl J Med 2015;372:11-20).

The main finding was a shift in the distribution of the primary-outcome scores in favour of the intervention. The adjusted common odds ratio was 1.67 (95% confidence interval [CI], 1.21 to 2.30). The shift toward better outcomes in favour of the intervention was consistent for all categories of the modified Rankin scale, except for death. The absolute between-group difference in the proportion of patients who were functionally independent (modified Rankin score, 0 to 2) was 13.5 percentage points (95% CI, 5.9 to 21.2) in favour of the intervention (32.6% vs. 19.1%). Importantly, there were no safety concerns. There was no significant between-group difference in the occurrence of serious adverse events during the 90-day follow-up period. Symptomatic intracranial haemorrhage, the most severe complication of endovascular treatment, was equal in both arms.

Shortly after publication of the results, the New York Times stated that the study was “a game changer” in the treatment of acute ischemic stroke.

The favourable results of MR CLEAN also had a major impact on four other on-going randomised studies on the efficacy of endovascular treatment of acute ischemic stroke due to intracranial large-vessel occlusion, as all four were halted by the respective Data Safety Monitoring Boards. Interim analyses of all four halted randomised studies showed positive results supporting the results of MR CLEAN.

SCIENTIFIC AND SOCIETAL IMPACT OF MR CLEAN

As the MR CLEAN trial included an unselected population, we had the opportunity to study pre-specified predictors of efficacy. This resulted in major new insights into patient selection for this treatment and provided directions for future studies. The most important findings were related to age and pre-treatment selection by imaging characteristics. First, MR CLEAN showed that age did not modify treatment effect. Hence, it is currently accepted not to withhold endovascular treatment from acute ischemic stroke patients even at very high age.

Second, although pre-selection on imaging characteristics led to an overall higher effect of endovascular treatment in the other randomised clinical studies, none of the characteristics, except degree of collateral flow, significantly modified the treatment effect in the unselected population included in MR CLEAN. Based on the findings of MR CLEAN it is now generally accepted that pre-selection of eligible patients is not warranted within the six-hour time window, and that collateral flow might be an important imaging characteristic to use in future trials aiming to determine the efficacy of endovascular treatment in patients who arrive at the hospital more than 6 hours after stroke onset.

Besides its scientific relevance, MR CLEAN also has a huge societal impact. It has set a new stage for the treatment of acute ischemic stroke. To implement this new treatment in practice, stroke care in the Netherlands and in the rest of the world needs to be reorganised as the current system has to

MR CLEAN, A MULTICENTRE RANDOMISED CLINICAL TRIAL OF ENDOVASCULAR TREATMENT OF ACUTE ISCHEMIC STROKE IN THE NETHERLANDS

evolve into an effectively organised system of care that can provide endovascular treatment to eligible stroke patients as quickly as possible. More importantly, MR CLEAN established a novel effective treatment for major stroke that gives patients the hope of regaining independency.

FUTURE PERSPECTIVES

The near future of research in endovascular treatment in acute ischemic stroke looks bright!

Two major prospects lie ahead of us. First, publication of the results of the five endovascular treatment studies led to the establishment of the HERMES collaboration. The main aim of this collaboration, in which MR CLEAN is the major contributor, is to analyse pooled individual patient data. This will allow us to determine with greater precision the effect size of endovascular therapy and to analyse subgroups.

Second, based on the success of MR CLEAN, a top-down programme of the Dutch Heart Foundation/CardioVascular Research Netherlands (CVON) was established to further improve the treatment of acute ischemic stroke in the Netherlands. The Vascular Neurology and Interventional Neuroradiology departments of CARIM are heavily involved in the preparation of the programme and will be principal investigators for the successor to MR CLEAN, i.e. MR CLEAN LATE. This randomised clinical study will investigate the efficacy of endovascular treatment in patients with acute ischemic stroke due to intracranial large-vessel occlusion who arrive at the hospital between 6 and 12 hours after stroke. Eligible patients are selected on the presence of collateral flow, the only imaging characteristic that modified treatment effect in MR CLEAN.

In the end, what started a couple of years ago as a novel research topic in vascular neurology has now become a major research line and flagship programme for the years to come.

TRAINING AND EDUCATION

05

INTRODUCTION

CARIM School for Cardiovascular Diseases offers a flexible and integrated education and training program that suits the individual ambitions of our students. The education program consists of a specialisation within the FHML Master of Biomedical Sciences and a Physician-Clinical Investigator Program (MSc/MD) and a contiguous PhD (doctoral) training program. The content of the education program has been developed by CARIM's top researchers, while its framework has been created by senior educators of Maastricht University, who have earned an excellent international reputation for their didactical system that is based on problem-based learning.

RESEARCH MASTER

In the Biomedical Sciences program, Master's students are informed about the FHML Research School programs in the first half year by attending school-specific lectures and parallel programs organised by School researchers. In the second half year, students may get acquainted in more detail with school-specific practical research. In this phase CARIM offers students the opportunity to do a CARIM junior research internship at one of CARIM's laboratories. This allows students to make up their mind about the school of choice in which to receive their practical research training. When students choose CARIM, they follow a CARIM senior research internship in their second year. This will lead to a notification of cardiovascular specialisation on their Master's certificate.

PHD PROGRAM

Our PhD program is accessible for talented and motivated students graduated from national and international Medical and Biomedical Masters. At the end of 2015, 96 PhD students attended our PhD program. Almost 50% of our PhD candidates come from foreign countries, guaranteeing an international atmosphere. The principal goal of the 4-year PhD training program is to support PhD candidates in developing themselves into independent and productive researchers in the cardiovascular field. To ensure high quality PhD training, CARIM offers frequent interaction of PhD candidates with a skilled and experienced supervisory team, thereby providing a stimulating and critical environment to further develop one's research skills. We also offer our PhD candidates a broad range of possibilities to attend seminars, master classes, and symposia to present their own research on national and international podia.

NUMBER OF PHD STUDENTS
(at 31.12.2015)

FUNDING SOURCE	2012	2013	2014	2015
UNIVERSITY	42	41	34	34
NWO	13	12	13	11
NON-PROFIT AND INDUSTRY	81	74	82	51
TOTAL	**136**	**127**	**129**	**96**

PHD DELIVERABLES

In 2015 38 PhD students finished their theses within our institute, and 5 theses were externally prepared. The table below illustrates the numbers of PhD students in the years 2008-2011, related to the period in which they obtained their degree. The graphics on page 32 present the number of PhD theses on the level of our research themes.

PHD STUDENT CAREERS
(date set 14.10.2016)

YEAR INTAKE	2008	2009	2010	2011
COHORT VOLUME (annual intake)	20	34	31	38
MALE	10	18	12	20
FEMALE	10	16	19	18
PHD FROM ABROAD	6	12	14	15
DROP OUT	4	6	2	1
DROP OUT > 1 YEAR	1	2	1	0
THESIS COMPLETED	14	22	18	22
AVERAGE DURATION (in months)	68	60	57	56
ONGOING	2	6	11	15

CARIM THESES 2015

Sanders-van Wijk S -
Title: 'Biomarkers in heart failure: towards individualized therapy'
Promotor: Prof. H.P. Brunner-La Rocca
Co-Promotor: Dr V.P. van Empel
February 5

Kusters D -
Title: 'Annexin A1 and annexin A5 in cardiovascular disease'
Promotor: Prof. C. Reutelingsperger
Co-promotor: Dr L.J. Schurgers
February 6

Bonaccio M -
Title: 'Health Benefits and social determinants of the mediterranean diet at a time of economic crisis: results from the moli-sani study'
Promotores: Prof. H. ten Cate, Prof. G. de Gaetano, Prof. L. Iacoviello
March 18

Ghossein-Doha C -
Title: 'Cardiac Adaptation during and after hypertensive gestation'
Promotor: Prof. M.A. Spaanderman
Co-promotor: Dr L.L.H. Peeters
April 17

Casiraghi F -
Title: 'Mesenchymal stromal cells to induce tolerance to solid organ transplantation'
Promotores: Prof. K.L.M. Leunissen, Prof. G. Remuzzi
April 22

Muris D -
Title: 'Microvascular dysfunction and diabetes: a vicious cycle?'
Promotor: Prof. C.D.A Stehouwer
Co-promotores: Dr A.J.H.M. Houben, Dr M.T. Schram
May 13

Zusterzeel R -
Title: 'Bundle Branch Block and Benefit from Cardiac Resynchronization Therapy'
Promotor: Prof. A.P.M. Gorgels
Co-promotor: Dr D.G. Strauss
May 20

Van Sloten T -
Title: 'Vascular dysfunction: at the heart of cardiovascular disease, cognitive impairment and depressive symptoms'
Promotor: Prof. C.D.A. Stehouwer
Co-promotor: Dr R.M.A. Henry, Dr M.T. Schram
May 20 - CUM LAUDE

Hanssen N -
Title: 'Methylglyoxal, the glyoxalase pathway and advanced glycation endproducts in type 2 diabetes and cardiovasculair disease'
Promotores: Prof. C.G. Schalkwijk, Prof. C.D.A. Stehouwer
Co-promotor: Dr K. Wouters
May 20 - CUM LAUDE

Van der Vorst E -
Title: 'Modulation of vascular inflammation; cell type specific effects by ADAMs and HDL'
Promotores: Prof. E.A.L. Biessen, Prof. M.P.J. de Winther (AMC), Prof. J.F.C. Glatz
Co-Promotor: Dr M.M.P.C. Donners
May 21

Cornelis T -
Title: 'Intensive and Home Hemodialysis; acute effects and Long-term outcomes'
Promotores: Prof. J.P. Kooman, Prof. K.M. Leunissen
Co-promotores: Prof. C.T. Chan, Dr F.M. van der Sande
June 10

Wang Y -
Title: 'New Biomaterials Derived from poly (lactic acids); novel approaches to combine biodegradation, X-ray Contrast and Controlled Local Drug Release'
Promotor: Prof. T. Delhaas
Co-promotores: Dr M.L.W. Knetsch, Dr D.G.M. Molin
June 16

Altara R -
Title: 'Novel Inflammatory Biomarkers for the Early Identification of Heart Failure'
Promotor: Prof. H.A.J. Struijker Boudier
Co-promotor: Dr W. Matthijs Blankesteijn
June 29

CARIM THESES 2015

Winckers K -
Title: 'The role of tissue factor pathway inhibitor in arterial and venous thrombosis'
Promotores: Prof. T.M. Hackeng, Prof. H. ten Cate
June 30

Zarzycka B-
Title: 'Modulation of protein – protein interactions in inflammatory diseases'
Promotor: Prof. T.M. Hackeng, Prof. G. Vriend
Co-promotores: Dr G.A.F. Nicolaes, Dr S.B. Nabo' clocks
July 2

Van Bragt K -
Title: 'Supply-demand balance in the atrium'
Promotor: Prof. U. Schotten
Co-promotores: Dr S. Verheule, Dr J.J. Luiken
July 3

Schalla S -
Title: 'Cardiovascular magnetic resonance; A key to imaging cardiac function'
Promotores: Prof. H.J.G.M. Crijns, Prof. J.E. Wildberger
July 6

Cardinaels A -
Title: 'High-sensitivity cardiac troponins in heart and kidney diseases: from lab to clinic'
Promotor: Prof. M.P. van Dieijen-Visser
Co-promotores: Prof. O. Bekers, Dr.ir A.M.A. Mingels
July 10

Van Middendorp L -
Title: 'Cardiac Dyssynchrony; structural, functional, transcriptional and pharmacological aspects'
Promotores: Prof. F.W. Prinzen, Prof. J.G. Maessen
Co-promotor: Dr F.A. van Nieuwenhoven
September 4

Peraramelli S -
Title: 'The role of the different Kunitz domains of TFPI in the down-regulation of the extrinsic coagulation pathway'
Promotores: Prof. T.M. Hackeng, Prof. J. Rosing
September 18

Spauwen P -
Title: 'Cognition and type 2 diabetes; the interplay of risk factors'
Promotores: Prof. F. Verhey, Prof. C. Stehouwer
Co-promotor: Dr M. van Boxtel
September 23

Pluijmert M -
Title: 'How cardiac myofibers keep pace; Mathematical Modeling Of Adaptive Myofiber Reorientation and Electromechanics'
Promotores: Prof. T. Delhaas, Prof. F.W. Prinzen
Co-promotor: Dr.ir P.H.M. Bovendeerd
September 24

Hilhorst M -
Title: 'Crescentic glomerulonephritis in ANCA associated vasculitis'
Promotor: Prof. J.W. Cohen-Tervaert
Co-promotor: Dr P. van Paassen
September 24

Bosch Y -
Title: 'Monitoring of hemostatic disturbances in cardio-pulmonary bypass patients'
Promotores: Prof. B. Mochtar, Prof. J.G. Maessen
Co-promotores: Dr P.W. Weerwind, Dr R. Al Dieri
October 7

Miglianico M -
Title: 'AMPK-glycogen interplay: an opportunity for drug design'
Promotor: Prof. J. Glatz
Co-promotores: Dr D. Neumann, Dr G.A.F. Nicolaes
October 23

Van Dooren F -
Title: 'Diabetes and Depression: exploring the Interface between Pathophysiological and Psychological factors'
Promotores: Prof. F. Verhey, Prof. J. Denollet, Prof. F. Pouwer
Co-promotor: Dr M. Schram
October 29

Maesen B -
Title: 'Structure-function relationship of atrial fibrillation waves in goat and man'
Promotores: Prof. U. Schotten, Prof. J.G. Maessen
Co-promotor: Dr S. Verheule
October 30

CARIM THESES 2015

Kumar N -
Title: 'Atrial fibrillation ablation: Pitfalls and potential solutions'
Promotor: Prof. J.G. Maessen
Co-promotores: Dr C. Timmermans, Dr S. Gelsomino
November 5

Pelkmans L -
Title: 'Innovative assays to detect bleeding and thrombotic tendencies: a focus on thrombin generation and fibrin formation'
Promotores: Prof. J.W.M. Heemskerk (de Jure), Prof. H.C. Hemker (De Facto)
Co-promotores: Dr B. de Laat, Dr H. Kelchtermans
November 12

Boersma R -
Title: 'Central venous catheters in hematological patients; Risky lifelines?'
Promotor: Prof. H.C. Schouten
Co-promotor: Dr K. Hamulyak
November 20

Oligschläger Y -
Title: 'Tour d'AMPK: Glycogen-cytoplasmic cycling of AMP-activated protein kinase'
Promotor: Prof. J. Glatz
Co-promotores: Dr D. Neumann, Dr J.J.F.P. Luiken
November 27

Chatrou M -
Title: 'Role of vascular smooth muscle cell mediated calcification in atherosclerosis'
Promotor: Prof. C.P.M. Reutelingsperger
Co-promotor: Dr L.J. Schurgers
December 2

Sharma A -
Title: 'Extracorporeal life support - Applications and considerations'
Promotor: Prof. J.G. Maessen
Co-promotor: Dr P.W. Weerwind
December 10

Nasrallah H -
Title: 'Left atrial vascular and metabolic remodeling in pig models of atrial fibrillation'
Promotor: Prof. U. Schotten
Co-promotor: Dr S. Verheule
December 16

Octavia Y -
Title: 'Endothelial nitric oxide synthase; Dr. Jekyll and mr. Hyde'
Promotores: Prof. H.J. Crijns, Prof. D.J. Duncker, EUR
December 16

Eijgenraam P -
Title: 'Studies on safety issues in anticoagulant management'
Promotor: Prof. H. ten Cate
Co-promotores: Dr A.J. ten Cate-Hoek, Dr R. van den Ham
December 17

See page 92 for an interview with Thomas van Sloten and Nordin Hanssen.

PHD THESES externally prepared

Mooij H –
Title: 'Functional consequences of inborn and acquired errors in endothelial glycocalyx heparan sulfates'
Promotores: Prof. E. Stroes, Prof. H. Vink
Co-promotores: Dr G. Dallinga-Thie, Dr M. Nieuwdorp
April 7

Dane M –
Title: 'Structure and function of the endothelial glycocalyx in the microcirculation'
Promotores: Prof. A. Rabelink, Prof. H. Vink
Co-promotor: Dr B. van den Berg
June 2

Wu Z –
Title: 'Non-linear optical microscopy in clinical translation: imaging of post-interventional endothelial regeneration'
Promotores: Prof. F. Kiessling, Prof. M. van Zandvoort
July 1

Zhen Zhao –
Title: 'Platelet JAM-A in vascular inflammation and remodeling'
Promotor: Prof. C. Weber
Co-promotores: Dr B. Huber, Prof. A. Baethmann, Dr R. Koenen
September 24

Zeemering S -
Title: 'Sparse Estimation; applications in atrial fibrillation'
Promotores: Prof. R.L.M. Peeters, Prof. U. Schotten, Dr R.L. Westra
November 26

INTERVIEW
JORDI HEIJMAN

There was a time, when he was working towards his Bachelor's degree in Knowledge Engineering, that after each discussion he had at the Cardiology Department, Jordi Heijman checked how many of the words he had actually understood. Now, with a Master's degree, a PhD degree with distinction and a Veni grant in his pocket, his knowledge of the specialist jargon leaves little to be desired. He has deliberately moved to a room among the cardiology staff at the hospital, and he attends the case consultation meetings each morning for even more inspiration and motivation. "This is where I can get the best of both worlds."

Even when he was deciding on a subject to study at university, Jordi Heijman knew he wanted to contribute to the application of scientific research. That is why he decided not to enrol in a programme like Theoretical Computer Science, but in the Knowledge Engineering programme at Maastricht University. It was a matter of chance that he ended up working at the Cardiology Department for his thesis project, but as far as he is concerned it was a very lucky chance. “As soon as I started there, I was captivated, and we got some good results. I then knew: ‘This is it’. It gave me the opportunity to apply my mathematical and computer science knowledge in interesting research relating to relevant clinical problems.” And so he received his PhD in 2012 for a project that was supervised partly by the Cardiology Department and partly by the Department of Knowledge Engineering (DKE). His thesis earned him the CARIM Dissertation Award, and in 2015 he received a Veni grant.

COMPUTER MODELS

The recurrent theme in his research is that of developing computer models in order to better understand cardiac arrhythmias. “My thesis work led to the first model of the entire signalling cascade of sympathetic activation, that is, the ‘flight-or-fight response’ that causes arrhythmias in some people. I worked for eighteen months in St. Louis, USA, with Prof. Yoram Rudy, a leading authority in the field. What I mostly learned there was a particular approach. I try to translate biological knowledge into mathematical equations and ultimately into a computer model. This translation process is something you have to learn: what assumptions can you make, what is the prevailing view? That’s something you can learn from someone with a lot of experience.”

He later applied his computer model in other research, such as a study of patients with a mutation in a particular ion channel. “Why were these people getting arrhythmias when they engaged in a particular activity? When something gives you a fright, your heart rate goes up, and that normally means that this channel is activated to limit the duration of each activation. A combination of experimental research and computer modelling showed that the channel is not functioning correctly in these patients. Developing such models is a lot of work, but it enables us to do things that can as yet not be done experimentally. For instance, the model gives us perfect control of all model parameters, whereas it’s not always possible to isolate this one channel in a cardiac cell that you want to study. That, and the integration of data from multiple experiments, is the added value provided by modelling.”

POSTDOC ON ATRIAL FIBRILLATION

After getting his PhD, Jordi wanted to widen his horizon and went to Heidelberg and Duisburg-Essen to do a postdoc about atrial fibrillation. He once more used computer models and discovered both parallels and differences between arrhythmias of the ventricles and of the atria. When it became clear at the end of 2014 that he would return to Maastricht, this research led to the application for a Veni grant. It took him less than a month to write up the research proposal he had already been carrying around in his head. “I think it was particularly the rebuttal that I wrote on the basis of the first reviewer comments that made the difference.” He is going to use the grant to examine in detail the role of the altered calcium handling in arrhythmias of the ventricles and atria. One of the questions his research will try to answer is how spontaneous calcium release affects the various ion channels in the cardiomyocyte.

“EVERYDAY CLINICAL PROBLEMS PROVIDE A LOT OF MOTIVATION AND INSPIRATION FOR MY RESEARCH”

HUGE ENJOYMENT

He describes his work as a hobby that got out of hand. He ‘hugely enjoys’ going to his office at the hospital’s Cardiology Department each day. “It was largely a conscious decision to have my office here, and not in a university department. I’m regularly to be found at the department anyway, as it’s where my students are and where I do my experiments. But if I had my office there as well, the distance from the clinic would be much bigger. The ultimate goal of our research should be to enable us to treat patients better. Here I’m more directly involved in everyday clinical problems, and they provide a lot of motivation and inspiration for my research.”

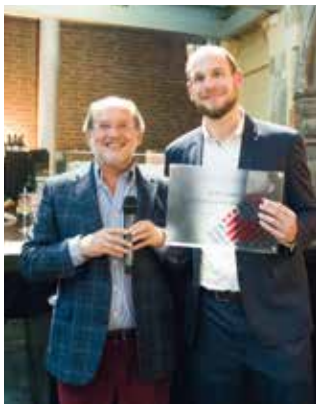
During his PhD research, his DKE supervisor Prof. Westra used a quotation from Louis Pasteur that stuck in his mind: “Chance favours the prepared mind”. “I can see that. For instance, I was lucky to already have a permanent position, which meant I could engage a PhD student indirectly through my Veni grant. But at the same time you have to try and seize all opportunities.” His research group is still small: “I have one PhD student here and one in Essen, and I’ll have a Master’s student starting to work here in September, but it definitely needs to grow in the coming years. We’ll be sending off another grant application tomorrow.”

CARIM AS A FRAMEWORK

Heijman mentions the ‘framework’ offered by CARIM for PhD students as one of the most important advantages of the research school, together with the concentration of a wide range of cardiovascular expertise at Maastricht, and the facilities offered. The only aspect he would like to see improved, and that goes for Dutch researchers in general, is better showing what they are good at. “We shouldn’t always be too modest. We could sometimes take our cue from our American colleagues in that respect. It’s the responsibility of each researcher to draw attention to the valuable results he has obtained, but CARIM also supports us with that.”

DISSERTATION PRIZE 2013/2014

Teba Alnima and **Martin Schmitt** both received the CARIM Dissertation Award 2013-2014 during the evening program of the CARIM symposium 2015 on November 4, 2015. Teba received the award for her thesis 'Carotid baroreflex activation therapy. Potential mechanisms in resistant hypertension' and Martin for his thesis 'JAM-A: Junctional adhesion molecule-A or Janus Acting Mediator in atherosclerosis'.



KNOWLEDGE TRANSFER

CARIM COURSE WEEK

From June 8 until June 12, the CARIM Course week took place. The course week consisted of parallel courses, covering several aspects of CARIM's research, alternated with a combined scientific program and a social program organised by I'M CARIM, the organisation of CARIM's PhD's. In 2015, three courses were organised by CARIM researchers: 'Drug Discovery and Development', 'Vascular Inflammation and Thrombosis' and 'Advanced Microscopy and Vital Imaging'. Almost 40 PhD and Master's students participated.

CARDIOVASCULAR GRAND ROUNDS

The Cardiovascular Grand Rounds Maastricht and the yearly CARIM Symposium are means to update the knowledge of our graduate students, our researchers and other external people with interest in the field of cardiovascular research. In the framework of the Cardiovascular Grand Round Maastricht, three successful lecture series were organised in 2015 by Dr **Blanche Schroen** and Dr **Paula da Costa Martins** (Dept. of Cardiology), with cardiovascular lectures given by national and international experts, on a weekly basis. For the current programs please visit www.carimmaastricht.nl, 'CARIM lectures' in the 'Education' section.

CARDIOVASCULAR GRAND ROUNDS MAASTRICHT

CARIM SYMPOSIUM 2015

CARIM's annual scientific symposium was held in Maastricht on November 4, 2015. As in previous years a substantial part of the program was the poster session, in which scientists of the institute presented their recent research findings. The lectures were centered around translational research and were given by a basic researcher and a clinician in 'duet-style'. Each duo highlighted a topic from their basic scientific and clinical point of view respectively. The traditional Robert Reneman lecture was presented by Professor Stéphane Hatem, Professor of Cardiovascular Physiology at the Heart Institute of Pitié-Salpétrière Hospital and director of the Inserm/University Pierre Marie Curie research laboratory in Paris. His research activities have been dedicated to understand the molecular and cellular basis of atrial fibrillation. His work has contributed to improve the knowledge on the formation of macromolecular ionic channel complexes, the mechanisms of the atrial fibrosis and more recently the relation between adipose tissue and atrial fibrillation. Another highlight of the symposium was a lecture given by Vici laureate Professor Leon de Windt.

CARIM LECTURES

In 2015, the first CARIM lecture was organised with a kick-off on December 2. The scope of the CARIM lectures (which will take place 3 to 4 times a year) is to stimulate interaction between the themes and by focussing on cellular processes and techniques that may benefit science across CARIMs themes. Future meetings will centre around e.g. advanced imaging, energy metabolism, autophagy, tissue regeneration, etc. This kick-off included lectures of CARIM's inflammation experts: Prof. **Erik Biessen:** 'Innate and Adaptive Immunity in Atherosclerosis', Prof. **Stephane Heymans**: 'Central Role of Immune Activation in Heart Failure', Dr **Rory Koenen:** 'Molecular and Cellular interaction in the pathogenesis of Atherosclerosis'.


CARIM
CARIM

OTHER CARIM LECTURES SEMINARS AND SYMPOSIA 2015

Complementary to the regular lecture series and CARIM symposium, several lectures, seminars and conferences were been organised by our research staff in 2015. Some of them are presented below.

In 2015 the existing collaboration network between CARIM scientists and scientists from the Institute of Cardiovascular Research (IMCAR) of the University Hospital RWTH Aachen (headed by Prof. **Joachim Jankowski**) was formalised through the erection of **IMCARIM**, which main ambition is to build a common ground for nephro-cardiovascular comorbidity research. As part of this alliance common Cardiovascular Seminars are being organised since the second half of 2015 with alternating monthly lectures organised in Aachen and in Maastricht, offering a platform for international top scientists in the field of vascular biology and nephrology to present their recent work. The lecture series has started with the symposium IMCARIM: CKD meets CVD, that took place on September 1. So far IMCARIM can be satisfied with three exciting lectures that had so far been organised in 2015: Prof. **Menno de Winther** (October 1), Dr **Rafael Kramann** (November 26), Dr **Leon Schurgers** (December 17).

Three meetings of the **Maastricht Working Group on Cardiovascular Systems Biology** initiative took place in 2015, organised by Dr **Pawel Kuklik** (Dept. of Physiology), Dr **Joost Lumens** (Dept. of BME) and Dr **John Walmsley** (Dept. of BME). This working group brings together researchers in the Maastricht area who are interested in the application of 'systems biology' approaches to the cardiovascular system. The main aim is to share research, experience and, through this exchange, inspire and initiate new research directions and collaborations.

The Vascular Network Group (VNG), formed in 2013 and led by Dr **Koen Reesink** and Prof**. Chris Reutelingsperger,** organises 2-monthly Vascular NetWorkshops (five in 2015) to facilitate inter-disciplinary exchange of ideas between basic and clinical researchers and joint research initiatives, across schools and themes. In 2015, the VNG has also supported the Daily Board of CARIM, by thorough review of the research and organisation, to establish the scientific, translational and strategic focus for (now) Theme Vascular Biology & Medicine (led by Prof. **Harry Struijker-Boudier** and Prof. **Coen Stehouwer**) for the next 5 years. From 2016 onwards, the Vascular NetWorkshops will be more specifically utilised to develop the 'Maastricht-stronghold' topics as currently defined: 1. Atherosclerosis, 2. Arterial stiffening and hypertension, 3. Diabetic vascular complications, 4. Neurovascular diasease, 5. Regenerative and reconstructive vascular medicine, and 6-Venous thrombosis and insufficiency.

On February 6, the mini-symposium **Vascular Inflammation** on the occasion of the PhD defense of **Kristof Schutters** (Dept. of Biochemistry) took place.

From February 11-13, the **Maastricht Consensus Conference on Thrombosis (MCCT)** took place. The symposium, orga-

nised by researchers of the **Department of Biochemistry**, contained plenary lectures by prominent scientists and experts in the field on a chosen theme, followed by highly interactive, intensive workshops in which the interaction between the experienced scientists, PhD students and post-docs is used to explore gaps in research or knowledge on specific topics.

The **5th MIMSA Symposium (Maastricht Inflammation in the Metabolic Syndrome and Atherosclerosis),** organised by Dr **Marjo Donners** (Dept. of Pathology) and Dr **Kristiaan Wouters** (Dept. of Internal Medicine), took place on March 24. This symposium aims to increase the contact between researchers interested in inflammation and immunity linked to cardio-metabolic diseases to stimulate and initiate collaborations. This edition's keynote speaker Jacob Bentzon (Aarhus University, Denmark) gave a lecture on new modeling approaches for experimental atherosclerosis research.

From April 1 until April 3, the **6th edition of the Maastricht AF meeting 'Crossing Borders'**, organised by Prof. **Harry Crijns** (Dept. of Cardiology) and Prof. **Jos Maessen** (Dept. of CTC) took place. In previous editions of the Maastricht AF meeting 'Crossing Borders' the main goal was bringing electrophysiologists and cardiac surgeons together to show the potential of Hybrid AF ablation procedures for their patients with complex atrial fibrillation. As the procedure has become established, this year's edition of the Maastricht AF meeting also gave the floor to expert opinions on the impact of what has been achieved so far and the way to go in the near future.

On May 13, the mini-symposium **Microvascular Dysfunction and Diabetes: a vicious cycle?** on the occasion of the PhD defense of **Dennis Muris** (Dept. of Internal Medicine) took place.

On May 21, the symposium **Lipoprotein dependent modulation of inflammation in the metabolic syndrome** was organised by Dr **Marjo Donners** (Dept. of Pathology).

A new edition of the **I'M CARIM Young Investigator Rounds** took place on July 7, where two CARIM PhD students presented their work, followed by an informal and open discussion.

From September 8 until September 11, the **8th International Conference on Annexins** was organised in Maastricht by Prof. **Chris Reutelingsperger** and Dr **Leon Schurgers** (Dept. of Biochemistry). Like its predecessors, the 8th International Conference reviewed all aspects of annexin biology including clinical and biomarker aspects, physical chemistry and structural features, biochemistry and cell biology, functional physiology, receptors and signaling, evolution, comparative genomics, annexin SNPs, imaging and molecular biology. The meetings bring together, from around the world, the most active researchers in the field to discuss the latest findings in this fascinating area of biology. It is a unique opportunity for the 'annexin community' to come together to discuss problems of mutual interest and concern.

Following the success of the 1st **European workshop on AMPK** in 2013, the 2nd edition took place from September 13 until September 16 in Maastricht, The goal of this meeting series, organised by Prof. **Jan Glatz** and Dr **Dietbert Neumann** (Dept. of Genetics & Cell Biology) is to bring together teams working on AMPK, to discuss and share latest data resulting from their ongoing research activities. In each session, following one state-of-the-art talk, the floor will be given in priority to young researchers (PhD students or post docs) to present their own projects.

From October 18 until October 20 the **1st International Brightlands Symposium on Cultured Meat** was held in Maastricht. The symposium covered technologies and subjects related to culturing meat, ranging from cell production, food technology all the way to ethical studies. Four top notch keynote speakers participated. Prof. **Mark Post** (Dept. of Physiology) and Dr **Nynke van den Akker** (Dept. of Physiology) were part of the organising committee. Furthermore several (internationally) high profile scientists were invited to present a lecture at CARIM, e.g.Prof. David Kass, Dr Sebastian Schmitter, Prof. Emilio Badoer, Dr Michael Rudnicki, Prof. Jörg Bartsch, Prof. Pyotr Platonov and Prof. Bas Mochtar.

INTERVIEW

NORDIN HANSSEN
THOMAS VAN SLOTEN

They are both training to become internal medicine specialists and their PhD research projects both focused on vascular damage. They share an interest in scientific research, which they hope to combine with their work at the clinic in the future. But the most remarkable similarity between Thomas van Sloten and Nordin Hanssen is that they were awarded their PhD with distinction on the same day, 20 May 2015, having worked under the same supervisor. Together, they look back and look ahead.

Nordin Hanssen's research concentrates on Advanced Glycation End Products (AGEs), which are compounds resulting from an interaction between sugars and proteins. These play a role in the process by which plaques rupture: proteins react with sugars and thereby lose their functionality, damaging the cells. "I studied the way in which this metabolic process makes atherosclerotic blood vessels more vulnerable and ultimately contributes to rupture. I examined this using human tissue, laboratory animals and cell cultures." The results showed that plaques with a higher risk of rupture contain higher concentrations of AGEs than the more resilient ones. And blood tests among patients with type 2 diabetes also showed that higher AGE levels are associated with a higher incidence of cardiovascular disease. Giving AGE inhibitors to lab animals reduces their atherosclerosis. The next step will be a study to test these inhibitors in humans.

Thomas van Sloten studied the relation between vascular dysfunction and brain diseases like stroke, dementia and depression. "My hypothesis was that vascular dysfunction, both in large and in small vessels, was one of the causes of these diseases." He did epidemiological research, based particularly on two large cohort studies, the Maastricht study and the Hoorn Study. "We found that vascular stiffness, especially stiffening of the carotid artery, predicts stroke. Estimation of carotid stiffness improved stroke risk prediction beyond other known cardiovascular risk factors." Another of their findings was that vascular stiffness and endothelial dysfunction can lead to brain damage, which can manifest itself as dementia and depressive symptoms.

SOME IMPRESSIVE PUBLICATIONS

Both researchers managed to get several of their PhD thesis chapters published in high-ranking journals. Hanssen got published in the *European Heart Journal* and in *Diabetes*, while Van Sloten made it into the *American Journal of Cardiology*. Both spent part of their PhD studies abroad. Nordin Hanssen: "I worked at the lab led by Professor Mark Cooper in Melbourne for seven months. It was great to learn new things in a different lab, with different people. They were very much focused on animal studies and cell cultivation. And Mark Cooper is always trying to find a medicine, an inhibitor of the mechanism he's researching. His question was always: 'Is it targetable?' But the main thing you learn is that things are basically the same everywhere. The scientific method is simply universal: you have to try and be objective, to critically evaluate other people's work as well as your own, and you have to try and improve health care." Thomas van Sloten: "I had the same experience. I spent three months in Washington, at Lenore Launer's lab. The research approach there was basically the same, and yet it was also different. Here you are expected as a researcher to collect most of your data yourself, whereas everything is facilitated there. The data are there, an IT expert and a statistician are available on site, and your task as a researcher is the analysis. That was great: real luxury. And since I was there on my own, without friends or family, I was extremely productive."

'DISCOVERING STUFF'

Whereas Nordin knew even before he had picked a subject to study at university that he was to go into research, Thomas found out that 'discovering stuff' was really cool while doing an honours programme as part of his medical studies. Thomas: "What I find exciting is testing hypotheses. It's great to see a hypothesis confirmed time and again. Although on the other hand it's also useful to be able to disprove it." They met during their PhD programme and found that they got along well. Nordin: "We both enjoy science and want to continue doing research in the future.

It was good to be able to bounce ideas off each other." Thomas: "It's not so very often that you get to see you co-supervisor and supervisor, so it's essential to have colleagues who can act as sounding boards. Nordin is very good at thinking along with you, even if he's not totally familiar with your topic. He's interested in lots of subjects and is very enthusiastic and encouraging. If you've managed to get a nice article published, he'll be the first to congratulate you." Nordin: "Thomas is a highly intelligent but also modest guy. He keeps an open mind for other people's ideas and

"WE CAN ALREADY DO A LOT, BUT THERE'S MORE TO COME"

is a good listener, which is also going to make him a good internist. And he's also very good at putting the essence of something into words, both in his presentations and his papers." Thomas: "Yeah, I like writing. Our professor, Coen Stehouwer, is very good at it. After you've spent ages working on an article, he still manages to make it much better in half an hour. That can be frustrating sometimes, but you also learn a lot from it."

PHD CEREMONIES ON THE SAME DAY

Since they both worked for the same professor and had completed their theses more or less at the same time, they came up with the idea of having their PhD ceremonies, where they had to defend their theses, on the same day. That way their colleagues would only have to go to the Minderbroedersberg hall once. Thomas went in first, and got his PhD 'cum laude' (with distinction). "I immediately thought: then Nordin's will also be cum laude." Nordin: "I would have loved to attend his defence, but I had to concentrate on my own introductory talk. But I did hear that his was a cum laude, which was fabulous for him of course." He then went on to also get his PhD with distinction. "I was over the moon." The fact that they had both produced some fine publications, had done independent research work abroad and had done multidisciplinary research (Nordin combining epidemiology with lab work and Thomas working on the interface between neurology, internal medicine and psychiatry) clinched it. Thomas: "Afterwards people said: 'You both knew in advance that you were going to get your PhD cum laude', but we really had no idea."

They regard the distinction as an honour. Thomas: "The fact that Professor Stehouwer, whom we hold in high esteem, applied for it, that's perhaps what makes it an even greater honour." Nordin emphasises that all his colleagues at the lab, as well as in other labs where CARIM researchers work, had been indispensable in completing his PhD thesis. "I very much wanted to work at the lab, but I made some real gaffes at first. My cell line would get infected by a fungus, or I'd made a beautiful gel and then dropped it. Fortunately, Professor Schalkwijk, my other supervisor, and his staff at the lab are very patient. They taught me a lot and helped me when I

couldn't manage something myself. We're now talking about it as *my* thesis, but in fact a lot of people were involved, who are very good at lab work and always teach new students very thoroughly how to do things."

A BIT OF LUCK

At first Thomas particularly struggled with writing a decent research paper. "Your first paper takes ages and involves a lot of agonising and effort. But you learn the tricks, as these papers do more or less follow a standard pattern. CARIM's Department of Biomedical Technology was a great help during my PhD project, as were the CARIM Course Week and the CARIM Research Days, where you get to know the other PhD students." But in addition to all this help, Nordin also very much found he needed a bit of luck. "I worked very hard and managed to get some nice publications, but you're also dependent on the quirks of fate. That's frustrating for those people for whom the balance happens to tip the other way. I'm proud of my work, but luck has to be on your side too."

They are both currently working in district hospitals as part of their internal medicine training, and both try to do some research in their spare time. Nordin: "The medical training takes precedence, and research is now more of a hobby." Thomas: "I'm hoping I'll be able to continue doing research. The next step is to apply for grants."

Nordin: "Research was my primary interest, although I also like hospital work. Health care has improved massively, all thanks to scientific research. And there will still be a need for research, because although we already can do a lot, there's more to come. At the clinic I see people with foot sores from diabetes, kidney failure and cardiac infarctions. My hope is that one day we'll think: "We weren't really on top of that in 2016, but now we are. I don't know if that's realistic, but I hope it is."

COLOPHON

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