CARIM ANNUAL REPORT 2013

School for Cardiovascular Diseases

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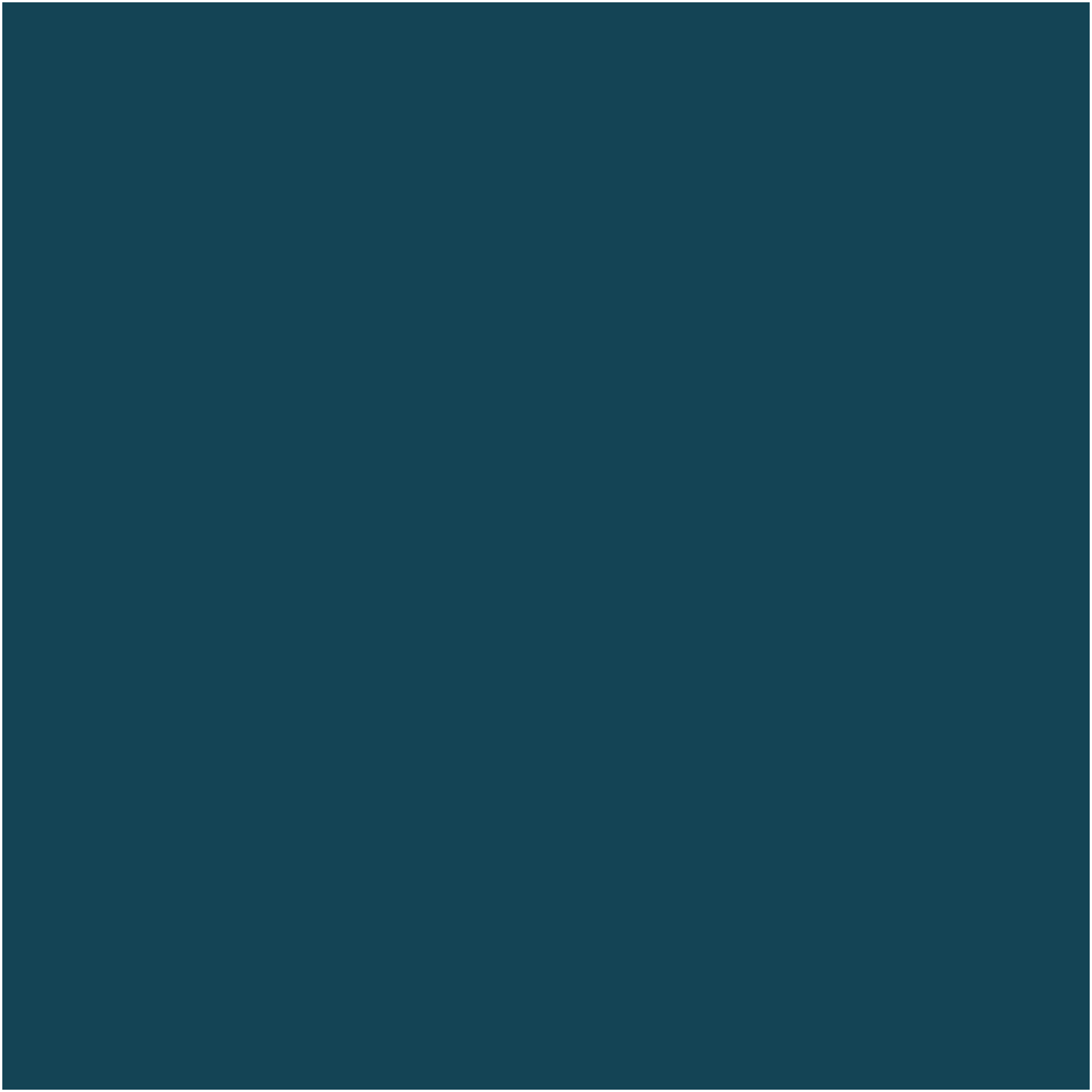

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PREFACE

The year 2013 was a special one for CARIM: The year of its 25th anniversary. CARIM's birthday was celebrated with a special, festive edition of the traditional yearly scientific CARIM Symposium focussing on its local, national and international context with recognized Dutch and international speakers and, of course, the traditional Robert Reneman lecture.

CARIM was founded in 1988 by Professor Rob Reneman, a renowned Dutch physiologist. In those days, a School for Cardiovascular Diseases at any university was by no means a common institution. Not only that it should assemble and coordinate those researchers following cardiovascular themes, but also that it might cross the boarders of research specialities in physiology, and pharmacology, biochemistry and pathology, cardiology, cardiac and vascular surgery and other disciplines, such as biomedical engineering, in an interdisciplinary fashion beyond the departmental units. That this idea can be considered today's commonplace is one of the merits of CARIM which has not only survived the storms and floods of more than two decades, but developed continuously and is now one of the leading institutions of its kind with a high international reputation.

Today, 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+ (MUMC+). With more than 250 researchers and staff in 27 PI groups (including about 100 PhD students) and an annual budget of approximately € 25 million Euros, CARIM is one of the largest cardiovascular research institutes in Europe, producing more than 600 scientific articles and around 30 PhD dissertations per year.

By its scientific directors, theme leaders and its financial director, CARIM has always been well adapted to the challenges of the time. To strengthen CARIM's scientific program, a Strategic Board has been installed in 2013. To improve academic education and the opportunities for students, the Training Program for MD's, master- and PhD students has been enforced and an initiative for a Marie Curie ITN within the EU program "Horizon 2020" between Maastricht, Aachen, Stockholm and London, aimed at joined doctorates between the institutions, has been started, coordinated by CARIM. The tenure track program of CARIM as well as the "Toptalenten" program of the university allow advanced young scientists to permanently enter academic rank and files. To further improve scientific quality, collaborations between Maastricht and other national and international academic institutions have been intensified or newly established. Examples are RWTH Aachen (joint doctorate within the EuCAR program) and the universities of Mainz and Münster in Germany.

Particular progress has been made in the field of cardiogenetics/-genomics and thrombosis/hemostasis by establishing joint professorships for mutual programs. A further asset is the "Maastricht Study" mainly organised and run by CARIM researchers since 2009, a longitudinal observation trial, aimed at comparing 5.000 diabetic versus 5.000 non-diabetic patients from the region in an extensive investigative protocol. Clinicians and basic researchers both can exploit a host of relevant data in a unique interdisciplinary, translational approach.

The implementation of the Maastricht Cardiovascular Centre (CVC), in which outstanding patient care and hospital organisation are given the scientific background provided by CARIM will provide MUMC+ a unique chance to excel in translational academic medicine.

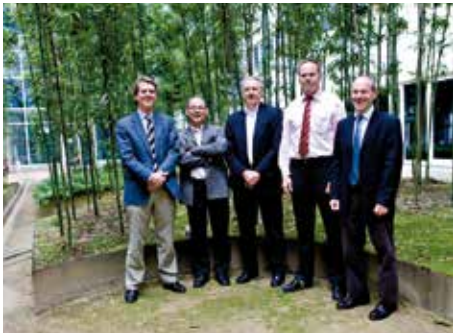
Last but not least, continuous education and scientific exchange are guaranteed by the weekly "Cardiovascular Grand Rounds" with lecturers from inside and outside the

institution, by the yearly “CARIM Symposium” and “CARIM Strategic Retreat” and by monthly “CARIM Joint Theme Seminars” just being established.

As elsewhere in our days, CARIM has to cope with severe budgetary constraints. However, these challenging circumstances also entail great possibilities. CARIM has to bring its research to an even higher level by sharpening the scientific profile and by increasing its visibility and influence in the cardiovascular field.

The current report will bring together the past and the present by a number of interviews in which CARIM’s founder and colleagues of the early days contrast their views with those of the present actors on the scene. One of them has entitled his interview with “You have to get out of your comfort zone”. While it is certainly correct and necessary to meet the challenges of today’s international biomedical science, CARIM does offer some comfort, too. The quality and enthusiasm of its researchers, the firm embedding in the scaffold-providing academic scene, a flat hierarchy and the help of the Dean’s office and the administrators that one can enjoy here in Maastricht, compensate to a certain degree for the many mishaps and frustrations that accompany the scientific career as much as the moments of success and celebration.

Professor Thomas Unger
Scientific Director CARIM
School for Cardiovascular Diseases



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PROFILE

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) Cardiac Function and Failure and III) Vascular Biology. These three themes comprise 27 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+. 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.

KEY FIGURES 2013

Annual budget: 24.877 K€
New contracts and grants: 7.362 K€
Researchers: 195 FTE
Technical and supporting staff: 76 FTE
Departments/disciplines: 13
Scientific articles: 605 (Wi-1: 518)
PhD theses: 34
Patents: 5

CARIM plays an important role in public-private research partnerships as main author and project manager of 6 out of 7 cardiovascular 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. Some of the CTMM programs were expanded with valorisation grants in 2013. Other public-private research partnerships in which our researchers participate are: the BioMedical Material program (BMM) and Top Institute Pharma. In addition, CARIM is a member of several international networks, including the EU seventh Framework Program (FP7) and the Leducq Transatlantic Network.

To translate research into clinical practice, CARIM, in close collaboration with the Heart-Vessel Centre (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).

‘I’m just an ordinary guy from Amsterdam’

In the early 1960s, Rob Reneman was sitting in a hotel lobby in Austria, when someone struck up a conversation with him. In the course of the conversation, he was offered the opportunity to become the agent for the Netherlands for “some type of cigarette lighter, I forget the brand name.” Reneman, who was then working as a doctor at the Central Military Hospital in Utrecht for his military service, was in Austria to settle the affairs of his late father, who had run an import-export business, and had died at a relatively young age. Rob rejected the offer. “I later heard that the company had a turnover worth millions, ha ha!” However, this was more than offset by the impressive scientific and administrative CV he later accumulated. An interview with CARIM’s now 79-year-old “founding father”, about politics, Amsterdam, intuition and playing marbles.

The red pencil with which he used to attack the manuscripts of his PhD students is legendary. This critical approach yielded an extremely thorough research culture, for which CARIM is still renowned today. His natural ability to combine basic research and clinical applications is another core value that has made CARIM’s reputation. But the main thing is cooperation.

During our two-hour talk, he mentions at least fifty names of people with whom he has had a pleasant working relationship, or people who are better in a particular field than he is, or people he has learned from, or whom he considers to show great potential. Just occasionally he cannot think of a name, which is actually not like Reneman at all, but “I’m not as young as I used to be, you know,” he sighs, “The number of grey cells is dropping off, and I have to be careful about using them wisely.” Some of the uses he put his grey cells to

in 2014 included evaluating the cardiovascular programme at the University Medical Centre Utrecht as chairman of the international evaluation committee, chairing the International Scientific Advisory Council of the Centre for Translational Molecular Medicine (CTMM), and writing two papers together with three colleagues who are also somewhat advanced in years: Ger van der Vusse, Theo Arts and Jim Bassingthwaighte from Seattle. The subject is the uptake of free fatty acids by cardiac muscle. Free fatty acids are the main energy source for the heart, but it is still unclear how exactly they are taken up. “We now think, using basic physico-chemical principles translated into an analytical model developed by Theo, that we’re coming to grips with the way lipophilic substances cross cell membranes and pass through watery compartments to be taken up by the cardiac muscle cell. We’re beginning to understand that now. In a way, life turns out to be simpler than you’d think. So that’s my latest tour de force.”

Hobby

The year 2015, when he turns eighty, would be a good time to stop, he reckons. “I also like to read books and do photography, and I’ve noticed in recent years that I find it more difficult to get up early.” He has never thought of stopping before. “My work is my hobby. I was 67 when my term as President of the Royal Netherlands Academy of Arts and Sciences ended. I was given the status of emeritus professor and a zero-time employment contract at the university. It took me some eighteen months to read up on the recent cardiovascular literature, and then I was back on the ball.” As he says himself, he has already been cutting down on his work in the last two years, by not starting a new project when one ended. “CTMM will end this year, so that will be finished. I’ve always thought in terms of projects. And I’ve arranged with CARIM that they can always call on me when I’m needed.” Although he is prouder of his scientific achievements, like his successful initiation of programmes on microcirculation, vascular ultrasound (together with Arnold Hoeks) and cardiac muscle mechanics, activation and metabolism, he nevertheless calls CARIM his baby. “You can’t give up on that.” It gives him great pleasure to see that the research programmes he has initiated are so successfully continued by the next generation.

Chauffeur-driven car

Rob Reneman had been working at Janssen Pharmaceuticals in Belgium for two years when in 1974 he was invited for an interview in Maastricht, where the medical school was being set up. “At Janssen I was head of the Department of Life Sciences, so I was in charge of some sixty people from seven disciplines. As long as you did your homework for product development, you had all the freedom and money you needed to do basic research. It was wonderful. If I’d been invited by an existing medical school, I would never have left. But I was attracted by this challenge of setting up something new. It meant a drop in salary, and losing a chauffeur-driven car, but my wife Wijnanda was always very good at that. When I was given the opportunity to go to Seattle for a post-doc in 1970, at a time when I had a job as a cardio-anaesthesiologist, her comment was: ‘Do we have bread and cheese for the kids? Right, let’s go’.”

Playing marbles together

His wife originally worked as a surgical nurse and later studied Dutch. Reneman did not meet her during his medical studies, however. “We used to play marbles together when we were twelve,” he smiles. “She’s originally from the Limburg town of Geleen. Our parents were friends and they would visit each other in Amsterdam or Limburg for many years. Her parents were Protestants, and they were always afraid that she would bring home a Roman Catholic boyfriend, so they sent her to Amsterdam to study. I started my studies at the same time, and bingo! That’s about 61 years ago now.” It meant that Reneman was already familiar with the Maastricht region at a young age.

Pooling strengths

His task in Maastricht, where he was appointed Professor of Physiology, first part-time and from 1975 on full-time, was to set up the Department of Physiology and a cardiovascular research programme. It was decided to organize research in programmes based upon projects. One year later, the decision was made to allocate faculty research funds not to departments but to the programme managements. “That basically laid the foundations for CARIM. When in 1988 new laws made it possible to set up a more independent institution within a university, we were the first in the Netherlands to make use of that, together with the Institute for Pharmacy in Leiden.” Even in the years before that, Reneman had worked hard to establish the three main research lines currently operational at CARIM. “We wanted to pool our strengths. There was funding available to attract good researchers from all over the Netherlands to Maastricht. We were able to set high standards. If a professor was among the top researchers in Europe, but was not prepared to conform to our joint research programme, we wouldn’t appoint him or her. It was my job to coordinate the various researchers, while still preserving their sense of self-respect, a task in which I could always rely on being assisted by Rob van der Zander, who was involved in all of the developments right from the start.” He also insists on mentioning the support he got from the faculty deans in those days, Harmen Tiddens and Co Greep. “Both of whom have sadly passed away since.” They supported him implementing his ideas.

Concerns

Looking back, he feels that the initial years were the best of all of CARIM’s 25 years so far. “We were able to attract top-researchers, in some years we managed to secure two major programme grants, and got funds from NWO stimulation programmes and EU subsidies. There was flexible money available. One of the strong points was that we didn’t have to produce a research paper the very next week. We were able to take our time to work on new developments, which got us excellent results.” The most difficult years in his view were those following the rather sudden departure of Mat Daemen as Scientific Director in 2011. “There was no successor, which meant a break with the policy we had pursued until then. When I retired as Scientific Director, we had already decided two years before that Harry Struijker Boudier would succeed me. And it had also been decided well in advance that Mat would succeed Harry. Miscommunication and other issues meant that it took eighteen months before Thomas Unger could take over after Mat left. In a situation of international competition, that’s an interregnum you can’t afford. I’ve seen other institutions in the country collapse after the leader left, as the succession had not been suitably arranged, and in fact the coherence here at CARIM also suffered. I talked to all management echelons then because I was very concerned.”

Common interest

He has always made sure he wouldn’t get in the way of his successors. “Only when it’s something that affects the common interest, like at that time. Otherwise, I won’t interfere.” Serving the common interest is one of the tips he has for others. “It’s hard to say why one person is more successful than another, but I think that social skills are as important as knowledge and creativity. That doesn’t mean you can always remain good friends with everyone; that’s impossible when you’re leading an academic institution. You will have to disappoint people sometimes; “I always tell them what I think”. I try to convince people with arguments. I can’t and won’t argue about peripheral issues and I won’t try to score off people. That means I can’t be bothered with politics.” When he was asked whether he might like to become the Minister of Education and Science, it took him less than half a minute to decide. “I’d be completely unsuitable for that. I’d have been sent packing by Parliament within a week, because I’m telling it like it is.” Reneman often introduces such straightforward opinions with “I’m just an ordinary guy from Amsterdam…”

Amsterdam
Talking about Amsterdam makes Reneman almost as enthusiastic as talking about research. “To me, there’s only one city. Amsterdam is emotion. When I’m walking along the canals, which we fortunately still manage to do quite often, it makes me feel very happy. When I stroll around in Amsterdam, I see the streets where I used to play soccer as a kid. It’s always easy to start a chat with someone at a pub. Actually, Maastricht is not bad in that respect either. I’ve often said that this city is the only alternative to Amsterdam.” He was born an only child in one of the better working-class neighbourhoods. His parents sent him to a strict Protestant primary school. “That was quite an ordeal. Even as a child, I knew there was something wrong, though I couldn’t put it into words. It was not a very pleasant time. On Monday morning, the teacher would ask us who had been to church. The only ones not to raise their hands were me and a friend I have known since I was three years old, and with whom I had dinner just a week ago. We were the outcasts.”

Don’t become a one-trick pony!

Starvation
He well remembers World War II, which started when he was nearly five. “I can still vividly see the round-ups. I lived through the terrible winter of starvation in 1944/45. That was awful. You’d see people collapse in the street from hunger. My father used to bake biscuits from sugar beets with microscopic quantities of flour. We were lucky in that we had two farmers in our family, and that my father had a business which enabled him to trade cigarette papers for food. The dark memories of that war will never go away.” The loss of two of his children, one after only two days and one at the age of 31, was another heavy blow that sometimes still haunts him. “If I have a work-related problem or suffer a setback, I can put it behind me in 24 hours. You learn from your mistakes, and then it’s over and done with. But it’s totally different with private matters.” He nevertheless considers himself a lucky man. “Apart from the deaths of my two children, my life has been very smooth. I never tried hard to secure a professorship, or the presidency of the Royal Netherlands Academy of Sciences, which I got in 1999. Maybe those things happened because I worked hard, in the common interest. It wasn’t unusual for me to work 80 hours a week. When I get an idea, I like to realise it, or find someone to realise it, at once. I’m an organiser. My wife did a fantastic job raising our children, mostly on her own. When I was still active in the clinic and came home late at night, I would often get the kids out of bed to play with them for a short while. That was the only time I saw them. Fortunately, I was able to make up for that later, and we get along really well. They all come to Maastricht a number of times a year. The highlight of the year is always the Christmas dinner, when we have sometimes 23 people at table.” Reneman has nine grandchildren by now, including the child of their protégé daughter.

People with great potential
Finally we return to his 25-year old brainchild, CARIM. What are his expectations for the future? “I’m afraid the coming period will not be easy, for one thing because some major sources of funding like CTMM, which have benefited us greatly in the past, are going to end. I think the university should take more interest in its top institutions. Current cutbacks mean that they no longer have flexible funds for new policies, like responding to new developments and offering young top-ranking researchers good career options. I’m very pleased with the tenure track programme at CARIM, which includes some people with great potential. I particularly admire the young women, who have small children at home and who are doing great work. My best advice to young researchers is to follow their own path and to believe in themselves. Follow your intuition and keep an eye open for what’s springing up in neighbouring gardens. Don’t become a one-trick pony! At least that’s what helped me a lot in life.”

Cardiovascular Centre of Excellence Maastricht UMC+

Thomas Unger and Michael Jacobs

An international Centre of Excellence (COE), that is what the Cardiovascular Centre Maastricht UMC+ (CVC Maastricht) aims to be "in the foreseeable future". But what exactly does that mean, a COE? And what is currently missing in Maastricht, where there is already a long and high-quality tradition in cardiovascular care, and 25 years of excellent research? Professors Michael Jacobs and Thomas Unger, in charge of the Heart and Vascular Centre (HVC) and CARIM, respectively, explain. "In a relatively small town, with a relatively small university, not having the resources foreign governments tend to pour into their institutions, we have to find the niches where we can excel."

Talking to the two men who are responsible for the clinical and research aspects of cardiovascular diseases in Maastricht clears things up considerably. Briefly: there is already a great deal of cooperation between the clinic and academia in this field in Maastricht, more so than in similar European institutions. But it can always be improved and expanded. And that is where money and size come in, immediately followed by the need to pick your battles. "We can't excel in every domain", says surgeon Michael Jacobs. "Therefore we chose two fields in the clinic: arrhythmia together with heart failure, and aortic pathology." On the CARIM side, five focal areas were chosen: thrombosis, arrhythmia, heart failure, macrovascular and microvascular. Excellence arises when basic research interacts with the clinic, they explain. Thomas Unger: "That synergy benefits society. And to be able to do that, your research and patient care need to be in the A-class, the only appropriate class in the biomedical field." Thrombosis is a good example, they think, of a topic that is already very productive in this sense. Thomas Unger: "I've never seen such an accumulation of

excellent thrombosis people in one institution as we have here in Maastricht."

One cardiovascular unit

In recent years, the clinic has put a lot of effort in reorganizing its cardiovascular care, Michael Jacobs says. "Cardiology, cardiac surgery, vascular surgery and vascular medicine were historically, and are still in the rest of the world, independent, solitary units. It took us ten years to make this into one organisation. That may sound a very obvious thing to do, but it's all about humans and then it's not that obvious anymore." Logistically and financially there is one cardiovascular unit now, plus a cardiovascular outpatient clinic. The next step was, some five years ago, to sit down together with CARIM management to align the research and care interests. "Everything that did not fit in this alignment was eliminated", according to the surgeon. Hence, all preconditions were then met to build a Centre of Excellence. Because, as Thomas Unger explains, "the immediate benefit is usually on the clinical side. Surgically, they are already excellent anyway, but we can optimize care organisation, devices and so on. On the research side, CARIM is already performing in the A-class. This can be measured by number of publications, impact factors, grants, awards and viability. On an international level we can keep up with places like London, Berlin and Paris."

Exploiting knowledge

It is quite a challenge to keep up with centres like the University of London in the research field, or the Cleveland Clinic in the States when it comes to cardiovascular care. Thomas Unger: "Not having the resources the British government pours into these institutions, we have to find the niches where we can excel." Michael Jacobs: "It's also about volume. Maastricht is a village, and we will never have the volume of a city like Cleveland. They have a referral area of five to ten million people, here it's 1.2 million max. Therefore it's our goal to be in the top 5 in Europe in our two specified domains."

Another big difference is the culture, they argue. Thomas Unger: "The Anglo-Americans have a very success-driven system, rooted in the Anglo-Saxon tradition. They want to exploit the knowledge, and they are not afraid of forming an elite that goes for excellence." And they have rich sponsors and angel money in the States, for example to build hospital facilities, Michael Jacobs explains. "We will manage to get funding through our board and the government, by showing that we offer true translational research, that we integrate the two parts of this building into one efficient productive cooperative organisation and that every invested euro is worth it." Which does not mean, they emphasize, that fundamental research is no longer valued in Maastricht. Thomas Unger: "If you choose to only invest in direct translational research, eventually there's not enough creativity and intelligence to keep excelling. We try to channel the creativity in the direction of the five themes."

Pretty unique

And then, with a new European cardiovascular training centre which will be built next door, with extra "brains and hands" for which the UMC+ board has already allocated long-term funding, and with the new animal facility for cardiovascular research (Thomas Unger's priority until the first sod is cut), CVC Maastricht is on its way to become the COE it aspires to be. Michael Jacobs summarizes: "As long as we work together, share one board and have one common target, we are already far ahead of many centres in Europe. We are pretty unique in that respect. Although I do realize we are slightly biased", he laughs.

‘I was able to focus on the content’

When Ward Vanagt (1975) started training to become a paediatrician at Maastricht University Medical Centre in 2005, he had not yet completed his PhD thesis. In 2007, CARIM arranged for him to be granted a two months’ leave so he could work on his research project full-time and obtain his PhD degree that same year. “That was very useful,” says the former PhD student. “If you can only work in the evenings and weekends, you do less in a year than what you can do in two months working full-time. I only realised with hindsight how important CARIM is.”

It was in his second year of studying medicine that Ward started to work as a research assistant at the laboratory led by Professor Frits Prinzen, where he saw how important and interesting the combination of research and patient care is. Ever since, thanks to Frits, he has always opted for this combination. Ward is a full-time member of the hospital’s medical staff and is seconded to CARIM for two days a week to do research, with a tenure track that will end in three years’ time.

Valuable information

As a paediatrician (having completed his training in 2010), Ward Vanagt is especially interested in research that leads to relatively rapid practical applications. For example, he recently investigated a drug that might protect the heart against a shortage of oxygen. He evaluated its effect on children who were undergoing heart surgery, as well as on test animals which were resuscitated after a cardiac arrest. “Unfortunately, the level of protection proved insufficient in both situations. That is valuable information, but unfortunately it’s not easy to get it published in a scientific journal. Even though everyone agrees that this is of equal scientific interest as a ‘success story’, this is the way things work in science. In

any case, it's important to ensure that others don't needlessly repeat my experiment."

Exciting

This research was a spin-off of his PhD project, in which he showed that the heart can be protected against the damage caused by oxygen shortage, for instance by means of a pacemaker. His research also showed that the location of the pacemaker electrode, especially in young children, is crucial for the heart's pump action. He currently works as a paediatrician specialized in congenital heart disease. "Patient care is exciting every day, and I enjoy the contacts with so many different people, whereas research is exciting at peak moments and you work with a small group of people. I also enjoy that a lot. They complement each other: experimental research allows you to test really new ideas, which would be unethical or even impossible with patients." Hence, he would very much like to continue doing research. "So it's very important for me to meet the criteria of my tenure track."

Collaboration

It was especially in retrospect that he realised the importance of an institute like CARIM. "You work at a department, in my case that of Physiology, but you always need help from other people or equipment, for instance from the Department of Pathology or that of Biomedical Technology. Thanks to CARIM that was always easily arranged. This type of PhD project is impossible without a parent institute that encourages collaboration and acts as a guarantor. There was always this trust and it was great to be able to focus on the research content, as logistical matters were taken care of. But you only really realise that with hindsight."

Ward Vanagt received his PhD on 21 December 2007, under the auspices of CARIM, supervised by physiologists Frits Prinzen, Tammo Delhaas and Ger van der Vusse, having written a thesis entitled 'Pacing-induced dyssynchrony. Blessing or curse'.

CARIM SCIENTIFIC DIRECTORS 1988-2013

Prof. Rob Reneman
Scientific Director: 1988-1999

Prof. Harry Struijker Boudier
Scientific Director: 1999-2006

Prof. Jan Rosing
Scientific Director (a.i): 2006

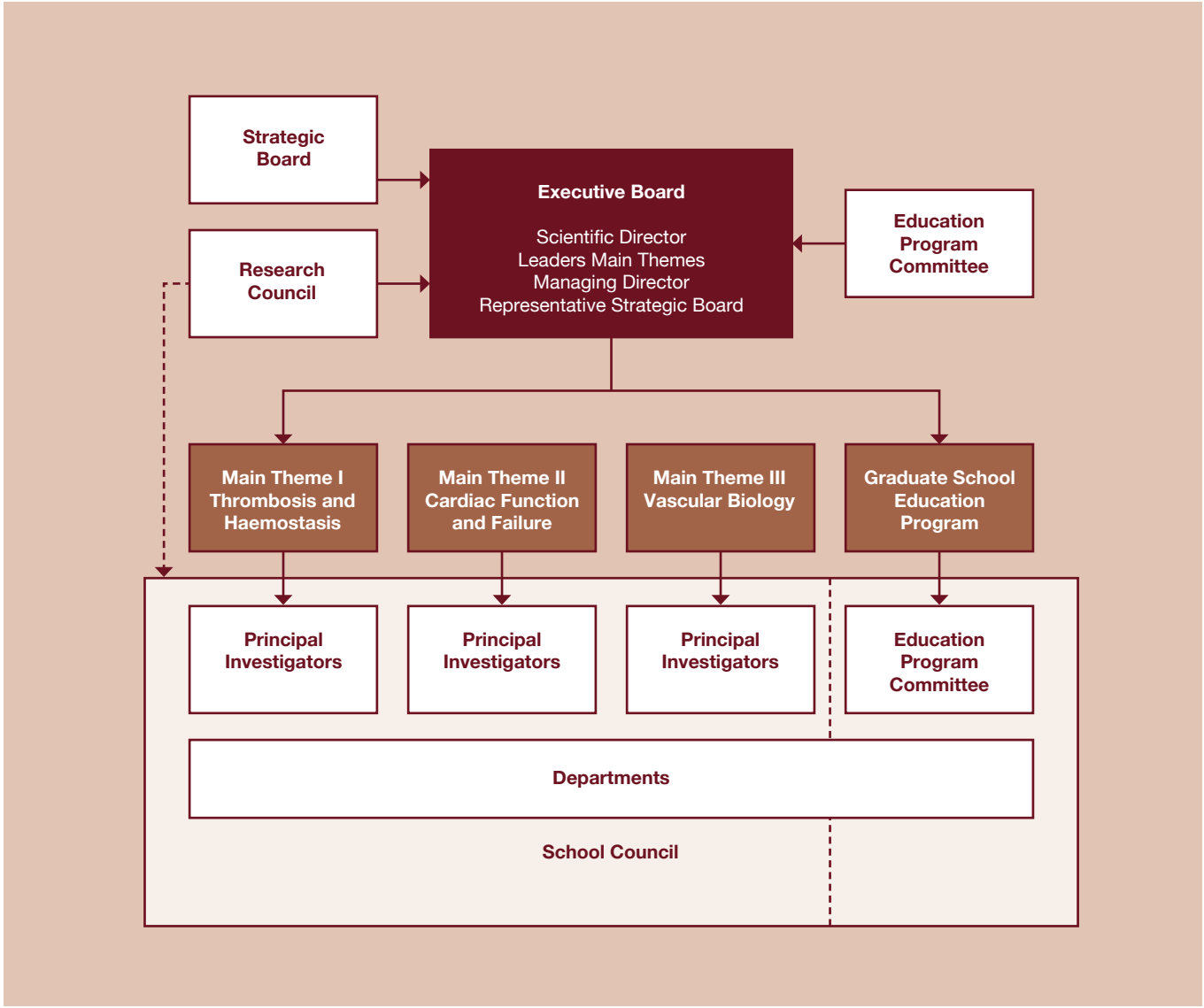
Prof. Mat Daemen
Scientific Director: 2006-2011

Prof. Mark Post
Scientific Director (a.i): 2011-2012

Prof. Thomas Unger
Scientific Director: Since April 2012

02_ ORGANISATION

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 SB, 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 3 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 PIs and department heads and meets four times a year.

Executive Board
- Professor Thomas Unger, Scientific Director
- Professor Tilman Hackeng, Leader Main Theme I
- Professor Harry Crijns, Leader Main Theme II
- Professor Coen Stehouwer, Leader Main Theme III
- Professor Leon de Windt, representative Strategic Board
- Rob van der Zander, Managing Director
- Petra Uittenbogaard, advisor and project manager (until August 2013)

Strategic Board
- Professor Stephane Heymans
- Professor Uli Schotten
- Professor Thomas Unger
- Professor Tilman Hackeng
- Professor Hugo ten Cate
- Professor Harald Schmidt
- Professor Leon de Windt

Principal Investigators (and Research Council)
- Professor Erik Biessen, Dept. of Pathology
- Dr Matthijs Blankesteijn, Dept. of Pharmacology
- 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 Physiology (from January 2013)
- Professor Leo Koole, Dept. of Biomedical Engineering
- Professor Peter de Leeuw, Dept. of Internal Medicine
- Professor Jos Maessen, Dept. of Cardiothoracic Surgery
- Professor Robert van Oostenbrugge, Dept. of Neurology (from February 2013)

- Professor Mark Post, Dept. of Physiology
- Professor Frits Prinzen, Dept. of Physiology
- Professor Chris Reutelingsperger, Dept. of Biochemistry
- Professor Harald Schmidt, Dept. of Pharmacology
- Professor Uli Schotten, Dept. of Physiology
- Professor Bert Smeets, Dept. of Genetics and Cell Biology
- Professor Coen Stehouwer, Dept. of Internal Medicine
- Professor Harry Struijker Boudier, Dept. of Pharmacology (from January 2013)
- Professor Hans Vink, Dept. of Physiology
- Dr Paul Volders, Dept. of Cardiology
- Professor Christian Weber, Dept. of Pathology
- Professor Joachim Wildberger, Dept. of Radiology
- Professor Leon de Windt, Dept. of Cardiology

Education Program Committee

- Dr Marc van Bilsen, PhD coordinator and chairman
- Dr Adriaan Duijvestijn, coordinator Research Master
- Dr Matthijs Blankesteijn, staff member
- Dr Eline Kooi, staff member
- Professor Hans Vink, staff member
- Dr Simone Sep, staff member (since September 2013)
- Yvonne Oligschläger, PhD student
- Siamack Sabrkhany, PhD student
- Emiel van der Vorst, 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 Yves Engelen 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, Joost von Weersch and Jan Willem Janssen.

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 MUMC+.

Basic Research Departments
Biochemistry
Biomedical Engineering
Genetics and Cell Biology
Pharmacology
Physiology

Clinical Departments
Cardiology
Cardio-thoracic Surgery
Clinical Chemistry
Internal Medicine
Neurology
Pathology
Radiology
Surgery

CARIM office: Tara de Koster, Riet Daamen and Esther Willigers

The researcher as courier between Maastricht and Munich

It was at CARIM that Remco Megens learned the importance of thorough research. “They certainly drove home the absolute need for quality”, he smiles. And his current manager, Christian Weber of the Institute for Cardiovascular Prevention (IPEK) at Ludwig-Maximilians Universität München and CARIM, taught him how sometimes you just have to get on with it. “It’s that combination that has shaped my work as a researcher.” The research environment in Munich, where he has been working since 2011, offers many opportunities and opens many doors. This more than compensates for the seven hours he spends on the train twice a week, as he is still living in Maastricht.

Remco Megens specializes in microscopy. The topic of his PhD thesis was the 2-photon microscope, with which he produced 3D images of the large arteries in living mice and studied their sensitivity to atherosclerotic plaque formation in relation to the structure of the arterial wall. “I’ve specialized further in that technology and I‘m still working with it at my lab. Recently I’ve also started to work with optical nanoscopy and I’m developing methods to use this type of equipment for cardiovascular research.”

His own lab

After a period in which Remco worked as a post-doc at CARIM and the pharmaceutical company AstraZeneca in Sweden, Christian Weber invited him in 2008 to come and work with him in Aachen. They had met while Remco was still a PhD student. “I loved the work. Things were moving very fast there, and still are, with large investments and lots of opportunities. I was given greater responsibility and more freedom. And then, just as my wife and I had bought a house in Maastricht and our second child was on the way, Christian

Weber told me he was moving to Munich, and invited me to join him there."

Dynamic environment

Since his wife had a permanent job and they had been building a life for themselves at Maastricht, moving house to Munich was not really an option. "And it would also have been a shame if I'd had to leave this lab at the time." Since then, Remco has been taking the train to Munich on Monday and travelling back on Thursday. "That's not always ideal of course, but my family are able to deal with it very well, and it's very rewarding for me professionally. Munich is a very interesting place for scientific research, with numerous opportunities for collaboration. Christian Weber's lab employs a lot of young and ambitious researchers, making it a very dynamic environment. We work in high gear and Christian Weber shows us every day that you need to be fully committed if you want to get anywhere in research. No ifs or buts, but just get on with it. Provided of course that you have the means to do so, but those are in ample supply too."

Network

Much of his network still consists of people he met during his time at CARIM. "At the time I was the only PhD student in the Biophysics Department, and I got to know colleagues from other departments through the courses that CARIM offered. I'm still in touch with some of them. And I've also benefited from CARIM's reputation." He now has a (zero-time) employment contract at the Biomedical Engineering department, and is working with Koen Reesink, Bart Spronk and others, as well as with his former supervisor Marc van Zandvoort. "Since I travel to Munich each week, I also function as a courier carrying materials back and forth. So they still see me regularly at CARIM."

Dr Remco Megens received his PhD on 14 March 2008, having been supervised by physicists Marc van Zandvoort and Dick Slaaf and physiologist Mirjam Oude Egbrink, and having written a thesis entitled 'Vital imaging of large arteries using two-photon laser scanning microscopy: focus on the arterial wall'.

When antisense makes sense: RNA therapy of factor V deficiency

Elisabetta Castoldi, Department of Biochemistry

Antisense technology is emerging as a powerful tool to modify pre-RNA splicing and may find application in the treatment of genetic diseases caused by splicing mutations. Here we describe the *in vitro* and *ex vivo* correction of a splicing defect responsible for a severe bleeding disorder.

Factor V deficiency

Coagulation factor V (FV) is a large glycoprotein produced by the liver. It is present in plasma (~80%) and platelets (~20%) and plays an essential role in the conversion of prothrombin to thrombin. Complete absence of FV is not compatible with life, but the FV requirement for minimal haemostasis is extremely low (<1%).

FV deficiency is an autosomal recessive disorder associated with a variable bleeding tendency, which is mainly determined by residual platelet FV. The most common symptoms are mucosal and trauma-induced bleeding, while joint and muscle bleeds are less common and intracranial haemorrhages are rare. Since no FV concentrate or recombinant FV preparation is available, treatment still relies on the administration of fresh frozen plasma and platelet concentrates, with all the well-known complications. To date, 150 different *F5* gene mutations have been identified in FV-deficient patients. Splicing mutations represent 11% of the total and are most often associated with severe bleeding symptoms.

Our patient

A couple of years ago a patient with undetectable FV and multiple life-threatening bleeding episodes (including two spontaneous intracranial haemorrhages) was referred to our laboratory. Genetic analysis revealed a homozygous mutation deep in intron 8 (IVS8+268A>G). This mutation introduces a

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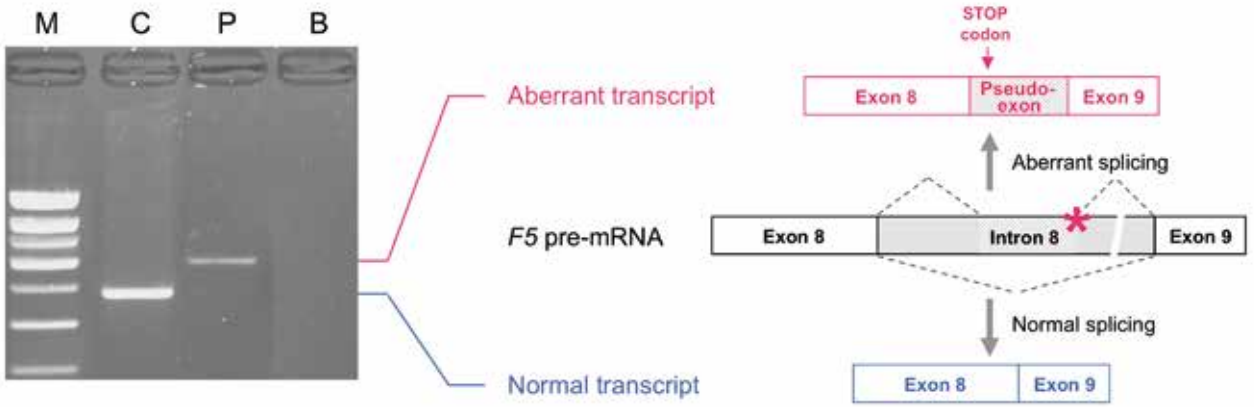


FIGURE 1 The patient's splicing defect. Left. Total platelet RNA from the patient and a normal control was isolated and reverse transcribed to cDNA. A *F5* cDNA fragment spanning exons 8-11 was amplified and analysed by agarose gel electrophoresis. M, molecular weight marker; C, normal control; P, patient; B, blank. Right. Schematic representation of the normal and aberrant splicing products. The red asterisk on the *F5* pre-mRNA marks the position of the IVS8 +268A>G mutation.

novel donor splice site, which - in combination with a constitutive acceptor splice site located upstream in the same intron - causes the retention of 111 nucleotides of intron 8 (a "pseudo-exon") in the mature *F5* mRNA (Figure 1). The presence of an in-frame stop codon in the pseudo-exon causes the aberrantly spliced transcript to be degraded and precludes the synthesis of functional FV. Analysis of platelet mRNA indicated that only a tiny fraction (<1%) of the patient's *F5* pre-mRNA was spliced correctly (Figure 1), accounting for the patient's undetectable FV level and severe bleeding diathesis.

Molecular therapy

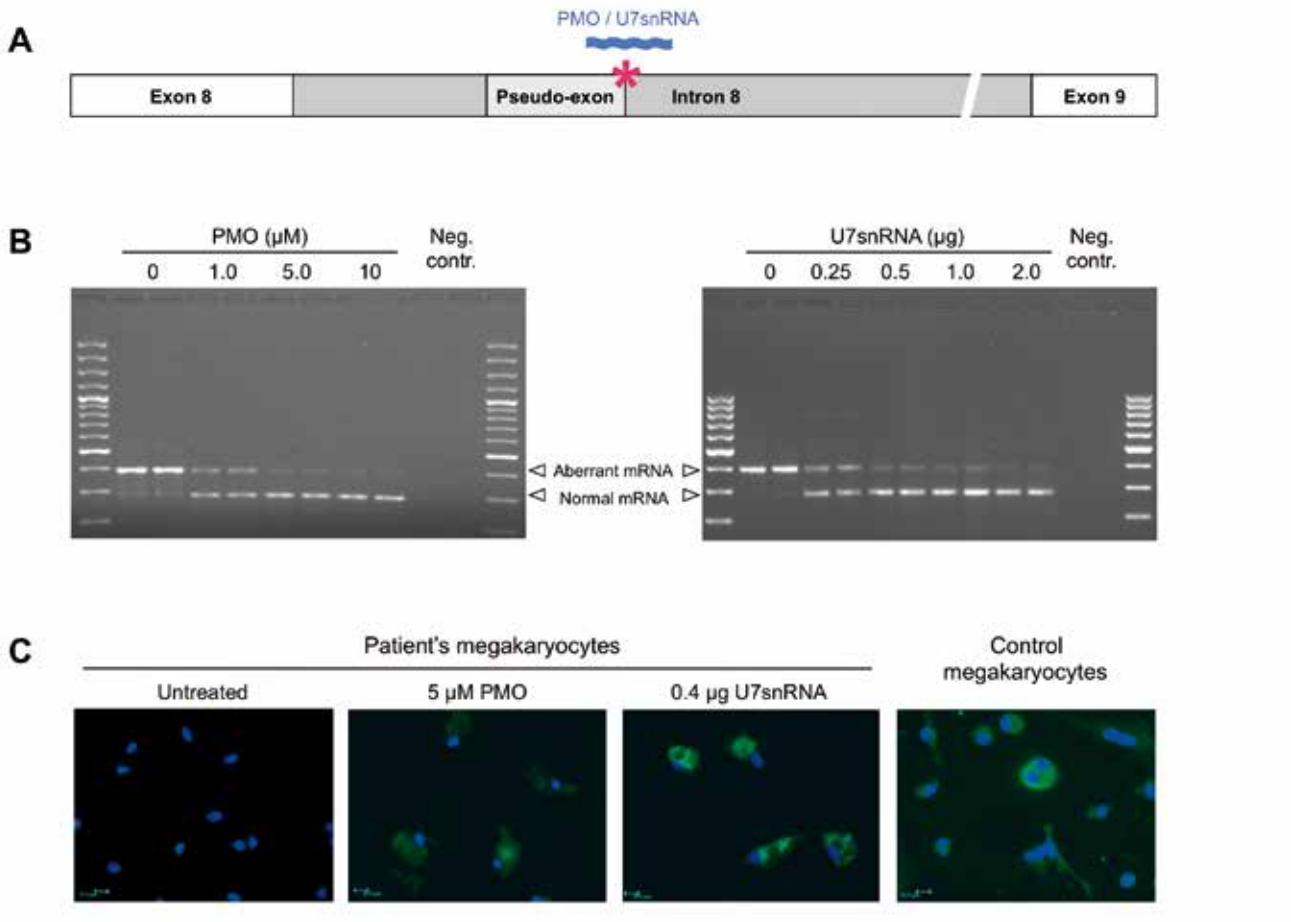
In an attempt to correct the patient's splicing defect, we designed antisense molecules complementary to the *F5* pre-mRNA at the mutation site, hoping that they would hide the incorrect splice site and suppress the aberrant splicing event (Figure 2A). Two different types of antisense molecule were tested: (1) a phosphorodiamidate morpholino oligonucleotide (PMO) and (2) an engineered U7 small nuclear RNA (U7snRNA). The ability of these molecules to correct the splicing defect was tested in an *in vitro* model and *ex vivo* on the patient's own cells.

The *in vitro* model consisted of a *F5* minigene encompassing exon 8, intron 8 (containing the patient's mutation) and exon 9. The *F5* minigene construct was introduced in COS-1 (kidney) and HepG2 (liver) cells and mRNA was analysed 48 hours post transfection. While untreated cells almost exclusively produced the aberrant transcript, treatment with increasing concentrations of the mutation-specific PMO or U7snRNA resulted in a progressive increase in the correctly spliced transcript (Figure 2B). This effect was specific, as control antisense molecules with irrelevant sequences did not affect the splicing pattern.

The *ex vivo* model consisted of the patient's megakaryocytes obtained by *ex vivo* differentiation of circulating haematopoietic progenitors. Megakaryocytes obtained from normal donors showed abundant FV expression (Figure 2C). In contrast, the patient's megakaryocytes did not show any sign of FV expression when left untreated, but became FV-positive after treatment with mutation-specific PMO or U7snRNA (Figure 2C).

Conclusion

In summary, mutation-specific antisense molecules were able to correct the patient's *F5* splicing defect *in vitro* and restore FV synthesis in the patient's megakaryocytes *ex vivo*. These findings provide proof-of-principle for the efficacy of antisense-based RNA therapy in severe FV deficiency.



References

Castoldi E, Duckers C, Radu C, Spiezia L, Rossetto V, Tagariello G, Rosing J, Simioni P. Homozygous *F5* deep-intronic splicing mutation resulting in severe factor V deficiency and undetectable thrombin generation in platelet-rich plasma. J Thromb Haemost 2011; 9: 959-68.

Nuzzo F, Radu C, Baralle M, Spiezia L, Hackeng TM, Simioni P, Castoldi E. Antisense-based RNA therapy of factor V deficiency: *in vitro* and *ex vivo* rescue of a *F5* deep-intronic splicing mutation. Blood 2013; 122: 3825-31.

FIGURE 2 Splicing correction by antisense molecules. (A) Correction strategy. The red asterisk marks the position of the IVS8 +268A>G mutation, and the blue ribbon represents the antisense molecules used to hide the incorrect donor splice site. (B) *In vitro* correction model. COS-1 cells transfected with the mutant *F5* minigene were treated with increasing concentrations of mutation-specific PMO (0-10 µM) or U7snRNA (0-2 µg). After 48 hours, mRNA was isolated and analysed by agarose gel electrophoresis. (C) *Ex vivo* correction model. Patient's and control megakaryocytes were obtained by *ex vivo* differentiation of circulating haematopoietic progenitors. FV protein expression in untreated cells and in cells treated with mutation-specific PMO (5 µM) or U7snRNA (0.4 µg) was visualised by immunofluorescence staining (green colour).

‘We can now make long-term investments’

Bas de Laat,
(Deventer, 1976),
Associate Professor,
CEO of Synapse BV

What are you researching?
“My research mostly focuses on a protein called thrombin, the final enzyme in the reaction pathway that makes the blood clot, that is, make it change from a liquid to a solid state. Professor Coen Hemker, one of the founders of the UM and the founder of the UM spin-off company Synapse BV developed a test that determines the risk of thrombosis or haemorrhage by testing a small blood sample. That test is now being used in about a thousand labs all over the world. Our research is continuing along those lines. Our knowledge is used to develop diagnostic tests. I’m working at both Maastricht University and Synapse, just like the other thirty staff here. To me, this is an ideal partnership. For instance, we’ve managed to obtain a patent on a protein, which is owned jointly by the UM and Synapse, on a fifty-fifty basis. Synapse shares ideas with the university, and the name Maastricht University is also mentioned in our papers, and we can make use of the UM’s research facilities.”

Why Maastricht?
“I was invited to become CEO of Synapse in 2010. At the time I was head of the Coagulation Department and worked as a researcher at the Sanquin blood bank. Synapse is my research group, of which I’m the manager and the co-leader with Coen Hemker as far as research is concerned. The unique aspect at Maastricht is this relationship between business and research. If you have an idea, Maastricht University offers you quite a few opportunities to start up your own company and use that to generate money that you can invest in research again. Many universities tend to look down on that, whereas I think that’s where the future lies.

The nice thing here is that we’re able to make long-term investments, as we have a steady source of funding. Our

research is not cut short because a grant expires. Our parent company, STAGO in France, has no shareholders but an owner, and that owner has decided to invest in thrombin generation for the next twenty years at least, so that offers us a uniquely secure position.

We have to spread the word “thrombin” around, obtain a number of patents each year, as well as producing a number of publications, ideas and perhaps a prototype. Apart from that, we’re also given the freedom to experiment. A good example is our research into the effect of oxygen shortage and exercise on thrombosis in the Alps, in 2013. It got us a lot of publicity, meaning that we increased the awareness of thrombosis and thrombin. Oxygen shortage increases the risk of thrombosis, as does exercise. We were the first to examine these effects separately, using a unique approach.”

What does CARIM mean to you?
“Excellent collaboration, regarding knowledge and facilities, which benefits both parties equally. A patent on a protein is going to generate lots of funds for research at CARIM.”

How far ahead are you looking?
“A few years, I’ve always planned ahead, and so far I’m on schedule. I was invited to join the Faculty’s top talent class in 2014, with as final goal of securing a full professorship. That makes me feel appreciated. I’m ambitious, and apparently they’ve noticed me. Full professor is a nice title, but the main thing is that it opens more doors to research funding. For example, two of my projects are being co-funded by the Netherlands Heart Foundation.”

What are you proud of?
“Being able to combine my private life with my work. I start work at seven thirty in the morning, which enables me to get home by five to have dinner with my wife and three children. I do often work in the evening, but apart from Sunday evening, I spend the weekends with my family. You get better at that over time. If you are surrounded by the right people, you can delegate quite a lot. In my view, the best researchers are those who really care about their work, and who really take it to heart when things go wrong. I know from experience that those are also the people who are most likely to become overworked. Nevertheless I prefer a really committed and enthusiastic researcher who might be slightly less intelligent to a brilliant person who is lazy.”

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FACTS AND FIGURES

Funding and expenditure at institutional level 2008-2013

	2008 K€	2009 K€	2010 K€	2011 K€	2012 K€	2013 K€
Funding						
Direct Funding structural	8.239	8.653	8.411	8.242	7.391	7.419
Direct Funding specific programs	3.044	3.606	3.603	2.830	2.717	2.272
Total Direct Funding (1)	**11.283**	**12.259**	**12.014**	**11.072**	**10.108**	**9.691**
Research grants (2)	1.411	1.201	2.140	1.284	1.566	1.730
Contract research (3)	8.812	9.385	9.900	13.202	13.464	13.456
	10.223	**10.586**	**12.040**	**14.486**	**15.030**	**15.186**
Total funding	**21.506**	**22.845**	**24.054**	**25.558**	**25.138**	**24.877**
Expenditure						
Personnel costs	13.534	14.656	15.024	15.984	16.492	17.501
Other costs	7.144	6.469	7.474	7.855	8.475	8.379
Total Expenditure	**20.678**	**21.125**	**22.498**	**23.839**	**24.967**	**25.880**
Result	**828**	**1.720**	**1.556**	**1.719**	**171**	**-1.003**

(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 2008-2013

	2008	2009	2010	2011	2012	2013
School level						
Scientific publications	466	514	544	571	635	605
Other publications	53	45	37	53	80	50
PhD theses	30	32	35	39	50	34
Total* (I)	**549**	**591**	**616**	**666**	**765**	**689**
Academic staff** (II)	**37,4**	**37,0**	**38,3**	**34,3**	**33,1**	**32,4**
Ratio I and II	**14,7**	**16,0**	**16,1**	**19,4**	**23,1**	**21,3**
Theme I						
Scientific publications	77	89	95	107	108	111
Other publications	6	9	6	12	12	13
PhD theses	9	9	5	8	8	7
Total	**92**	**107**	**106**	**127**	**128**	**131**
Theme II						
Scientific publications	141	153	190	214	246	240
Other publications	10	11	6	13	25	20
PhD theses	11	8	9	14	20	17
Total	**162**	**172**	**205**	**241**	**291**	**277**
Theme III						
Scientific publications	275	321	312	309	353	331
Other publications	35	26	25	28	45	22
PhD theses	15	15	21	17	22	12
Total	**325**	**362**	**358**	**354**	**420**	**365**

* 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 2013

Funding	Theme I	Theme II	Theme III	Total Support K€
Type 2	300	431	-	731
Type 3	942	2.198	2.154	5.294
Type 4	465	359	264	1.087
Type 5	250	250	250	750
Total	**1.957**	**3.238**	**2.668**	**7.862**

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 2013: 1.705 K€)

Type 5 = Annual support (750 K€) Cardiovascular Center-CARIM “Pieken vanuit de Breedte”

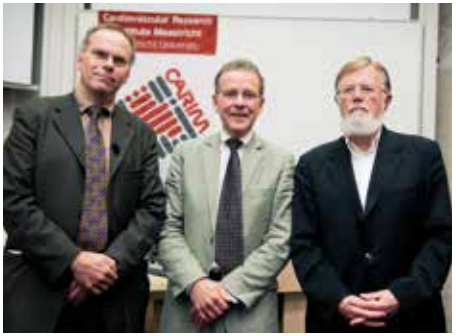
Summary of scientific and technical staff CARIM 2013 (in FTE)

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	7,3	4,5	1,1	-	-	2,3	0,3	13,8	2,9	1,6	4,8	5,8	0,4	44,8
Cardiac function and failure	11,9	7,1	2,5	1,0	8,0	3,7	0,1	18,1	12,6	-	1,3	0,6	1,0	67,8
Vascular biology	13,3	8,2	4,2	0,6	0,5	2,9	1,9	26,6	18,8	-	0,7	0,2	4,5	82,1
Total	**32,4**	**19,8**	**7,8**	**1,6**	**8,5**	**8,9**	**2,3**	**58,5**	**34,3**	**1,6**	**6,7**	**6,5**	**5,9**	**194,7**

	OBP 1	OBP 2	OBP 3	OBP 4	OBP azM	TOTAL
Thrombosis and haemostasis	5,4	-	2,8	3,2	1,3	12,8
Cardiac function and failure	13,6	2,8	3,4	-	-	19,8
Vacular biology	14,8	-	23,9	2,0	2,6	43,3
Total	**33,8**	**2,8**	**30,1**	**5,3**	**3,9**	**75,8**

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









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‘It can always go either way’

Judith Sluimer (Gouda 1977), Assistant Professor, Department of Pathology

What are you researching?
“In my PhD project I discovered that one of the characteristics of an unstable plaque in people with atherosclerosis is oxygen shortage. I have used a Veni grant to show that the composition of a plaque can be influenced by adding extra oxygen to the blood. That makes it more stable. I’m still building on that research. I also study why the new blood vessels that the body develops at sites with an oxygen shortage leak at the plaques, as that produces new inflammations.”

What was a major event for you in 2013?
“My tenure track ended, and I was given tenure. The main thing for me is not the contract security, but it does mean that if I secure a grant now, I can spend it on experiments instead of my salary. That’s the main advantage. All my grants have ended, so now it’s time for a new grant: the senior post-doc grant from the Netherlands Heart Foundation. The early career grants are partly based on your own merits, but to a large extent also on the research team that you’re working in as a PhD student. From now on, I have to show that I can maintain high quality research and secure grants on my own strength.”

What does CARIM mean to you?
“In the past, the annual symposia and the PhD courses they offered really helped to give me the feeling I am part of CARIM. Now I’m a new member of the strategic board, which has done things like reorganizing the Research Council. I like being able to do something for CARIM in return. When I returned from the US, where I’d spent 18 months, it took some time to get settled in again. That’s when you find you know people at CARIM who can help you with all kinds of things. It was like a home base. When I’m at a conference abroad I feel like I’m a CARIM person more than a UM person.”

How do you maintain a balance between work and private life?
"I've got two small kids at home, which helps. And doing sports once or twice a week to clear your head also works very well. And visiting friends and relatives. You need to do fun things in addition to your work. That's what I always tell my PhD students too. During the final years of my PhD project I never went on holiday; I wanted to finish the project, I just kept going all the time. But that PhD project taught me the hard way that holidays and leisure time are just as important. Sometimes you just need to ease off a little before you can go all-out again. Since I got my PhD, everything's been going well. I can now tell when I'm working too hard and need to relax a little."

How far ahead are you looking?
"I try to plan ahead for five years, both in terms of the content of my research and in strategic terms. If I fail to secure funding during the next five years, I won't be able to appoint the next batch of PhD students, and then I'll quit. Science is all or nothing for me. That may seem a bit stark, but if I can't get the funds, then I will give someone else a chance to prove themselves. Five years is a reasonable period to prove what you can do. But past performance definitely doesn't guarantee future success.

I've been lucky with all those grants. Just as with submitting papers, it can always go either way. It depends on the reviewers, whether they're in a good mood and whether they're interested in your project. One committee may turn down your grant application straight away, while another invites you for an interview based on the same application. Of course if you can present your project face-to-face, it means you have more control over the outcome, but as long as it's only on paper, it's sometimes just a matter of luck."

Improving electrical therapies for heart failure: the ultimate ‘systems medicine’

Frits Prinzen, Department of Physiology

Currently, device therapies are becoming increasingly important for the treatment of cardiac diseases. A good example is cardiac resynchronization therapy (CRT) for heart failure. This therapy employs electrical stimulation (pacing) of both the right (RV) and left ventricle (LV) to re-synchronize electrical activation and to re-coordinate contraction of the heart. CRT is a valuable therapy that prolongs life and improves its quality in about one fifth of all heart failure patients.[1 2]

Although this therapy is widely employed, the research group working on electro-mechanics of the heart thinks that CRT can be applied even more effectively and possibly also (in modified fashion) for patients who are currently not being considered.[3]

Just as with any therapy, important factors that determine therapeutic success are a correct diagnosis of the patient and a good understanding of the mechanism of the therapy. This is not straightforward for CRT. First of all, CRT exercises its effect on pump function by electrical stimulation. Many factors may affect the coupling of electrophysiology to mechanical function, such as maladaptive changes that often occur in the failing heart. Ideally, therefore, abnormalities of electro-mechanical coupling should be known for each patient. Secondly, CRT operates at the interface between different subspecialties of cardiology (electrophysiology, heart failure, interventional cardiology). Proper application of CRT thus requires all-round cardiological knowledge.

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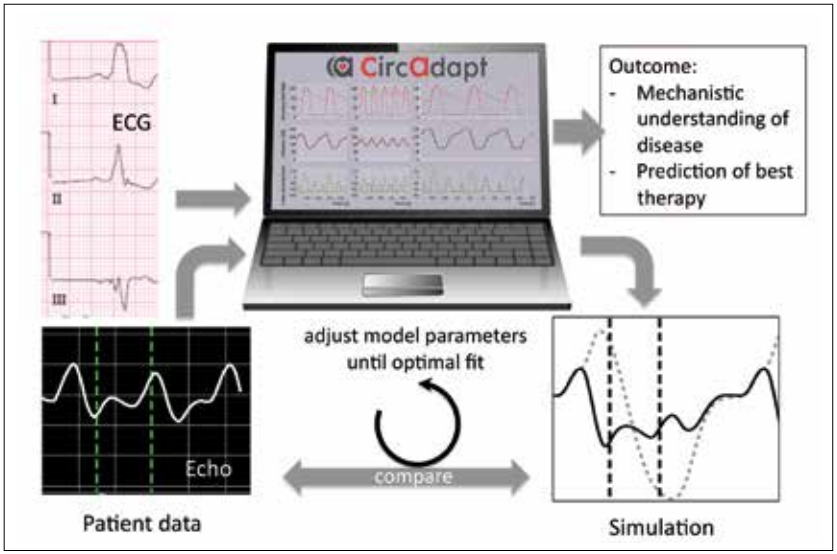

Legend to figure
Schematic representation of patient-specific modelling of electro-mechanics of the heart. The CircAdapt model contains "standard" values for parameters describing a large number of physiological variables (such as contractility, stiffness, timing of electrical activation and even baroreflex activity). CircAdapt is rendered patient-specific by feeding physiological signals into the model (such as those derived from the electrocardiogram (ECG) and echocardiogram (echo)) and by adjusting the model parameters until the signals calculated by the model are close to the measured ones. Shown here are ECG and echo-derived strain curves from a CRT patient.

Our research group consists of physiologists, cardiologists (paediatric as well as "adult"), biomedical engineers and cardiac surgeons, allowing a true multidisciplinary approach that involves animal experiments, clinical studies and computer simulations. In recent years several examples showed how this triple approach produces innovative results. Several years ago, experimental results showed that the LV side of the interventricular septum could be a novel site for pacing that preserves cardiac structure and function better than conventional pacing sites.[4] This finding has led to the development of a new prototype pacing electrode by Medtronic and to the ZonMW Clinical Fellow project by cardiologist Dr Kevin Vernooy. As part of this project, the first 12 patients have been successfully implanted with this novel electrode, a worldwide scoop for MUMC.

As part of his Netherlands Heart Foundation post-doc grant, biomedical engineer Dr Joost Lumens used the CircAdapt computer model to explain the paradoxical finding in both animal and patient studies that pacing from a single LV site yields equally large benefits as pacing the RV and LV simultaneously. The model discovered that LV pacing increases RV contraction, which in turn supports the function of the LV.[5] This discovery may lead to the application of pacing therapies in other cardiac diseases.

Over the last five years we have collected a considerable amount of knowledge in the COHFAR-CTMM project. This project, a collaborative effort of AMC, VUMC, UMCG, UMCU and MUMC, has led to the discovery of new biomarkers and to a patent application for an algorithm for better, automated tuning of the CRT pacemaker to the individual needs of the patient.

Interestingly, useful biomarkers proved to be those derived from "physiological" measurements like echocardiography[6,7] and electrocardiography,[8] rather than from molecular measurements. This may be explained by the fact that physiological signals are the end result of the action of many (hundreds or thousands) of molecules and pathways. Therefore, a single good physiological measurement may be more informative than measuring dozens of molecules. And with the electrocardiogram and echocardiogram, the cardiologist possesses two simple, highly complementary measurements. Combining data from these two measurements in computer models, fed with a large number of biological, chemical and physical pro-

perties of the heart and circulation, can substantially improve the diagnosis.

Important steps towards this end have been made in the development of the CircAdapt model,[9] for which an educational tool is also available (www.circadapt.org). We have shown that modifying only a limited number of parameters in the model suffices to yield many of the different echocardiographic patterns that are observed in patients. 6 The patient-specific models thus created could also be used to explore therapeutic approaches in the virtual world before applying an irreversible therapy (e.g. device implant) in the patient. We believe that this use of mechanistic computer models coupled to physiological patient data is a promising approach in the evolving field of “systems medicine”.

References

1. Prinzen FW, Vernooy K, Auricchio A. Cardiac resynchronization therapy: State-of-the-art of current applications, guidelines, ongoing trials and areas of controversy. Circulation. 2013;128:2407-2418
2. Vernooy K, van Deursen CJ, Strik M, Prinzen FW. Strategies to improve cardiac resynchronization therapy. Nat Rev Cardiol. 2014;11:481-93.
3. Lumens J, Arts T, Broers B, Boomars KA, van Paassen P, Prinzen FW, Delhaas T. Right ventricular free wall pacing improves cardiac pump function in severe pulmonary arterial hypertension: A computer simulation analysis. Am J Physiol Heart Circ Physiol. 2009;297:H2196-2205.
4. Mills RW, Cornelussen RN, Mulligan LJ, Strik M, Rademakers LM, Skadsberg ND, van Hunnik A, Kuiper M, Lampert A, Delhaas T, Prinzen FW. Left ventricular septal and left ventricular apical pacing chronically maintain cardiac contractile coordination, pump function and efficiency. Circulation: Arrhythm Electrophysiol. 2009;2:571-579
5. 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, 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; 62:2395-403
6. Lumens J, Leenders GE, Cramer MJ, De Boeck BW, Doevendans PA, Prinzen FW, Delhaas T. Mechanistic evaluation of echocardiographic dyssynchrony indices: Patient data combined with multiscale computer simulations. Circ Cardiovasc Imaging. 2012;5:491-499
7. Leenders GE, Lumens J, Cramer MJ, De Boeck BWL, Doevendans PA, Delhaas T, 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
8. Van Deursen CJM, Strik M, Rademakers LM, Van Hunnik A, Kuiper M, Wecke L, Crijns HJGM, Vernooy K, Prinzen FW. Vectorcardiography as a tool for easy optimization of cardiac resynchronization in canine lbbb hearts. . Circ. Arrhythm. Electrophysiol. 2012;5:544-552
9. Lumens J. Creating your own virtual patient with circadapt simulator. Eur Heart J. 2014;35:335-337.

‘Adaptation is the norm’

He considers himself very fortunate to have had a pleasant working relationship with all of CARIM’s Scientific Directors over the past 25 years. “That’s very important,” says Rob van der Zander, Managing Director of CARIM since its foundation. After he had previously already worked at the university for a few years, Professor Rob Reneman invited him back when CARIM was about to be launched in 1988. “I’m sometimes amazed how well I’ve been able to work together with him and all of his successors. That means a lot to me. Everybody’s different, has their own style of working. But adaptation is the norm.” Representing the CARIM office, Rob van der Zander looks back at 25 years of CARIM.

At the time when CARIM was founded, Rob van der Zander ran a one-man planning and control department. A few years later, he was joined by Riet Daamen and Esther Willigers, who are both still working there. And some time after that Martin Tossings joined the team as controller. On the day of the interview, it is exactly two years ago that Tossings died in an accident, in the year in which he was to have retired. “That was the darkest day in all my years at CARIM. We still miss him every day.”

Proud

When asked what he is proud of, he mentions the cooperation with his close colleagues at the department, although the word proud makes him hesitate for a moment. “Proud, well, I don’t know…. Well yes, I’m happy to be part of CARIM. And proud of the reputation that the institute has gained for itself and its prospects for the future. And also proud of the pleasant way I can work with my colleagues. All of us at the CARIM office feel very committed to our work and that of the researchers. We want to contribute to CARIM’s success. We assist the researchers in applying their intellectual creativity.”

Decentralised
One of the factors that has helped determine the shape of CARIM in the course of 25 years is the decentralised organisational structure. Initially, it was the Board of the Medical Faculty that decided about appointing researchers and support staff, or about other investments. Nowadays, CARIM itself has the authority and budget to do that. Its budget and the income from third party contracts have grown considerably. For many years now, CARIM has been receiving more money from external funding bodies like the EU, the Netherlands Organisation for Scientific Research (NWO) and charities than from the government. “That says something about the quality of our research.” Funding has gradually shifted from individual projects to more comprehensive programmes (sometimes in collaboration with other institutes) and currently, personal grants are becoming ever more important. The next phase is expected to be characterised by participation in large international consortia that apply for grants from Brussels, and by a focus on valorisation. Rob van der Zander: “You have to adapt to each change. But our maxim has always been that adaptation is the norm. So far we’ve managed to maintain our position amidst the developments around us and to remain successful.”

Flexibility
This kind of flexibility is also a quality required of all employees. It was in the anniversary year that CARIM started to reorganise its support staff. So far, a particular support staff member was assigned to one researcher and would work in the same department for many years. CARIM has now decided to abandon this principle, by focusing on where a particular expertise is needed. The researchers are also finding out that the sky’s no longer the limit. “A department that was top of the range ten years ago does not necessarily have to be so now. So if a vacancy arises in a department because someone leaves or retires, they will not automatically be replaced by a new researcher. Of course I understand that such a department may not be too happy about this, but we have to invest in young talent. We do that by offering a tenure track; a five-year contract that will, in principle, be converted into a permanent contract if a number of criteria are met. We have to sow the seeds now if we still want to be at the top in five years’ time.”

Recurrent theme
A crucial development for the future will be the formation of more international research networks, he expects. “The big money will have to come from Europe. Money remains a recurrent theme, and I don’t think we have a lot to expect from the Dutch government anymore.” An important issue in direct public funding will be to shorten PhD tracks. And of course the partnership with the Maastricht University Medical Centre in the Cardiovascular Center of Excellence Maastricht. “If the MUMC+ becomes a legal entity, that can provide a considerable incentive. I’m sure that will happen within the next five years,” is the optimistic conclusion of this realist.

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EVENTS AND HIGHLIGHTS

SCIENTIFIC HIGHLIGHTS 2013

In 2013 the hard work of our researchers paid off in **605 scientific publications** in peer refereed journals (518 WI-1 publications, excluding abstracts, and 38 Letters to the editor), **34 PhD theses**, **5 patents**, 731.000 Euros funding received in competition from national and international science foundations and 6.4 million Euros funding from third parties, charities, EU-framework programs, industry, etc. In 2013, the overall average Impact Factor is 4.9.

TOP PUBLICATIONS

with the highest Impact Factor in 2013 (CARIM researcher as first and/or last author)

Dirkx E, Gladka MM, Philippen LE, Armand AS, **Kinet V, Leptidis S, el Azzouzi H, Salic K,** van der Nagel R, **Bourajjaj M, da Silva GJJ, Olieslagers S,** de Weger R, **Bitsch N,** Chanoine C, **Kisters N, Seyen S,** Morikawa Y, **Heymans S, Volders PGA,** Eschenhagen T, Thum T, Dimmeler S, Cserjesi P, **da Costa Martins PA, De Windt LJ –**
Nfat and miR-25 cooperate to reactivate the transcription factor Hand2 in heart failure.
Nature Cell Biology 2013; 15: 1282-93 IF 20.761

Heymans S, Corsten MF, Verhesen W, Carai P, van Leeuwen REW, Custers K, **Peters T, Hazebroek M, Creemers EE, Stoger L, Wijnands E, Janssen BJ,** Pinto YM, Grimm D, Stassen F, Schurmann N, Vigorito E, Thum T, Yin X, Mayr M, de Winther MPJ, **de Windt LJ,** Lutgens E, **Wouters K,** Zacchigna S, Giacca M, **van Bilsen M, Papageorgiou AP, Schroen B –**
Macrophage MicroRNA-155 Promotes Cardiac Hypertrophy and Failure.
Circulation 2013; 128: 1420-1432 IF 15.202

Janousek J, van Geldorp IE, Krupickova S, Rosenthal E, Nugent K, Tomaske M, Fruh A, Elders J, Kubus P, Hiippala A, Kerst G, Gebauer RA, Frias P, Gabbarini F, Papagiannis J, Clur SA, Nagel B, Ganame J, Marek J, Tisma-Dupanovic S, Friedberg M, Tsao S, Nurnberg JH, Wren C, de Guillebon M, Volaufova J, **Prinzen FW, Delhaas T,** Assoc European Pediat C –
Permanent Cardiac Pacing in Children: Choosing the Optimal Pacing Site A Multicenter Study.
Circulation 2013; 127: 613-623 IF 15.202

▶▶

TOP PUBLICATIONS

with the highest Impact Factor in 2013
(CARIM researcher as first and/or last author)

Prinzen FW, Vernooy K, Auricchio A –
Cardiac Resynchronization Therapy State-of-the-Art of Current Applications, Guidelines, Ongoing Trials, and Areas of Controversy.
Circulation 2013; 128: 2407-2418 IF 15.202

Christ A, Temmerman L, Legein B, Daemen MJ, **Biessen EA –**
Dendritic cells in cardiovascular diseases: epiphenomenon, contributor, or therapeutic opportunity.
Circulation 2013; 128(24): 2603-2613 IF 15.202

El Azzouzi H, Leptidis S, Dirkx E, Hoeks J, van Bree B, Brand K, McClellan EA, **Poels E,** Yin XK, **Sluimer JC,** van den Hoogenhof MMG, Armand AS, Langley S, **Bourajjaj M,** Kurihara H, **Olieslagers S,** Krishnan J, Vooijs M, Stubbs A, Pinto YM, Schrauwen P, Krek W, Mayr M, **da Costa Martins PA, De Windt LJ –**
The Hypoxia-Inducible MicroRNA Cluster miR-199a similar to 214 Targets Myocardial PPAR delta and Impairs Mitochondrial Fatty Acid Oxidation.
Cell Metabolism 2013; 18: 341-354 IF 14.619

Engelen L, Ferreira I, Stehouwer CD, Boutouyrie P, Laurent S, Reference Values for Arterial Measurements Collaboration –
Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors.
European Heart Journal 2013; 34: 2368-80 IF 14.097

Vanhoutte D, **van Almen GC, Van Aelst LNL,** Van Cleemput J, Droogne W, **Jin Y,** Van de Werf F, Carmeliet P, Vanhaecke J, **Papageorgiou AP, Heymans S –**
Matricellular proteins and matrix metalloproteinases mark the inflammatory and fibrotic response in human cardiac allograft rejection.
European Heart Journal 2013; 34: 1930-1941 IF 14.097

Engelen L, Ferreira I, Stehouwer CD, Boutouyrie P, Laurent S, Jouven X, Empana JP, Bozec E, Hofman A, Simon T, Pannier B, Mattace-Raso FU, Franco OH, Kavousi M, Vermeersch S, van Rooij FJ, Witteman J, Riezschel E, Segers P, Van Bortel L, **van Greevenbroek M,** De Bacquer D, Van Daele C, **Schalkwijk C, van der Kallen C, van de Laar R, Knapen MHJ, Staessen J, Vermeer C, Braam L –**
Reference intervals for common carotid intima-media thickness measured with echotracking – relation with risk factors.
Eur Heart J 2013; 34: 2368-2380 IF 14.097

Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchett A, Böhm M, Christiaens T, Cifkova R, Grobbee DE, De Backer G, Dominiczak A, Galderisi M, Jaarsma T, Kirchhof P, Nilsson PM, Kjeldsen SE, Laurent S, Manolis AJ, Ruilope LM, Schmieder RE, Waeber B, Sirnes PA, Sleight P, Viigimaa M, Zannad F, Redon J, Wood DA, Dominiczak A, Narkiewicz K, **Struijker Boudier HAJ –**
2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC).
Eur Heart J 2013; 34(28): 2159-219 IF 14.097

Lievens D, Habets KL, Robertson AK, Laouar Y, Winkels H, **Rademakers T, Beckers L, Wijnands E,** Mallat Z, Boon L, Mosaheb M, Ait-Oufella H, Flavell RA, Rudling M, **Weber C,** Binder CJ, Gerdes N, **Biessen EA,** Daemen MJ, Kuiper J, Lutgens E –
Abrogated transforming growth factor beta receptor II (TGFβRII) signalling in dendritic cells promotes immune reactivity of T cells resulting in enhanced atherosclerosis.
Eur Heart J 2013; 34(48): 3717-3727 IF 14.097

TOP PUBLICATIONS

with the highest Impact Factor in 2013
(CARIM researcher as first and/or last author)

Versteylen MO, Kietselaer BL, Dagnelie PC, Joosen IA, Dedic A, Raaijmakers RH, Wildberger JE, Nieman K, Hofstra L, Crijns HJ, Niessen WJ, Daemen MJ –
Additive Value of Semiautomated Quantification of Coronary Artery Disease Using Cardiac Computed Tomographic Angiography to Predict Future Acute Coronary Syndrome.
Journal of the American College of Cardiology 2013; 61: 2296-2305 IF 14.086

Juni RP, Duckers HJ, Vanhoutte PM, Virmani R, Moens AL –
Oxidative Stress and Pathological Changes After Coronary Artery Interventions.
Journal of the American College of Cardiology 2013; 61: 1471-1481 IF 14.086

Lumens J, Ploux S, Strik M, Gorcsan J, Cochet H, Derval N, Strom M, Ramanathan C, Arts T, Ritter P, Haïssaguerre M, Jaïs P, Delhaas T, Prinzen FW, 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; 62: 2395-2403 IF 14.086

Ploux S, Lumens J, Whinnett Z, Montaudon M, Strom M, Ramanathan C, Derval N, Zemmoura A, Hocini M, Denis A, De Guillebon M, Shah A, Jais P, Ritter P, Haissaguerre M, Wilkoff BL, Bordachar P –
Noninvasive Electrocardiographic Mapping to Improve Patient Selection for Cardiac Resynchronization Therapy Beyond QRS Duration and Left Bundle Branch Block Morphology.
Journal of the American College of Cardiology 2013; 61: 2435-2443 IF 14.086

Johnson DM, Heijman J, Bode EF, Greensmith DJ, van der Linde H, Abi-Gerges N, Eisner DA, Trafford AW, Volders PGA –
Diastolic Spontaneous Calcium Release From the Sarcoplasmic Reticulum Increases Beat-to-Beat Variability of Repolarization in Canine Ventricular Myocytes After beta-Adrenergic Stimulation.
Circulation Research 2013; 112: 246-56 IF 11.861

Wantha S, Alard JE, Megens RTA, van der Does AM, Doring Y, Drechsler M, Pham CTN, Wang MW, Lindbom L, Wang JM, Gallo RL, von Hundelshausen P, Hackeng T, Weber C, Soehnlein O –
Neutrophil-Derived Cathelicidin Promotes Adhesion of Classical Monocytes.
Circulation Research 2013; 112: 792-801 IF 11.861

Van der Veer E, de Bruin RG, Kraaijeveld A, de Vries MR, Bot I, Pera T, Segers FM, Trompet S, van Santbrink PJ, van Gils JM, Roeten M, Beckers C, Janssen A, van Solingen C, Bijkerk R, Swildens J, de Boer HC, Peters EH, Rousch M, Doop M, van Berkel TJ, Schalij M, van der Wal AC, Richard S, Pickering JG, Hiemstra PS, van Zonneveld AJ, Goumans MJ, Rabelink TJ, de Vries AA, Quax PH, Jukema JW, Biessen EA –
Quaking, an RNA-binding protein, is a critical regulator of vascular smooth muscle cell phenotype.
Circ Res 2013; 113(9): 1065-1075 IF 11.861

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TOP PUBLICATIONS

with the highest Impact Factor in 2013 (CARIM researcher as co-author)

Smoller JW, **Reif A,** Cross-Disorder Group of the Psychiatric Genomics Consortium; Genetic Risk Outcome of Psychosis (GROUP) Consortium –
Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Cross-Disorder Group of the Psychiatric Genomics Consortium; Genetic Risk Outcome of Psychosis (GROUP) Consortium.
Lancet 2013; 381(9875): 1371-9 IF 39.06

Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, Mowry BJ, Thapar A, Agartz I, Goddard ME, Witte JS, Absher D, Akil H, Amin F, Anttila V, Andreassen OA, Anjorin A, Anney R, Arking DE, Asherson P, Bailey AJ, Azevedo MH, Backlund L, Badner JA, Banaschewski T, Barchas JD, **Reif A,** Barnes MR, Barrett TB, Bass N –
Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs.
Nature Genetics 2013; 45: 984-94 IF 35.209

Versteeg HH, **Heemskerk JWM,** Levi M, Reitsma PH –
New fundamentals in hemostasis.
Physiological Reviews 2013; 93: 327-358 IF 30.174

Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Brayne C, Barkhof F, Benavente OR, Black SE, Breteler M, Chabriat H, Duering M, DeCarli C, de Leeuw FE, Doubal F, Fox NC, Greenberg S, **van Oostenbrugge R,** Hachinski V, Kilimann I, Mok V, Pantoni L, Speck O, Werring D, Stephan BCM, Teipel S, Viswanathan A –
Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration.
Lancet Neurology 2013; 12: 822-838 IF 23.917

Gray SP, Di Marco E, Okabe J, Szyndralewiez C, Heitz F, Montezano AC, de Haan JB, Koulis C, Touyz RM, El-Osta A, Andrews KL, Chin-Dusting JPF, **Wingler K,** Cooper ME, **Schmidt H,** Jandeleit-Dahm KA –
NADPH Oxidase 1 Plays a Key Role in Diabetes Mellitus-Accelerated Atherosclerosis.
Circulation 2013; 127: 1888-902 IF 15.202

Schuijt TJ, Bakhtiari K, Daffre S, DePonte K, Wielders SJH, Marquart JA, Hovius JW, van der Poll T, **Nicolaes GAF,** Fikrig E, Bunce MW, Camire RM, Meijers JCM, van 't Veer C –
Factor Xa Activation of Factor V Is of Paramount Importance in Initiating the Coagulation System: Lessons From a Tick Salivary Protein.
Circulation 2013; 128: 254-266 IF 15.202

American College of Cardiology Foundation, American Heart Association, European Society of Cardiology, Heart Rhythm Society, Wann LS, Curtis AB, Ellenbogen KA, Estes NA, Lowe JE, Ezekowitz MD, Jackman WM, January CT, Page RL, Slotwiner DJ, Rydén LE, Stevenson WG, Tracy CM, Fuster V, Cannom DS, **Crijns HJ,** Le Heuzey J, Curtis AB, Ellenbogen KA, Halperin JL, Kay GN, Lowe JE, Wann LS, Olsson SB, Prystowsky EN, Tamargo JL –
Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines.
Circulation 2013; 127(18): 1916-26 IF 15.202

TOP PUBLICATIONS

with the highest Impact Factor in 2013 (CARIM researcher as co-author)

Hamshere ML, Langley K, Martin J, Agha SS, Stergiakouli E, Anney RJ, Buitelaar J, Faraone SV, Lesch KP, Neale BM, Franke B, Sonuga-Barke E, Asherson P, Merwood A, Kuntsi J, Medland SE, Ripke S, Steinhausen HC, Freitag C, **Reif A,** Renner TJ, Romanos M, Romanos J, Warnke A, Meyer J, Palmason H, Vasquez AA, Lambregts-Rommelse N, Roeyers H, Biederman J, Doyle AE, Hakonarson H, Rothenberger A, Banaschewski T, Oades RD, McGough JJ, Kent L, Williams N, Owen MJ, Holmans P, O'Donovan MC, Thapar A –

High loading of polygenic risk for ADHD in children with comorbid aggression.

American journal of psychiatry 2013; 170(8): 909-16 IF 14.721

Berti D, Hendriks JML, Brandes A, Deaton C, **Crijns H,** Camm AJ, Hindricks G, Moons P, Heidbuchel H –

A proposal for interdisciplinary, nurse-coordinated atrial fibrillation expert programmes as a way to structure daily practice.

European Heart Journal 2013; 34: 2725-2730 IF 14.097

Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Helio T, Linhart A, **Heymans S,** Jahns R, Klingel K, Maisch B, McKenna W, Schultheiss HP, Mogensen J, Pinto YM, Ristic A, Seggewiss H, Tavazzi L, Elliott PM, Thiene G, Yilmaz A, Charron P –

Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases.

European Heart Journal 2013; 34: 2636-48 IF 14.097

Messerli FH, Bangalore S, Torp-Pedersen C, **Staessen JA,** Kostis JB –

Cardiovascular drugs and cancer: of competing risk, smallpox, Bernoulli, and d'Alembert.

European Heart Journal 2013; 34: 1095-1098 IF 14.097

Groenveld HF, Tijssen JGP, **Crijns H,** Van den Berg MP, Hillege HL, Alings M, Van Veldhuisen DJ, Van Gelder IC, Investigators RI-

Rate Control Efficacy in Permanent Atrial Fibrillation: Successful and Failed Strict Rate Control Against a Background of Lenient Rate Control.

Journal of the American College of Cardiology 2013; 61: 741-748 IF 14.086

Vonk-Noordegraaf A, Haddad F, Chin K, Forfia P, Kawut S, **Lumens J,** Naeije R, Newman JH, Voelkel N, Oudiz R, Provencher S, TorbickiA, Hassoun P –

Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology.

J Am Coll Cardiol 2013; 62: D22-33 IF 14.086

Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Guyton RA, Pressler SJ, Hochman JS, Kovacs RJ, Ohman EM, Sellke FW, Shen WK, Estes NA 3rd, Wann LS, Curtis AB, Ellenbogen KA, Ezekowitz MD, Jackman WM, January CT, Lowe JE, Page RL, Slotwiner DJ, Ellenbogen KA, Stevenson WG, Tracy CM, Fuster V, Rydén LE, Cannom DS, **Crijns HJ,** Curtis AB, Le Heuzey JY, Kay GN, Wann S, Olsson SB, Prystowsky EN, Tamargo JL-

Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.

J Am Coll Cardiol 2013; 61(18): 1935-44 IF 14.086

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TOP PUBLICATIONS

with the highest Impact Factor in 2013 (CARIM researcher as co-author)

Bieghs V, Hendrikx T, **van Gorp PJ, Verheyen F,** Guichot YD, Walenbergh SMA, Jeurissen MLJ, **Gijbels M,** Kalhan SC, Rensen SS, **Bast A,** Plat J, Koek GH, Leitersdorf E, Hofker MH, Lutjohann D, Shiri-Sverdlov R –
The Cholesterol Derivative 27-Hydroxycholesterol Reduces Steatohepatitis in Mice.
Gastroenterology 2013; 144: 167-178 IF 12.821

Leoni G, Alam A, Neumann PA, Lambeth JD, Cheng GJ, McCoy J, Hilgarth RS, Kundu K, Perretti M, Murthy N, Kusters D, **Reutelingsperger C,** Parkos CA, Neish AS, Nusrat A –
Annexin A1, formyl peptide receptor, and NOX1 orchestrate epithelial repair.
Journal of Clinical Investigation 2013; 123: 443-454 IF 12.812

Den Exter PL, van Es J, **Erkens PMG,** van Roosmalen MJG, van den Hoven P, Hovens MMC, Kamphuisen PW, Klok FA, Huisman MV –
Impact of Delay in Clinical Presentation on the Diagnostic Management and Prognosis of Patients with Suspected Pulmonary Embolism.
American Journal of Respiratory and Critical Care Medicine 2013; 187: 1369-1373 IF 11.041

Planavila A, Redondo I, Hondares E, Vinciguerra M, **Munts C,** Iglesias R, Gabrielli LA, Sitges M, Giralt M, **van Bilsen M,** Villarroya F –
Fibroblast growth factor 21 protects against cardiac hypertrophy in mice.
Nature Communications 2013; 4: 2019 IF 10.015

PATENTS

Quinlan PT, Vermeer C
Vitamin containing product (published)
US Patent 8354129

Vermeer C
Use of vitamin K for weight maintenance and weight control (published)
US patent 2013-0267606-A1

Vermeer C, de Borst M
Use of vitamin K to decrease allograft failure and patient mortality after organ transplantation
WO2013/182578-A1

Vermeer C, de Borst M
New biomarkers to estimate the risk of allograft failure and patient mortality after organ transplantation
WO2013/182579-A1

Prinzen FW, Engels E, Aranda Hernandez A
Method and apparatus for optimization of cardiac resynchronization therapy using vectorcardiograms derived from implanted electrodes
Medtronic, September 2013

SCIENTIFIC GRANTS, AWARDS AND HONORS

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

NWO Aspasia

In April 2013 the Netherlands Organisation for Scientific Research (NWO) granted an Aspasia to Dr **Eline Kooi** (Dept. of Radiology) for her project "Strain as a causative factor for intraplaque hemorrhage and plaque destabilization- a novel qualifier of plaque vulnerability?" In this project, a novel non-invasive ultrasound method will be developed and validated to directly assess the local strain within the plaque in vivo. Aspasia ensures that more female assistant professors progress to the level of associate or full professor.

NHS E. Dekker Program

In the framework of the E. Dekker program of the Dutch Heart Foundation, Dr **Marjo Donners** (Dept. of Genetics and Cell Biology) received a Senior Postdoc grant for her project "ADAM10 and ADAM17: Complementary sheddases with gate keeper and immune-modulatory functions regulating atherosclerotic plaque progression and stability", which was an extension of a previous Dr. E. Dekker fellowship. Dr **Kristiaan Wouters** (Dept. of Internal Medicine) also received a Senior Postdoc grant (350 €K) for investigating the role of RAGE in KC activation and the development and regression of hepatic inflammation. Mice deficient for RAGE will be used to investigate whether RAGE plays a role in the development of experimental NASH and the production of cardiovascular risk factors. This knowledge should lead novel specific targets for therapeutic interventions and new prognostic tools. (Read a full interview with Kristiaan on pages 64-65).

CVON

In January, 3 CARIM PIs received a confirmation of two successful CVON (Cardiovasculair Onderzoek Nederland) multicenter grant applications in which they participate: the HBC-project on the heart-brain connection and the PREDICT project on sudden cardiac death. CVON, a mutual initiative of the NHS, KNAW, ZonMw and NFU, aims to improve the national and international position of cardiovascular research in the Netherlands, by supporting large and strong research themes. Prof. **Hans Peter Brunner-La Rocca** (Dept. of Cardiology) and Prof. **Robert van Oostenbrugge** (Dept. of Neurology) both participate in the HBC-project, a project led by the Amsterdam Medical Centre and Leiden University Medical Centre. Dr **Paul Volders** (Dept. of Cardiology) is involved in the PREDICT project on sudden cardiac death. This research consortium is a cooperation of the Amsterdam Medical Centre, University Medical Centre Utrecht, MUMC+ and University Medical Centre Groningen.

Kootstra Fellowship

During the first round of the Kootstra Talent Fellowships 2013, Dr **Ellen Dirkx** (post doc Dept. of Cardiology) was granted a fellowship. 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.

Furthermore, in 2013, Ellen Dirkx received a Marie Curie, Talents up and an EMBO Long Term Fellowship to visit the ICGEB Trieste in Italy to refine the functional implication of the microRNA-106b~25 cluster in heart failure. Her project will add new knowledge to our current understanding on the transcriptional and post-transcriptional networks in the processes leading to heart failure and gives us the opportunity to exploit the functions of the miRNA-106b~25 cluster for therapeutic advantage for heart failure. In this context, Ellen currently works at the Molecular Medicine laboratory of Prof. Mauro Giacca to identify direct downstream targets of the microRNA-106b~25 cluster during hypertrophic remodeling, by performing Ago2 immunoprecipitations of hearts overexpressing the microRNA-106b~25 cluster, followed by deep sequencing and bio-informatics analysis.

OTHER AWARDS, PRIZES AND GRANTS

In 2013 many CARIM researchers were awarded with prizes and travel grants. Below, some of them will be highlighted.

BHF grant for Koen Reesink

The British Heart Foundation granted Dr **Koen Reesink** and two of his British colleagues for their project proposal "Non-invasive Pressure-Volume Analysis (NIPVA): extending comprehensive left ventricular pump function assessment to more patients and settings". Their project is a collaboration between CARIM's Department of Biomedical Engineering and the Department of Physiology and Disease Prevention of Imperial College London.

Jan van der Meer Award

On May 31, Dr **Gerry Nicolaes** (Dept. of Biochemistry) was awarded the Jan van der Meer Research Prize on Haemostasis and Thrombosis for his contributions to coagulation research in the Netherlands during the 9th Groninger Symposium on Coagulation. Dr Nicolaes performs research to decipher the relationships between the 3D structure and functions of proteins involved in haemostasis. His research, amongst others, facilitates the rational design of novel antithrombotics.

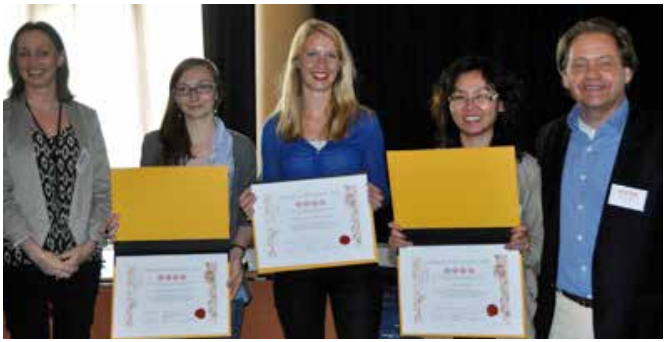
World Technology Award

On November 15, Professor **Mark Post** received the World Technology Award for Environment at the World Technology Award Gala in New York for growing the world's first hamburger from cultured beef, which was presented in August 2013. The World Technology Network is a curated membership community comprised of the world's most innovative individuals and organisations in science, technology, and related fields.

NVTH Award for Scientific Excellence

Recipients of the Netherlands Society for Thrombosis and Haemostasis (NVTH) Award for Scientific Excellence 2013 in the basic and clinical sciences (€ 2000.-).

Clinical sciences recipients: from left to right: Suzanne Cannegieter (LUMC; board member NVTH): Rinske Loeffen (CARIM Theme I); Carina Stoof (EUR); Nienke van Rein (LUMC); Tilman Hackeng (president NVTH).



Basic sciences recipients: from left to right: Suzanne Cannegieter (LUMC; board member NVTH): Barbara Zarzycka (CARIM Theme I); Sascha de Stoppelaar (AMC); Vivian Du (UMCU); Tilman Hackeng (president NVTH).
April 2013, Koudekerke, The Netherlands

EVENTS AND HIGHLIGHTS

NMR Facility

In 2013, the **Martin Paul Pavillion for Protein NMR studies** was officially opened at the Department of Biochemistry. Here, the latest generation Bruker HD 700 MHz NMR spectrometer with cryo probe was installed. NMR stands for Nuclear Magnetic Resonance and relies on a large superconducting magnet (in this case with a magnetic field of 16.4 Tesla) for the study of a large variety of molecules in solution. The NMR equipment at the CARIM institute is available to assist various researchers at Biochemistry, but is also accessible to other parties within MUMC and/or to biotech companies via the Enabling Technologies platform.

Furthermore, Professor **Kevin Mayo** was appointed as the Hein Wellens visiting professor 2013 at the Department of Biochemistry. Professor Mayo has been integral in the process of bringing high field NMR to Maastricht and this effort has culminated in the purchase and delivery of the new Bruker 700 MHz spectrometer to CARIM and the Dept. of Biochemistry.

Special Corona PhD Defense Daniel Johnson

Dr **Daniel Johnson**, who defended his dissertation on March 8, had a very special corona (PhD defense committee): four of the members served as each other's (co-)supervisors in the past and were now involved in this 'fifth-generation defense'. Johnson has Professor **Harry Crijns** as his supervisor and Prof **Paul Volders** as co-supervisor.

Volders graduated in 1999 with Professor **Marc Vos** as co-supervisor, Vos graduated in 1989 with Professor **Anton Gorgels** as co-supervisor and Gorgels graduated in 1985 with Professor (Emeritus) **Hein Wellens** as supervisor, who also served as supervisor for Vos and Volders. Johnson's PhD defense unites these five generations of cardiologists/cardiac researchers – a momentous and memorable occasion.

The dissertation, entitled "Enhanced Prediction and Prevention of Drug-Induced Torsades de Pointes", is about cardiac arrhythmias as unintentional side effects of certain medications.

Vascular Network Group initiative

Initiated in the summer of 2013 by a series of workshops, the Vascular Biology theme has been organising itself in a more networked manner, spanning the broad variety of research approaches and resources while developing across other themes and schools. With this, the current research infrastructure is well-suited to adopt a systems approach to develop and integrate mechanistic knowledge from basic, clinical and population research into a translational program, within the emergent societal context of cardiovascular complications with aging and metabolic disorders.

The **Vascular Network Group (VNG)** that emerged is a semi-open organisational structure led by Dr. **Koen Reesink** (Dept. of Biomedical Engineering), Prof. **Chris Reutelingsperger** (Dept. of Biochemistry), Prof. **Robert van Oostenbrugge** (Dept. of Neurology), and Prof. **Hans Vink** (Dept. of Physiology). The VNG organises Vascular NetWorkshops bi-monthly, in which clinical and basic research groups or initiatives present themselves to the broader audience to discuss both current developments and opportunities for future collaboration and funding.

Red meets White

In June 2013, several CARIM staff members participated in “the red meets white study” of which Dr Bas de Laat (CEO Synapse BV) was lead researcher. Twenty five Dutch scientists and volunteers climbed Europe’s highest mountain, Mont Blanc in the French Alpes, seeking to better understand the effects of hypoxia and low blood oxygen levels on blood agulation. To identify the effect of physical activity on haemostasis, one group existing of healthy volunteers will actively climb the Mont Blanc (the Mountain Team). The other group of healthy volunteers will use the cable car (the Cable Car Team). Blood was drawn every other day by experienced researchers at different heights. To study the effect of barometric pressure we will also test capillary blood. (Read a full interview with Bas on pages 30-31).

‘A kind of CARIM in the US’

Xander Wehrens (1975) did most of the experimental work for this PhD project in the United States. “It was obvious to me then that I felt more at home here than in the Netherlands. Here people appreciate it when you work hard and get results.” As a result, he left for Columbia University to do a post-doc immediately after getting his PhD in 2002. He is now a full professor at Baylor College of Medicine, where he is trying to unite cardiovascular researchers from various disciplines in one Cardiovascular Research Institute. “The inspiration for this plan was CARIM.”

Xander Wehrens was born in Heerlen and decided to study medicine at Maastricht University because of its problem-based learning system. “I had some spare time in my first year, and one of my mentors suggested that I might be interested in research, as I was always asking ‘why?’” He became a research assistant at the Department of Genetics and Molecular Cell Biology. While he was doing his clinical internships Pieter Doevendans offered him a PhD position, after which he divided his time between his internships and the research project. His PhD project concerned the hereditary long QT syndrome and the way congenital mutations change the functioning of the sodium channel. “We found that there are different types of dysfunctions. Not all mutations produced the same final outcome, i.e. a channel that does not close properly. We were the first to show that these variants also resulted in different responses to drugs.”

Research climate in the US

While doing experiments at Columbia University for a year in 1999, Xander found that he liked the American research climate. He has been working at Baylor College of Medicine since 2005, and became a full professor of physiology and cardiology there in 2011. “The Netherlands has good researchers, but it’s a small country. It’s difficult to find the infrastructure I need for my current research at one university

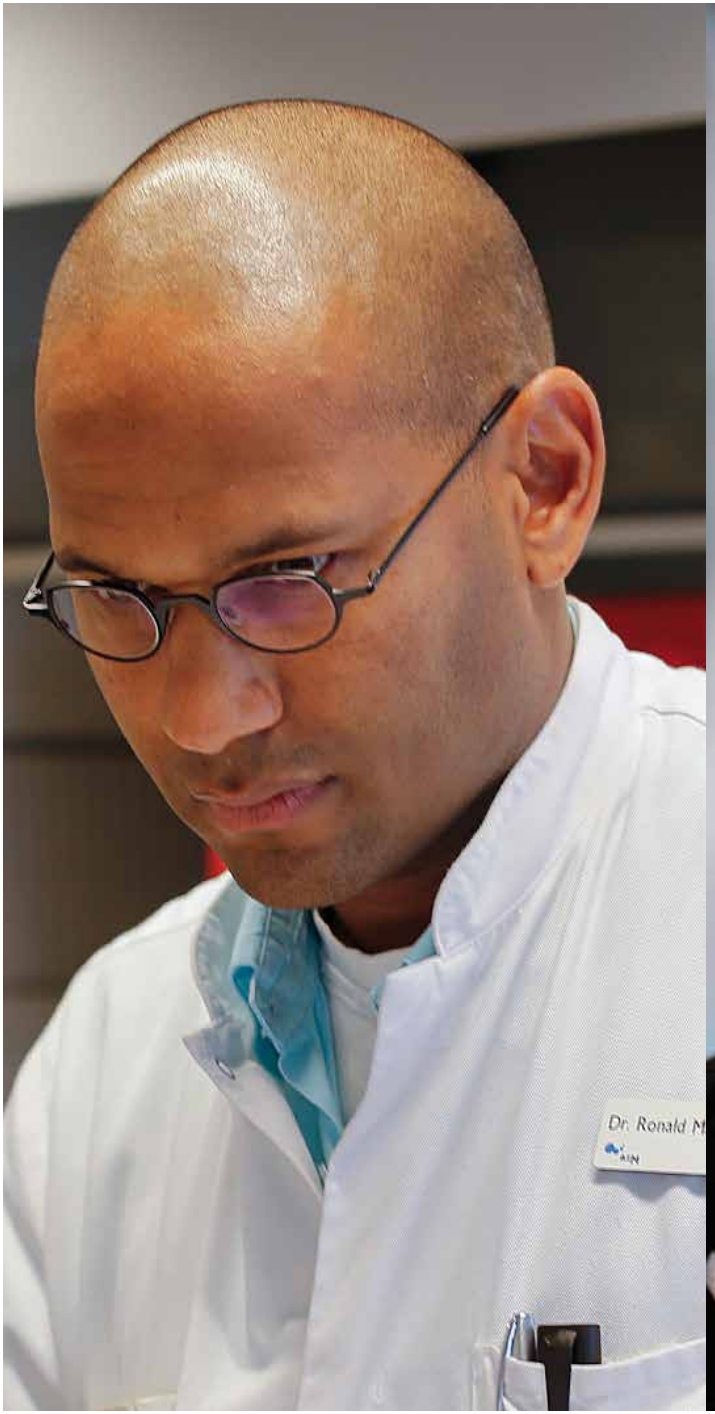
there." The Wehrens Lab is examining the regulation of ion channels in healthy and diseased hearts. It has published major findings on cardiac calcium channels and the way they can contribute to common heart diseases such as atrial fibrillation and heart failure. His research group now includes some eighteen staff, including two assistant professors, post-docs and trainee cardiologists. "There are also more possibilities for expanding your research team in the US than in Holland." The closest contact that the former CARIM PhD student still has with the Institute is his collaboration with Leon de Windt. "He was a post-doc in Maastricht when I was studying there, and we've remained in contact ever since, exchanging students and writing papers together."

CARIM

It was at CARIM that Xander saw the importance of interdisciplinary collaboration. "I've always kept that in mind. People at Baylor College of Medicine had been meaning to organize all researchers in the cardiovascular field within one institute, so I proposed a plan and for the last two years I've been directing the Cardiovascular Research Institute. Stimulating collaborations in order to boost the quality of research is now one of my most important tasks. We have been making excellent progress."

Although practical considerations eventually led him to abandon the idea of combining a job as a physician with research work, his background in medicine definitely provides added value. "I know what's important for patients and what kind of research is relevant to patient care. It's my ambition to develop something that will enhance that care. In that respect the person I learned the most from is Andrew Marks, my post-doc mentor at Columbia. His advice was to not to focus on smaller projects, with perhaps only a little bit of progress made each time, but on major ideas, which may lead to important breakthroughs."

Prof. Xander Wehrens received his PhD degree at CARIM on 22 March 2002, having been supervised by the cardiologist Hein Wellens and the pharmacologist Robert Kass (Columbia University), on the basis of a thesis entitled 'Novel Insights in the Congenital Long QT Syndrome'.


Dr. Ronald

The Maastricht Study

Dr Ronald Henry,
Dr Miranda Schram,
Department of
Internal Medicine

The Maastricht Study

In 2009, Maastricht UMC+ announced the start of The Maastricht Study, a large population-based observational cohort study of diabetes, cardiovascular disease and other chronic diseases. Three years on, has The Maastricht Study lived up to its expectations? The answer is unequivocally yes. The study's first goals in terms of research, academic collaboration, grants and societal impact have been achieved. Even better, The Maastricht Study's best years still lie ahead, especially when the first follow-up survey is going to be implemented, but let us take a moment to look back, see where the study stood in 2013, and look forward.

Looking back

The rationale behind The Maastricht Study remains the fact that type 2 diabetes mellitus is a major global health burden. For instance, 800.000 individuals are currently suffering from type 2 diabetes in the Netherlands, and this number will have risen to 1 million by the year 2025. Additionally, type 2 diabetes remains fifth on the list of non-communicable diseases that deprive people of the largest number of healthy life years. This is illustrated by the fact that individuals diagnosed with type 2 diabetes mellitus will lose 16-18 quality-adjusted life years due to diabetes and will die, on average, 6 years earlier than their counterparts without diabetes. Furthermore, the treatment costs of the disease itself and its complications remain persistently high, despite improved therapeutic approaches and new drugs. Another important development is the recognition of a growing body

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of evidence that type 2 diabetes mellitus also accelerates the development and progression of other chronic diseases or co-morbidities (e.g., depression and chronic obstructive pulmonary disease).
All of this has contributed to the need for a better understanding of the pathophysiology of type 2 diabetes mellitus and its complex interaction with other chronic diseases. To investigate these issues, a large population-based cohort study was designed, which became The Maastricht Study. Its main focus is to identify determinants of the development and progression of type 2 diabetes mellitus itself, its "classic" complications (e.g., cardiovascular disease) but also its emerging co-morbidities. For this purpose, a dedicated research facility was built (The Maastricht Study Research Centre at Randwycksingel in Maastricht), and a standardized deep-phenotyping research protocol (16 hours divided over four study visits) was designed by multidisciplinary teams from different research schools within Maastricht UMC+. The study aimed to include 5.000 participants with type 2 diabetes mellitus and 5.000 without. Eligible for participation were all individuals aged between 40 and 75 years and living in Maastricht, Margraten-Eijsden, Meerssen or Valkenburg. The standardized research protocol, which participants are still undergoing today, consisted of extensive laboratory assessments, a physical examination, a 6-minute walk test, a 7-day accelerometer measurement, general questionnaires, an echocardiogram, vascular ultrasound measurements, autonomic function testing, spirometry, MRI of the brain and liver, capillaroscopy, ambulatory sleep-disordered breathing monitoring, microbial throat and skin swaps, fundoscopy, optical coherence tomography, as well as a series of other measurements and questionnaires.

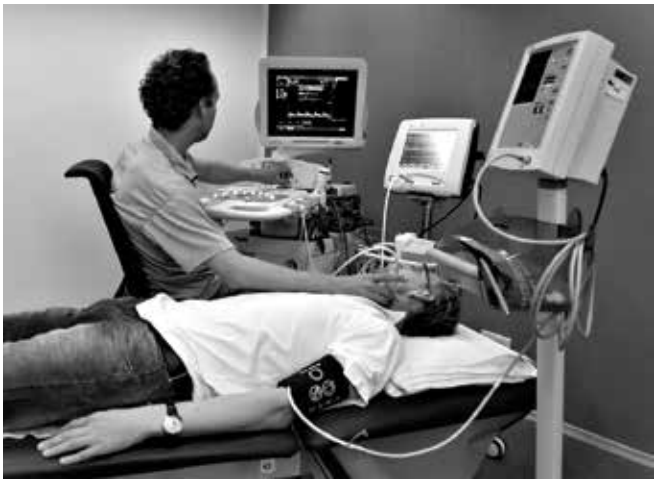
Where The Maastricht Study stood in 2013

In 2013, The Maastricht Study Research Centre was run by a staff of 38 persons and a management team of seven; nearly 2000 individuals had been recruited and completed the entire research protocol. In total, The Maastricht Study cohort in 2013 consisted of 3,923 participants (1162 with type 2 diabetes mellitus), and the data infrastructure contained approximately 30 Terabytes of participant data. From a research perspective, The Maastricht Study employed 24 PhD students (ten PhD students funded by The Maastricht Study / Department of Internal Medicine; eight PhD students co-funded by investigators of other MUMC+ research schools, and six PhD students either fully externally funded (two projects) or fully funded by other MUMC+ research schools (four projects)). Internationally, close collaboration was established with the Department of Cardiology of the University of Milano, and Dr Athanase Protogerou joined the Maastricht Study as a Marie-Curie beneficiary. In close cooperation with the Maastricht Health Campus and external consultants, the Maastricht Study started to professionally explore the possibilities for setting up public-private partnerships to achieve an accelerated cycle of valorization. For this purpose, a series of meetings have been held with both biomedical and pharmaceutical companies.
In terms of scientific output, the first data set became available ((n=866); data sets are becoming available in a time-dependent cumulative manner) and since then a series of abstracts and a first paper on the design of the study have been submitted for publication. The Maastricht Study also held its first scientific meeting for a broad audience. Another important event in 2013 was the implementation of the first of the annual follow-ups on disease incidence and mortality. From a public health perspective, the first set of analyses showed that the prevalence of cardiovascular disease risk factors, including pre-diabetes, was higher than expected based on figures for other parts of the Netherlands.
At an individual level, participants appreciated their exit interviews, in which they are given feedback on a set of clinically relevant measurements and advice on how to (further) improve their health. As commitment and satisfaction

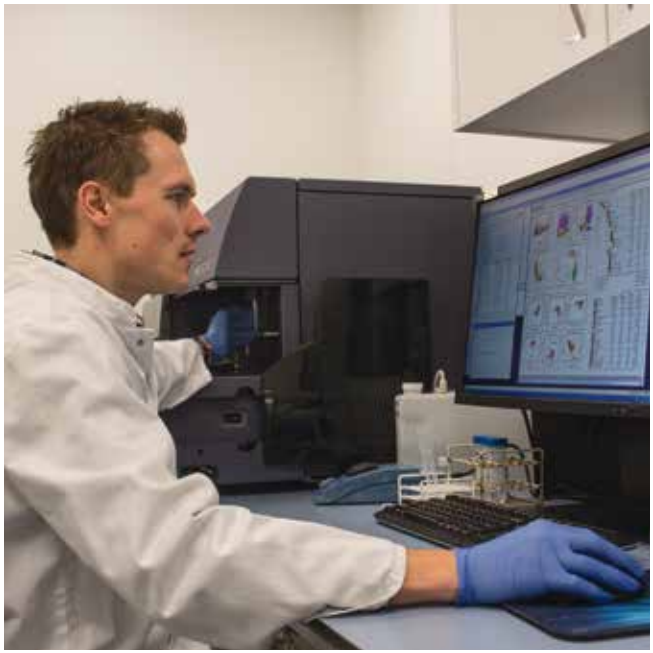
of participants are extremely important for cohort studies to ensure their participation in follow-up examinations, exit polls were held using anonymous questionnaires. The results of these exit polls showed that participants overall rated their appreciation of the visits to The Maastricht Study as 9.3 out of 10. There were relatively few unexpected clinical abnormalities in 2013. Only 3 acute referrals to the emergency department were made for hypertension, severe cardiac ischemia during exercise testing and a suspected case of acute glaucoma after the administration of mydriatics. Another 23 participants were brought to the attention of their general practitioner for further guidance or referral (in one case a retinal melanoma was discovered during the The Maastricht Study eye examination). Twelve patients were directly referred to the outpatient clinic of the Department of Internal Medicine for a variety of minor conditions which needed further investigation. A further 13 were referred to the Department of Cardiology, either for 24-hour ECG abnormalities or structural abnormalities seen on their echocardiogram. Only 4 participants dropped out and did not complete the protocol, for various reasons. Noteworthy is the fact that in addition to the mayor and aldermen of Maastricht those of the municipality of Eijsden-Margraten also decided to participate in The Maastricht Study themselves. Finally, the Diabetes Research Fund Limburg was established in 2013, based on close cooperation between the Health Foundation Limburg, The Dutch Diabetes Foundation and The Maastricht Study, with the goal of raising funds among the public to support diabetes research in general at Maastricht UMC+.

Looking forward

The second Maastricht Study data set will become available in 2014. It will consist of data of 3400 participants, 1000 of whom have type 2 diabetes. The number of PhD students is expected to increase to 28, while at the same time the first five Maastricht Study PhD students will defend their theses either at the end of 2014 or the beginning of 2015. The scientific output in terms of manuscripts by The Maastricht Study is expected to rise steeply. Importantly, a series of extra visits are being planned for 2014, to give each participant the opportunity to also undergo an X-ray of the knees, a DXA scan of the body, a CT-Xtreme of the wrist and an MRI of the brain and abdomen. These parts of the protocol were included in the study at a later stage, as the process of applying for permission from the Dutch Health Council took longer than expected. A challenge for 2014 will be the digital management of all data, as this is expected to grow towards 50 Terabytes. The challenge lies in the heterogeneity of the data itself, which ranges from questionnaires, laboratory values and 24-hour electrocardiograms to ultrasound and MRI images, and the fact that no standard data infrastructure is commercially available. The Maastricht Study is expected to remain the unique, innovative population-based deep-phenotyping cohort study it was intended to be. In 2014, further collaborative projects between various departments of MUMC+ will become operational and the (scientific) return on investment is expected to increase.



‘You have to get out of your comfort zone’



Kristiaan Wouters
(Hasselt 1981),
Researcher,
Department of Internal Medicine

What are you researching?
“I’m currently doing the final experiments of a research project for which I was given a Veni grant in 2012. The project is about the link between atherosclerosis and overweight, focusing on the role of macrophages. My hypothesis is that these cells have the same effect as dendritic cells in obese adipose tissue, i.e. inducing systemic inflammation and thereby increasing atherosclerosis. I’ve found quite a bit of evidence that my hypothesis is correct, but the ultimate test still needs to be done. Fortunately, I was awarded the Dr Dekker senior post-doc grant in 2014, for research into the relationship between liver inflammation, commonly observed in overweight people, and atherosclerosis. This means I can now appoint my first PhD student, and a second one will be working half-time. So far, I had to do all the lab work myself, as well as teach and write grant applications, and that sometimes hampered the continuity of the research project in my view.”

Why Maastricht?
“Maastricht University has a solid reputation in research into cardiovascular diseases and obesity. I got to know the university as a student and PhD student. I like the mentality here in Holland: people are open and straightforward, certainly compared to Belgians. I quickly felt at home here. And another important point: all my friends and relatives, as well as my wife’s, are living nearby. Before this, I spent four years in Lille, at the Institut Pasteur. One thing I learned there was to be target-oriented, to work toward publishing a paper with a certain impact. At first, I didn’t understand why my PhD supervisor was always going on about doing some work abroad. He was pleased with my work, so why couldn’t I just stay where I was? But he told me that was not how it works. And he was right: if you can be successful in a foreign lab,

outside your comfort zone, that really means something. It also gives you better chances in the grants carousel, even though there's more than one road that leads to Rome. In any case, staying within your comfort zone doesn't work."

What does CARIM mean to you?
"An important aspect is CARIM's international reputation, something you can associate yourself with. Moreover, the interactions among the tenure trackers make for great synergy. I really appreciate it that the tenure trackers are invited to the strategic meetings, just like the principal investigators. To me, that's a sign of confidence, and it's also good for my network. I've recently joined CARIM's Research Council, which I find nice to do."

What are you proud of?
"That's a difficult one…. In recent years I've written a number of grant applications that were very good, but narrowly failed to succeed. I'm just as proud of those as of the Dekker grant, which I did get. But I've also set up a whole new flow cytometry approach for tissue macrophages, which we can use for the adipose tissue project and the liver project, and I'm regularly approached by people who want to collaborate with me. Proud is a word I don't easily use, but I'm certainly pleased with it. It's in my nature to look ahead and be slightly apprehensive about the future. Maybe that means I don't enjoy my successes enough, or that I'm not proud enough of them."

How do you maintain a balance between work and private life?
"We have a daughter aged 2.5, I play football for an hour each week, and I go cycling. For the past six months I've worked about sixty hours a week. When I come home, I have dinner, play with my little girl for a while, and then it's back to work. I assume I'll get more of my evenings back when I'll be able to delegate the lab work a bit more."

05_ TRAINING AND EDUCATION

INTRODUCTION

CARIM offers a flexible and integrated education and training program that suits 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 participate in the CARIM course week program and 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 can 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 students of the UM Research Master Biomedical Sciences, or for excellent students from other national or international biomedical Masters. At the end of 2013, 127 PhD students attended our PhD program.

Number of PhD students (31-12-2013)

Funding source	PhD students 2010	PhD students 2011	PhD students 2012	PhD students 2013
University	31	48	42	41
NWO	8	14	13	12
Non-profit + Industry	78	79	81	74
TOTAL	**117**	**141**	**136**	**127**

On Thursday 12 September 2013, **Annette Christ** became the first EUCAR student to earn a joint PhD degree from Maastricht University (UM) and RWTH Aachen. EUCAR is the Euregional collaboration between these two universities, financed by the Netherlands Organisation for Scientific Research (NWO). Christ, who successfully defended her dissertation in Aachen on 5 September 2013, received her degree in Maastricht on September 12 2013 with a stamp from both UM and the RWTH.

Title:
"Dendritic Cells in Hyperlipidemia-Associated Atherosclerosis"

Supervisors:
Professor MJAP Daemen; Professor M Zenke
Co-supervisor:
Professor EAL Biessen

PhD DELIVERABLES

PhD student careers from 2008 till 2013

In 2013, 34 PhD students finished their theses within our institute, and 2 theses were externally prepared. The table below illustrates the numbers of PhD students in the years 2008-2013, related to the period in which they obtained their degree. The graphics on page 34 present the number of PhD theses on the level of our research themes.

Year intake	2008	2009	2010	2011	2012	2013
Cohort volume (annual intake)	26	41	40	42	21	16
Male	14	23	17	22	9	7
Female	12	18	23	20	12	9
PhD from abroad	9	19	16	18	8	4
Thesis completed	12	10	1	2	-	-
Drop out	4	5	3	1	2	-
Drop out > 1 year	2	2	2	1	1	-
Average duration (in months)	58,1	50,6	-	-	-	-
Ongoing	10	26	36	39	19	16









2
years CA



25


CARIM THESES IN 2013

Erkens P -
The role of primary and secondary care in the management of pulmonary embolism: a shifting paradigm?
Promotores: Prof. M Prins, Prof. H ten Cate
Co-promotor: Dr H Stoffers
Maastricht University, February 20, 2013

Donfrancesco C -
The assessment of cardiovascular risk for primary prevention in the Italian adult population
Promotores: Prof. C Hemker, Prof. G de Gaetano (Campobasso, Italy)
Maastricht University, February 28, 2013

Palmieri L -
Surveillance of cardiovascular diseases in the Italian adult population
Promotores: Prof. C Hemker, Prof. G de Gaetano (Campobasso, Italy)
Maastricht University, February 28, 2013

Van de Laar R -
Lifestyle and arterial stiffness in young adults: A life-course approach
Promotores: Prof. C Stehouwer, Prof. M Prins, Prof. J Twisk, VUA
Co-promotor: Dr I Ferreira
Maastricht University, March 7, 2013

Johnson D -
Enhanced prediction and prevention of drug-induced Torsades de Pointes
Promotor: Prof. H Crijns
Co-promotores: Dr P Volders, Dr N Abi-Gerges (UK)
Maastricht University, March 8, 2013

Hendriks J -
Integrated Chronic Care for patients with Atrial Fibrillation
Promotores: Prof. H Crijns, Prof. H Vrijhoef
Co-promotor: Dr R Tieleman
Maastricht University, March 14, 2013

Veldhorst-Janssen N -
Intranasal delivery of rapid acting drugs
Promotores: Prof. M Marcus, Prof. C Neef
Co-promotor: Dr P van der Kuy
Maastricht University, March 2, 2013

Lancé M -
A circle of improvement in bleeding management: from laboratory to clinic and back
Promotores: Prof. M Marcus, Prof. J Heemskerk
Co-promotor: Dr Y Henskens
Maastricht University, May 17, 2013

Hermans M -
Getting a grip on myotonic dystrophy type 1
Promotor: Prof. Y Pinto
Co-promotores: Dr C Faber, Dr I Merkies
Maastricht University, June 21, 2013

Rademakers T -
Plaque angiogenesis and lymphangiogenesis: can small vessels influence atherosclerosis?
Promotores: Prof. E Biessen, Prof. M van Zandvoort
Co-promotor: Dr S Heeneman
Maastricht University, June 26, 2013

CARIM THESES IN 2013

Van Garsse L -
Echocardiographic predictors for recurrence of ischemic mitral regurgitation after restrictive annuloplasty
Promotor: Prof. J Maessen
Co-promotor: Dr S Gelsomino
Maastricht University, June 27, 2013

Christ A -
Dendritic cells in hyperlipidemia-associated atherosclerosis
Promotores: Prof. M Daemen, Prof. M Zenke
Co-promotor: Prof. E Biessen
Maastricht University, September 12, 2013

Ronden R -
Modulation of rental ADMA handling in hypertension
Promotor: Prof. P de Leeuw
Co-promotores: Dr A Kroon, Dr A Houben
Maastricht University, September 12, 2013

Blaauw E -
Stretch-mediated cardiac hypertrophy and extracellular matrix remodelling
Promotores: Prof. G van der Vusse, Prof. F Prinzen
Co-promotor: Dr M van Bilsen
Maastricht University, September 13, 2013

Vasina E -
Platelet-derived microparticles in vascular inflammation
Promotores: Prof. J Heemskerk, Prof. C Weber
Co-promotores: Dr R Koenen, Dr S Cauwenberghs
Maastricht University, September 19, 2013

Compeer M -
On the molecular pharmacology of endothelia Receptors or how EndothelinA agonists can make a difference
Promotor: Prof. J De Mey
Maastricht University, September 20, 2013

Bramer S -
Peri-operative Atrial Fibrillation in Cardiac Surgery; Impact on outcome
Promotores: Prof. J Maessen, Prof. C van Heugten
Co-promotores: Dr A van Straten, Dr E Bereklauw
Maastricht University, October 18, 2013

Beijers H -
Mechanisms of cardiovascular disease in the Metabolic syndrome and type 2 diabetes mellitus: Focus on adverse intermediate phenotypes
Promotor: Prof. C Stehouwer
Co-promotores: Dr I Ferreira, Dr B Bravenboer
Maastricht University, October 31, 2013

Otten J -
Circulating Monocytes in Atherosclerosis: Local or Systemic Actors?
Promotor: Prof. E Biessen
Maastricht University, November 6, 2013

Linz D -
Experimental Studies on New Therapeutic Approaches in Atrial Fibrillation
Promotores: Prof. U Schotten, Prof. M Böhm
Co-promotor: Dr S Verheule
Maastricht University, November 14, 2013

Joosen I -
Risk Stratification in Coronary Artery Disease; The Role of (bio)markers and Coronary CT-Angiography
Promotores: Prof. L Hofstra, Prof. J Wildberger
Co-promotores: Dr B Kietselaer, Dr M Das
Maastricht University, November 20, 2013

CARIM THESES IN 2013

Shadid N -
Ultrasound-guided foam sclerotherapy for treating varicose veins
Promotor: Prof. P Steijlen
Co-promotores: Dr A Sommer, Dr P Nelemans
Maastricht University, November 20, 2013

Versteylen M -
Clinical cardiac computed tomographic angiography implications for risk stratification
Promtores: Prof. L Hofstra, Prof. H Crijns
Co-promotores: Dr B Kietselaer, Dr M Das
Maastricht University, November 20, 2013

Angin Y -
Novel factors and mechanisms in control of CD36-mediated cardiac fatty acid transport
Promotor: Prof. J Glatz
Co-promotores: Dr J Luiken, Dr D Neumann
Maastricht University, December 4, 2013

Trappenburg M -
Contribution of cellular microparticles to Pre-thrombotic states
Promotor: Prof. H ten Cate
Co-promotores: Dr A Leyte, Dr W Terpstra
Maastricht University, December 4, 2013

Schutters K -
Annexin A5: shifting from molecular imaging tool to therapeutic agent in cardiovascular diseases
Promotor: Prof. C Reutelingsperger
Co-promotor: Dr L Schurgers
Maastricht University, December 5, 2013

Strik M -
Electrical substrate for cardiac resynchronization therapy: identification and treatment
Promotores: Prof. F Prinzen, Prof. A Auricchio
Maastricht University, December 6, 2013

Daniels A -
Diabetic cardiomyopathy: in search of proof
Promotor: Prof. G van der Vusse
Co-promotores: Dr M van Bilsen, Dr F van Nieuwenhoven
Maastricht University, December 11, 2013

Heijnen B -
Linking the renin-angiotensin system to immune mechanisms: the key in hypertension development?
Promotor: Prof. H Struijker Boudier
Co-promotor: Dr B Janssen
Maastricht University, December 11, 2013

Ganushchak Y -
Prospective development of extracorporeal life support: from protoscience to science
Promotor: Prof. J Maessen
Co-promotor: Dr P Weerwind
Maastricht University, December 11, 2013

Geelen T -
Haemophilus influenza in respiratory disease: from the bug to the body
Promotor: Prof. C Bruggeman
Co-promotor: Dr F Stassen
Maastricht University, December 12, 2013

CARIM THESES IN 2013

Leptidis S -
PPARs and microRNAs at the heart of metabolic regulation in cardiac disease
Promotor: Prof. L de Windt
Co-promotores: Dr H Azzouzi, Dr P da Costa Martins
Maastricht University, December 17, 2013

Pison L -
Hybrid ablation of atrial fibrillation
Promotores: Prof. H Crijns, Prof. J Maessen
Co-promotor: Dr S Gelsomino
Maastricht University, December 18, 2013

Gabriels K -
Cardiovascular disease: Role of immuno- and radiotherapy
Promotores: Prof. M Daemen, Prof. E Biessen
Co-promotores: Dr S Heeneman, Dr F Stewart
Maastricht University, December 20, 2013

PHD THESES EXTERNALLY PREPARED

Mulders T -
Premature Atherosclerosis: Sounds Familial?
Promotor: Prof. E Stroes
Co-promotores: Dr S Pinto-Sietsma, Dr H Vink
University of Amsterdam, April 2, 2013

Hermans M -
Getting a grip on myotonic dystrophy type 1
Promotor: Prof. Y Pinto
Co-promotores: Dr C Faber, Dr I Merkies
Maastricht University, June 21, 2013

CARIM THESIS AWARD 2011-2012

Dr **Jordi Heijman** received the CARIM thesis award 2011-2012 at the CARIM Symposium on Wednesday October 30. This award is given biannually for the best thesis written by a CARIM PhD student. Jordi conducted his research in the Department of Cardiology under the supervision of promotores Prof. Harry Crijns and Prof. Ralf Peeters, and co-promotores Dr Paul Volders and Dr Ronald Westra. In his thesis "Computational analysis of ß-adrenergic stimulation and its effects on cardiac ventricular electrophysiology", Jordi studied the combined computational and experimental approach to investigate ß-adrenergic stimulation and its effects on ventricular electrophysiology in physiological and pathological conditions. In a number of cardiovascular diseases, an increased sympathetic tone has been associated with the development of potentially lethal ventricular tachyarrhythmias. At the level of the single ventricular myocyte, activation of ß-adrenergic receptors by norepinephrine released from cardiac sympathetic nerve ending activates an intracellular pathway resulting in modulation of a number of ion channels and Ca2+ handling proteins. These changes form the basis of the altered electrical and contractile function during sympathetic stimulation. All original chapters of his thesis have been published in renowned journals. Jordi's PhD research has led to 4 publications with two additional manuscripts in preparation and received the distinction 'cum laude'.

Dr Jordi Heijman (left) and
Professor Thomas Unger (right)

FHML

'TOPTALENTENPROGRAMMA 2013'

Five young CARIM researchers have been selected for the UMC for the 'Toptalentenprogramma 2013'. This program scouts internally for potential academic leaders (focused on education, scientific research and/or academic care) and supports these young, promising talents in their advanced post-doc phase to become tenured or even advance to professorship. From CARIM, Dr **Eline Kooi,** Dr **Judith Cosemans,** Dr **Blanche Schroen,** Dr **Rory Koenen** and Dr **Bas de Laat** have been selected.

KNOWLEDGE TRANSFER

CARIM Course week

From June 2 until June 5, the CARIM Course week took place. Four parallel courses have been organised by CARIM researchers: Drug Discovery and Development, Heart Failure Research: Getting to Excellence, Non-Invasive Biomedical Imaging and Advanced Microscopy and Vital Imaging. The course week consisted of three parallel courses, covering several aspects of CARIM's research, alternated with a combined scientific program and a social program organised by I'MCARIM, the organisation of CARIM's PhD's. Almost 40 PhD and Master students participated.

Cardiovascular Grand Rounds Maastricht

The Cardiovascular Grand Rounds Maastricht is one of our 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 2013 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.

CARIM SYMPOSIUM 2013

On October 30, CARIM's 25th anniversary was celebrated with a special, festive edition of the traditional yearly scientific CARIM Symposium. Recognized national and international speakers were invited to talk about CARIM's local, national and Euregional context. The traditional Robert Reneman lecture was given by Prof. John Yudkin, emeritus Professor of Medicine at University College London and was titled: "Consilience and the science of glucose lowing". His interest in international health led him to set up University College London's International Health and Medical Education Centre in 1999. He was the initiator of the UK's first Intercalated Bsc in Global Health, a model for similar programs in numerous other UK medical Schools. His recent work has concentrated on the medicalization of risk reduction, particularly in diabetes.

Another key element of the day was a lecture on today's cardiovascular research scene in Europe given by Prof. Panos Vardas, President of the European Society of Cardiology. A representative poster session reflecting recent scientific achievements at CARIM are further highlighting the celebration program together with lectures by Prof. John Kastelein, Prof. Yigal Pinto, Prof. Karin Sipido, Prof. Martin Paul, Dr Judith Sluimer, Prof. Michael Jacobs, Prof. Monika Stoll, Prof. Thomas Münzel and Prof. Nikolaus Marx.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Robert Reneman lecturers 1993-2013

1993 M. Verstraete, Leuven, Belgium
1994 J. Sixma, Utrecht, the Netherlands
1995 P. Vanhoutte, Courbevoie, France
1996 W. Schaper, Bad Neuheim, Germany
1997 P. Davies, Philadelphia, USA
1998 M. Pfeffer, Boston, USA
1999 Y. Nemerson, New York, USA
2000 V. Fuster, New York, USA
2001 M. Schneider, Houston, USA
2002 F. Rosendaal, Leiden, the Netherlands
2003 A. Zeiher, Frankfurt, Germany
2004 P. Poole-Wilson, London, UK
2005 D. Wagner, Boston, USA
2006 S. Wickline, St. Louis, USA
2007 J. Molkentin, Cincinnati, USA
2008 B. Furie, Boston, USA
2009 K. Walsh, Boston, USA
2010 J. Lusis, Los Angeles, USA
2011 W. Ouwehand, Cambridge, UK
2012 D. Kass, Baltimore, USA
2013 J. Yudkin, London, UK

Robert Renemen lecture 2013:
Prof. John Yudkin and Prof. Thomas Unger

Prof. Rob Reneman and Prof. Thomas Unger

OTHER CARIM LECTURES, SEMINARS AND SYMPOSIA 2013

Complementary to the regular lecture series and CARIM symposium, several lectures, seminars and conferences were organised by our research staff in 2013. Some of them are presented below.

From March 24 until March 27, Professor **Marc van Zandvoort** organised in cooperation with Professor Fred Brakenhoff (University of Amsterdam) the **Focus on Microscopy** congress at the MECC. Focus on Microscopy 2013 is the continuation of a yearly conference series presenting the latest innovations and newest trends in optical microscopy, and their application in biology, medicine, and material sciences.

On April 12, the **first scientific meeting of the Maastricht Study** took place were the first results were presented by PhD students. Additionally, a brief update on the progress of the study was presented.

The **MIMSA (Maastricht Inflammation in the Metabolic Syndrome and Atherosclerosis)** mini-symposium, organised by Dr **Marjo Donners** (Dept. of Pathology) and Dr **Kristiaan Wouters** (Dept. of Internal Medicine), took place twice in 2013 and will be continued in 2014. The topic of the mini-symposium is focused on inflammation related to the metabolic syndrome and atherosclerosis. The aim is to provide a platform for young researchers (post-docs and PhD students) to present and discuss their data in an informal meeting (i.e. unfinished projects, plans or problems encountered) and to get acquainted with each other's research to stimulate collaborations. Each time a senior researcher from another university is invited to give a keynote lecture.

On September 15-17 2013, the **first European workshop on AMPK**, organised by Prof. **Jan Glatz** and Dr **Dietbert Neumann** (Dept. of Genetics & Cell Biology) took place. The goal of this new meeting is to bring together European 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 was given in priority to young researchers (PhD students or post-docs) to present their own projects. The poster session then allowed for deepened discussions with all participants.

XXIV Congress of the ISTH

From June 30th - July 4th 2013, the XXIV Congress of the International Society of Thrombosis and Haemostasis (ISTH) was held in de RAI in Amsterdam, organised by (from left to right) Marcel Levi (AMC), Pieter Reitsma (LUMC), Suzanne Cannegieter (LUMC), **Tilman Hackeng** (MUMC+), and Frits Rosendaal (president, LUMC). With 8283 delegates this was the largest ISTH conference to date. An international scientific advisory board awarded 133 Young Investigators Awards worldwide, of which 32 (24%) went to the Netherlands (633 delegates: 8%). From these 32 awards, 7 went to Maastricht, showing international and national excellence of CARIM in the field of Thrombosis and Hemostasis. The recipients were Martijn Chatrou, Marie-Claire Kleinegris, Marisa Ninivaggi, Francesca Nuzzo, Farida Omarova, Sameera Peraramelli, and Kristien Winckers.

COLOPHON

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Tara de Koster, CARIM

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