

CARIM ANNUAL REPORT 2009

School for Cardiovascular Diseases



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CONTENTS

	PREFACE	5
01	PROFILE	7
	INTERVIEW / YOUNG PHD STUDENTS WIN PRESTIGIOUS GRANTS	17
02	ORGANIZATION	23
	INTERVIEW / COOPERATION BETWEEN CARIM AND IMCAR VALUABLE TO RESEARCHERS	27
03	SUMMARY SCIENTIFIC OUTPUT	33
04	EVENTS AND HIGHLIGHTS 2009	37
	INTERVIEW / VIDI SUBSIDIES FOR TWO MAASTRICHT UMC+ CARDIOLOGISTS	47
05	EDUCATION	53
	INTERVIEW / WORLD'S LARGEST RESEARCH STUDY ON LINK BETWEEN CHRONIC DISEASES	67
	LIST OF ABBREVIATIONS	73
	COLOPHON	76



PREFACE

It is with joy and pleasure that I present the Annual Report 2009 of CARIM School for Cardiovascular Diseases. Last year, when we presented a rejuvenated version of our annual report, we received a lot of positive and enthusiastic feedback of both our internal and external relations. Our Annual Report 2008 gave a full overview of the research programs of our institute, the people working within these programs and the performances of each specific program. As the lifecycle from scientific ideas to results and innovation takes several years, we have chosen to give such an overview of our programs every two to three years. This year we decided to pay more attention to the highlights of 2009, which was a very successful year for CARIM, and to the achievements of our young research talents.

We are very aware of the increasing competition in the field of cardiovascular research. That is why the Executive Board of CARIM decided to introduce several measures to further improve the quality within our institute. We did not invent these measures on our own, but we learnt from positive experiences and pitfalls of other top research institutes in the Netherlands. In October our management team paid visits to the Netherlands Cancer Institute (NKI) in Amsterdam and the Hubrecht Institute in Utrecht. As a result of these visits, a CARIM Research Council has been installed. Main task of the Research Council is to review all the project proposals before they are submitted to the grant organizations. We believe that this new policy will both stimulate the quality of our project proposals, and above all contributes to an academic environment in which long life learning is an important condition. Furthermore we started to bring together our PI's in 8 clusters. The development of these clusters and an internal quality cycle is a main activity in the coming years. In the future the three CARIM Main Themes will evaporate.

There is this beautiful Italian word that expresses the will and eagerness to achieve ones goals: "grinta". If a person

has a lot of "grinta", it means that he or she has "will-power", and is "very determined" in his actions. It is only with this "grinta" that our researchers obtain project grants to conduct their cardiovascular research within our institute. Two young talented PhD students and six successful CARIM researchers achieved remarkable results last year. To give you as a reader, more insight in their research careers and their eagerness with which they contribute to broaden not only their own horizons, but also the horizons of the research embedded within CARIM, this year's annual report includes four duo interviews.

Although these interviews provide podium to eight of our researchers, I must underline that the results presented here are based on the work of all our researchers, research assistants and supporting staff. I would like to thank them all for their efforts and collaboration in 2009. And off course CARIM would not be able to conduct the research activities without the continuous support of Maastricht University, the Academic Hospital Maastricht, our partner institutes, our regional, national and European government and all the non-profit organizations and industries that provide us with project grants.

I hope that you will enjoy reading the duo interviews and the scientific highlights in this Annual Report 2009. And again we would appreciate your feedback. ■

Mat J.A.P. Daemen
Scientific Director CARIM
School for Cardiovascular Diseases

01_ PROFILE

PROFILE

In 1988, the Maastricht research efforts on cardiovascular diseases were concentrated in the Cardiovascular Research Institute Maastricht (CARIM), an institute under the Dutch University Education Act (WWO). In 1992, together with the Institute for Cardiovascular Research (ICaR) of the Free University in Amsterdam (VU), CARIM was recognized as a Research School on Cardiovascular Diseases by the Royal Netherlands Academy of Arts and Sciences (KNAW). The accreditation was renewed in 1997, 2002 and from 2008 CARIM is recognized as a local research school. From 1993, the European Union has recognized CARIM as an international training site for Early Stage Researchers in the framework of the Marie Curie Program. CARIM School for Cardiovascular Diseases is one of the five schools of the Faculty of Health, Medicine and Life Sciences (FHML) of Maastricht University and is embedded within the Maastricht University Medical Center+ (Maastricht UMC+).

KEY FIGURES 2009

Annual budget: 19.2 K€
Researchers: 177.8 fte
Technical and supporting staff: 61.5 fte
Departments/disciplines: 15
Scientific articles: 509 (Wi-1: 471)
PhD Thesis: 29
Patents: 7

Mission Statement

CARIM's mission can be summarized in six words: prevent, cure, care, discover, valorize and teach. CARIM has the ambition to be one of the leading research institutes in translational cardiovascular research in Europe. CARIM, in close collaboration with the Cardiovascular Center of the University Hospital Maastricht, aims to develop an internationally recognized center of excellence in cardiovascular medicine.

Prevent, Cure, Care, Discover

- We study basic mechanisms as well as early diagnosis and individual risk stratification of cardiovascular diseases, allowing faster translation of new research concepts to clinical practice.

Valorize

- We evaluate new findings, products and techniques that can be applied in healthcare, often in collaboration with private companies.
- We publish the results of our scientific research in high-ranking international journals.

Teach

- We train Master students, PhD students and MD students to become independent researchers.
- We train post-docs to become leading scientists in the field of cardiovascular diseases.

Organization of our research

The organization of the research school is presented on page 23. The Executive Board (EB) of the school consists of the Scientific Director, the Managing Director, the Leaders of the Main Themes and the Education Program Coordinator. The EB is responsible for the management of the school and meets monthly to discuss and decide upon issues at

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strategic and tactic level. The Scientific Director has the full and integral responsibility for the school and reports to the Dean. The research within CARIM concentrates on three major themes: Theme I: Thrombosis and Haemostasis, Theme II Cardiac Function and Failure, and Theme III Vascular Biology. Each theme consists of multiple (multi-disciplinary) research programs, led by a program leader whom within CARIM is called Principal Investigator (PI). Each PI is responsible for the scientific progress of the program, the mentoring of PhD students and post-docs and the financial basis of the program. All three themes involve basic as well as clinical programs. The PI's, together with all the chairmen of the departments connected to CARIM, constitute the School Council. The School Council meets two times a year and is headed by the Scientific Director. The Education Program Committee coordinates both the PhD and Master's programs and advises the Executive Board on all issues regarding these educational programs. Our International Scientific Advisory Board (ISAB) meets biannually and advises the CARIM board on research and educational strategies. At the end of 2009 the Executive Board established the Research Council. This council advises the board and PI's on the quality of all research proposals and meets monthly.

In October our School Council discussed a proposal on the reorganization of the 23 CARIM research programs. We have started to bring together our 23 PI's into eight research clusters, with the aim to stimulate cooperation between programs that partially overlap each other, to eventually get more earning power in European and national (NWO) grant programs. In 2010 and 2011 these eight clusters will be further developed, so that in the long term the three main themes will disappear. To guarantee a good balance between individuality and collectivity, the PI-structure will be maintained. The three senior researcher positions in

CARIM's Executive Board (at present the theme leaders) will stay necessary to support the Scientific Director in the decision-making process on strategic and financial issues, the human resource management, organization and management of the school.

Funding

CARIM receives its basic funding from Maastricht University, through the Faculty of Health, Medicine and Life Sciences (FHML) and the University Hospital Maastricht (azM). This basic funding is primarily intended to finance CARIM's tenured staff, post-docs, PhD students, technicians, research infrastructure and PhD teaching program. In addition to the university and hospital funding, a significant part of our research program is supported by non-profit organizations and industry.

PARTNERSHIPS AND CONSORTIA

Eindhoven University of Technology (TU/e)

Since 1991 the research collaboration between Eindhoven University of Technology (TU/e) and CARIM focuses on three areas of mutual interest:

- 1 biomolecular targeting and bioinformatics;
- 2 biomedical imaging and signaling;
- 3 biomechanics and tissue engineering.

Within the TU/e undergraduate program on Biomedical Technology, students participate in CARIM's research program in the last year of their training.

EuCAR

In 2008 CARIM, together with the Institute for Molecular Cardiovascular Research (IMCAR) of the Universitätsklinikum Aachen (UKA), implemented the Euregional Cardiovascular International Research Training Group (EuCAR) on "Arterial Remodeling". This initiative for an international bilateral cardiovascular graduate school is supported by the main national funding bodies Deutsche Forschungsgemeinschaft (DFG) and the Netherlands Organization for Scientific Research (NWO). Together with IMCAR we share several research positions (Weber, Van Zandvoort, Lutgens), and a well-developed research infrastructure (mouse facility in Aachen, peptide synthesis modeling in Maastricht).

ICIN

The Netherlands Heart Institute (ICIN) is an alliance of the 8 university cardiology departments in the Netherlands. ICIN research projects are carried out in the participating cardiology centers or the laboratories of other partners in research. Several CARIM researchers have close ties with the (ICIN) and participate in ICIN's coordination program. Four ICIN researchers (2 PhD students and 2 post-docs) work in the CARIM laboratory of Leon de Windt. Professor Harry Crijns and Professor Mat Daemen are both members of the Scientific Advisory Board.

International status

CARIM holds a strong position in the international cardiovascular research area. We participate in several FP6 and FP7 Networks of Excellence: the European Vascular Genomics Network (EVGN), the European Network on Diagnostic Molecular Imaging (DiMI), InGenious HyperCare Network and the CardioRisk Consortium. CARIM is a recognized training center for Early Stage Researchers Marie Curie. CARIM's research program is supported by international non-profit organizations as well as by internationally operating (pharmaceutical and medical device) industries. About 20% of our current scientific staff is non-Dutch. ■

Funding and expenditure at institutional level 2004-2009

K€	2004		2005		2006		2007		2008		2009	
Direct Funding	7.570	49%	7.426	45%	7.807	46%	8.055	40%	8.239	45%	8.653	45%
Research Funds	1.932	13%	1.869	11%	1.572	9%	1.751	9%	1.411	8%	1.201	6%
Contracts	5.832	38%	7.182	44%	7.766	45%	10.426	51%	8.812	47%	9.384	49%
Total	15.334	100%	16.477	100%	17.145	100%	20.232	100%	18.462	100%	19.238	100
Personnel	10.208	65%	11.710	71%	11.163	66%	13.401	68%	13.534	77%	14.656	83%
Other costs	5.538	35%	4.687	29%	5.827	34%	6.361	32%	4.100	23%	2.862	17%
Total	15.746	100%	16.397	100%	16.990	100%	19.762	100%	17.634	100%	17.518	100%
Result	-412		80		155		470		828		1.720	

Direct Funding = funding provided directly by the Faculty HML

Research Funds = funding received in competition from national and international science foundations (NWO/ZonMw, STW, KNAW)

Contracts = funding from third parties for specific research activities, from charities, EU-framework programs, industry, etc.

Research output in 2004-2009

	2004	2005	2006	2007	2008	2009
PhD theses	43	32	35	37	29	29
Scientific publications	409	436	490	497	465	509
Other publications	71	58	42	49	54	46
Total (I)	523	526	567	583	548	584
Academic staff in fte (II) *	38,8	38,5	35,7	35,9	37,4	37,0
Ratio I en II	13,9	13,7	15,9	16,2	14,7	15,8

PhD theses: including PhD theses externally prepared

Scientific publications: Wi-1 publications in refereed SCI-SSCI indexed journals, 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)

*Academic staff: PhD students and post-docs not included

New contracts and grants concluded in 2009

Funding	Theme I	Theme II	Theme III	General	Total Support K€
Type 2	100,000	1,875,000	0	-	1,975,000
Type 3	3,565,000	4,862,568	13,413,640	623,000	22,464,208
Type 4	376,000	530,500	1,017,000	-	1,923,500
Type 5	250,000	250,000	3,250,000	-	3,750,000
Total	4,291,000	7,518,068	17,680,640	623,000	30,112,708

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

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

Type 4 = Industry, incl. CTCM

Type 5 = Annual support (750 K€) Cardiovascular Center-CARIM "Pieken vanuit de Breedte" and support through University Hospital Maastricht: donation Weijerhorst Foundation to the Maastricht Study (3M€)

Summary of scientific and technical staff CARIM 2009 (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	PhD-stud	
Thrombosis and haemostasis	6.8	3.8	2.0	1.0	2.0	1.0	-	6.6	3.3	0.8	2.0	2.0	0.4	-	31.7
Cardiac function and failure	14.5	6.5	4.9	0.6	1.2	0.5	0.3	11.6	7.4	0.7	5.8	2.1	2.2	2.3	60.6
Vascular biology	15.7	13.3	4.1	1.1	1.0	0.6	-	21.2	14.6	-	5.4	2.5	4.9	1.4	85.8
Total	37.0	23.6	11.0	2.7	4.2	2.1	0.3	39.4	25.3	1.5	13.2	6.6	7.5	3.7	178.1
	OBP 1			OBP 2			OBP 3			OBP 4			OBP azM		TOTAL
Thrombosis and haemostasis	6.7			0.4			2.2			1.5			-		10.8
Cardiac function and failure	12.8			1.4			2.9			0.3			0.6		18.0
Vascular biology	18.2			2.8			6.9			1.8			3.0		32.7
Total	37.7			4.6			12.0			3.6			3.6		61.5

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

“It is only with this ‘grinta’ that our researchers obtain project grants to conduct their cardiovascular research within our institute. Two young talented PhD students and six successful CARIM researchers achieved remarkable results last year.”

Mat J.A.P. Daemen, Scientific Director CARIM

[Grinta]: Italian word; will-power, to be very determined



Laura Steinbusch

INTERVIEW

YOUNG PHD STUDENTS WIN PRESTIGIOUS GRANTS

‘In the field of cardiovascular research there are plenty of opportunities.’

They don't really know each other. Or rather: they've never met or even heard of each other. Nevertheless, life scientist Laura Steinbusch (27) and medical student Tom Seijkens (24) have quite a lot in common. Both are young, ambitious PhD students at CARIM. And in 2009, they both received prestigious grants.

Tom Seijkens may only be 24 years old, but he has already seriously contemplated his future. After completing his bachelor's degree in Medicine at Maastricht University (UM), he decided to enrol in two Master's studies simultaneously, while also – quite remarkably – starting his PhD programme at the same time.

His PhD research focuses on atherosclerosis. Tom explains what his work involves: “Atherosclerosis is a chronic inflammatory disease of the arteries; which may result in a heart attack or stroke. Our research shows that the interaction between the proteins CD40 and CD40L plays an important role in the inflammation underlying atherosclerosis. Inhibiting CD40 and CD40L results in the formation of smaller and more stable atherosclerotic plaques, which greatly reduces the chance of clinical complications. However, CD40 and CD40L also play important roles in the immune system. Therefore completely blocking both proteins is not desirable. That's why we are currently studying how to inhibit the inflammatory response caused by CD40 and CD40L, while

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EXTENSIVE EXPERIENCE

leaving their function within the immune system unaffected.”

Extensive experience

The research by Tom Seijkens’ team also includes studies on the role of CD40-CD40L in bone marrow. Tom: “Here, stem cells produce white blood cells, red blood cells and blood platelets. Our research team and other teams around the world have provided evidence that CD40 and CD40L on white blood cells and blood platelets, contribute to the cause of atherosclerosis. Our current study focuses on the role of both proteins in the production of these cell types. We expect this will give us a greater understanding of the underlying processes of atherosclerosis. The results of the pilot study indicate that CD40-CD40L does play a role in the biology of these stem cells. In this study we will use several techniques to gather additional data. For example, we will use immunohistochemical staining, fluorescent activating cell sorting and in vivo experiments.” The research team in Maastricht doesn’t work on this by itself. Tom: “We work in close cooperation with Dr. Tjwa’s laboratory in Frankfurt. This lab has extensive experience with haematological research methods and it has the latest technology at its disposal. This will help us to conduct highly innovative research.”

Talent Fellowship

In 2009 Tom Seijkens won the Kootstra Talent Fellowship in the category ‘Talented students in Health, Medicine or Life Sciences’. Tom: “Receiving this grant gave me the chance to combine my graduate studies with my PhD programme. This probably wouldn’t have been possible without the fellowship. The fellowship amounts to just over 21,000 euros, which was matched by CARIM. So the total amount was about 42,500 euros.”

The talents of molecular life scientist Laura Steinbusch didn’t go unnoticed either. The European Foundation for the Study

THE HEART’S ENERGY CONSUMPTION

of Diabetes awarded her with a Travel Fellowship. She used this fellowship to conduct research abroad. Laura: “It was a great way to gain experience.

During the five years in which I did my coursework, I did quite a few internships at different institutes and in different research areas. During my internship in the French city of Lyon, for example, I noticed that researchers elsewhere have access to different facilities, have different opportunities and habits. I believe I can learn a lot from this. That’s why I wanted to continue visiting other labs for shorter or longer periods of time. Not only while studying, but also while conducting my PhD research, which I hope to complete by the end of 2011. The visits have taken the shape of several short trips. For example, I’ve been in Leiden and Amsterdam for a few weeks and at the start of 2010 I spent five weeks in Brussels.”

The heart’s energy consumption

Laura Steinbusch is studying the heart’s energy consumption, with an emphasis on the travel and movement of one particular fatty acid transporter, CD36, in the cardiac myocyte. “I’m looking whether this could provide clues for the treatment of heart problems occurring in type 2 diabetes, more commonly known as diabetes caused by obesity.” Laura could afford an internship in Brussels because she received a Travel Fellowship in 2009. “This kind of fellowship allows me, and indirectly also the lab in which I work here in Maastricht, to learn and implement new techniques. In addition, having a network outside the UM and outside The Netherlands is useful to help progress any research you may be working on. For me, it’s also a way to get to know any research group I may want to work with after I’ve finished my doctoral studies.”

Applying for grants

If you want to continue working on research studies, you need

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Tom Seijkens

BRIDGING THE GAP

to apply for grants. Both Laura and Tom are convinced about that. Laura: "As a researcher at CARIM, I believe too few PhD students use these opportunities, even though they are perfect springboards to a scientific career. I estimate that at CARIM, there are about one hundred PhD students annually. But only a few of them will take advantage of the possibilities that grants can offer in potential." Tom, who has been part of the CARIM's Pathology department for three years, agrees. He is very positive about the Kootstra Fellowship. "It offers students a chance to start their PhD research early. Often that won't be possible otherwise."

Bridging the gap

Tom Seijkens hopes to complete his PhD research within three years. He's not quite sure yet what he wants to do after this. "I'm interested in patient care as well as basic scientific research. However, I think that combining the two would be a great challenge to take on." Tom realizes that this is not always an obvious combination. "Many of my fellow students focus primarily on the clinical aspects of medicine. And within the academic programme there has also been limited emphasis on scientific research. Even though there has been growth in recent years, there still seems to be a gap between the clinic and the lab; despite the benefits of combining the two. As a clinician you will notice things in the hospital, which you can then study in the lab. And in reverse, you can take your findings in the lab to the clinic. That's why I expect the combination of working in both clinic and lab to have a bright future."

Large concentration of universities

Laura has developed quite a taste for internships abroad. "Once I've earned my PhD at CARIM, hopefully in 2011, I would like to go abroad again. Together with my boyfriend,

who is also working on his PhD." The couple has already started looking for potential locations they could move to together. "We are looking at areas with a large concentration of universities and research institutes. The area on the German-Swiss border near Basel and the East Coast of the United States, for example." Laura believes that having won a few grants will make it easier for her to obtain additional grants in the future. "There are quite a few possibilities", she says. "Especially in the field of cardiovascular disease research there are plenty of opportunities. Perhaps I can apply for a pilot-grant. This is a smaller grant that will enable you to conduct a preliminary analysis. You can then use the results of this analysis to apply for a much larger grant. The pilot-grant usually consists of a sum between 15,000 and 50,000 euros." Laura has a clear vision of what she wants to do next. "I'll either continue in diabetes research, concentrating on changes in the brain rather than in the heart. The other option is heart metabolism, but then in athletes, for example, instead of diabetics. But first I need to finish my PhD and then I'll see what happens."

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PASSPORTS



Name:

Laura Steinbusch

Age:

27

Laura Steinbusch studied Molecular Life Sciences (MLW) at Maastricht University. She is now a PhD student, working with dr. Joost Luiken and professor Jan Glatz of the Molecular genetics department. Her PhD research focuses on 'Sub cellular trafficking of CD36 as target for restoring cardiac dysfunction in type-2-diabetes'. In 2009, Laura received two conference grants. One of them was awarded by the Dutch Diabetes Research Foundation, while the other one was the Albert Renold Travel Fellowship for Young Scientists provided by the European Federation for the Study of Diabetes.



Name:

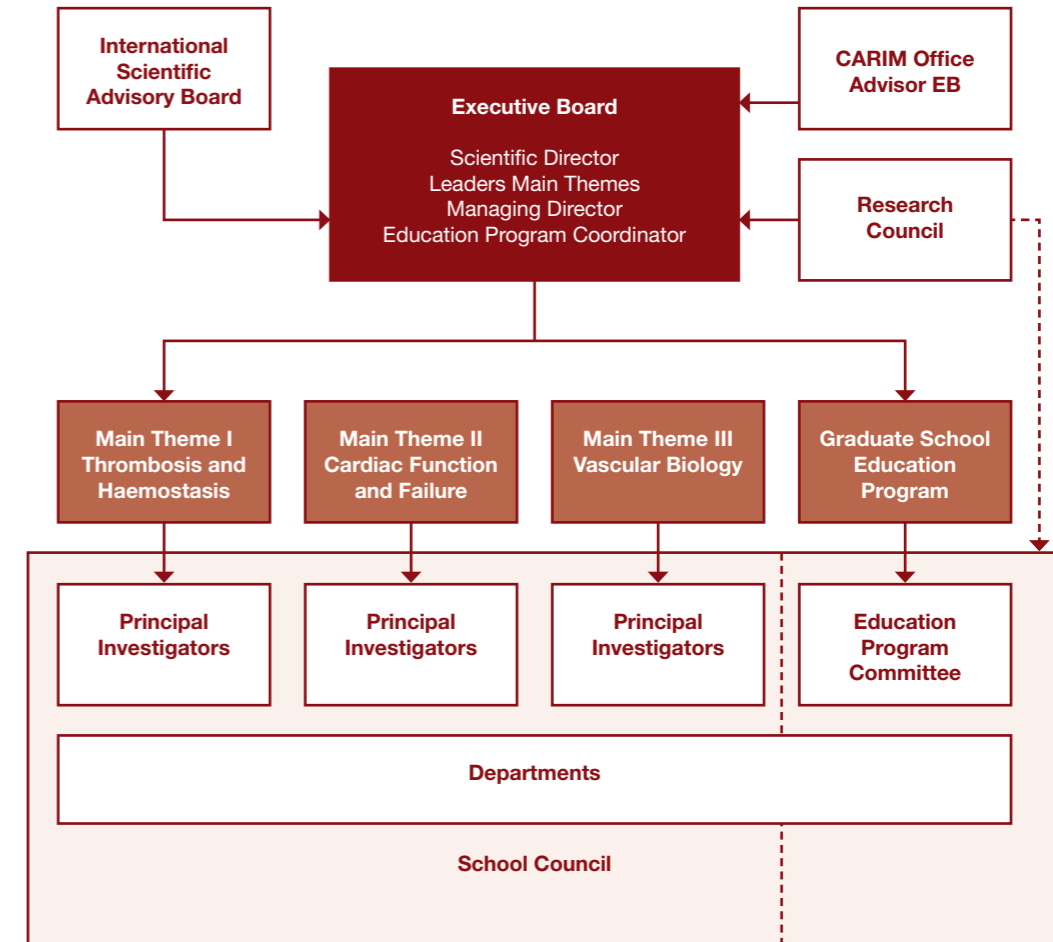
Tom Seijkens

Age:

24

Tom Seijkens received his bachelor's degree in Medicine in 2008 from Maastricht University. He then enrolled in the master's programme in Medicine as well as the CARIM Research Master in Cardiovascular Biology and Medicine, both at the UM. In addition, he is a PhD student, working with dr. Esther Lutgens of the Pathology department at CARIM. In 2009, Tom received the Kootstra Talent Fellowship. This grant is made available by the Executive Board of the Maastricht UMC+ to develop talent amongst young scientific researchers. His research focuses on the role of CD40 and CD40L in atherosclerosis and haematopoiesis.

02_ ORGANIZATION



ORGANIZATION



CARIM's current Executive Board (from left to right)

Harry Crijns, Leader Main Theme II, Adriaan Duijvestijn, Education Program Coordinator, Mat Daemen, Scientific Director, Petra Uittenbogaard, advisor, Rob van der Zander, Managing Director, Mark Post, Leader Main Theme III, Tilman Hackeng, Leader Main Theme I

International Scientific Advisory Board

- Professor Pim van Aken, chairman
- Professor Günther Breithardt, Universitätsklinikum Münster, Germany
- Professor David Lane, Imperial College London, UK
- Professor Alain Tedgui, INSERM Paris, France
- Professor Renu Virmani, CVPPath, International Registry of Pathology, Gaithersburg Maryland, USA
- Professor Anthony Ware, Lilly Corporate Center Indianapolis, USA
- Professor John Yudkin, University College London, UK

Executive Board

- Professor Mat Daemen, Scientific Director
- Adriaan Duijvestijn, Education Program Coordinator
- Professor Harry Crijns, Leader Main Theme II
- Professor Tillman Hackeng, Leader Main Theme I
- Professor Mark Post, Leader Main Theme III
- Rob van der Zander, Managing Director
- Petra Uittenbogaard, advisor and project manager

Education Program Committee

- Adriaan Duijvestijn, chairman
- Matthijs Blankesteyn, staff member
- Vanessa van Empel, MD (since March 2010)
- Professor Jan Lodder, MD staff member (till January 2010)
- Hans Vink, staff member
- Kelly van Bragt, PhD student
- Ellen Dirkx, PhD student (since January 2010)
- Romy Kremers, master student (since February 2010)
- Auke Otten, master student (since October 2009)
- Timo Rademakers, PhD student
- Matthijs Ruiten, PhD student (till January 2010)

Research Council

- Professor Mat Daemen, chairman
- Professor Harry Crijns
- Professor Tilman Hackeng
- Professor Johan Heemskerk (deputy member: Prof Hugo ten Cate)
- Professor Jo de Mey (deputy member: Dr. Hans Vink)
- Professor Mark Post
- Professor Frits Prinzen (deputy member: Prof Stephane Heymans)
- Professor Chris Reutelingsperger (deputy member: Dr. Gerry Nicolaes)
- Dr. Uli Schotten
- Professor Johannes Waltenberger (deputy member: Prof Leo Koole)
- Professor Leon de Windt (deputy member: Dr. Matthijs Blankesteyn)
- Professor Joachim Wildberger
- Dr. Menno de Winther

CARIM Office

CARIM Office consists of Riet Daamen, Saskia Vocks, Esther Willigers and Johanna Roona. The administrator is Martin Tossings.

HR-support

Two persons of the central Human Resources Department of Maastricht University are related to CARIM; Patrick Janssen and Yves Engelen.

Administrative support

The central Administrative Service Center (ASC) of Maastricht University provides support on accounting the CARIM research projects on a part-time basis. In 2009 the administrative staff consisted of: Angela Beekman, Henny Kerckhoffs, Pieter-Jan Smit and Nancy Smits.

Participating departments and disciplines

The research in the three main themes involves the research activities of people working in several departments/disciplines of Maastricht University Medical Center+:

Basic Research Departments

Biochemistry
Biomedical Technology
Biophysics
Genetics and Molecular Cell Biology
Pharmacology and toxicology
Physiology

Clinical Departments

Cardiology
Cardio-thoracic Surgery
Clinical Chemistry
Internal Medicine, including Immunology
Medical Microbiology and Virology
Neurology
Pathology
Radiology
Surgery



INTERVIEW

COOPERATION BETWEEN CARIM AND IMCAR VALUABLE TO RESEARCHERS

‘The institutes
benefit from each
other’s strengths’

There is a growing interest in cross border cooperation and exchange of scientific research in the field of cardiovascular diseases. That is also exactly what young researchers Esther Lutgens and Rory Koenen have experienced. Both of them are very aware of what is happening internationally. Because not only do they work for the Dutch research institute CARIM in Maastricht, but also for IMCAR, the Institut für Molekulare Herz-Kreislaufforschung at RWTH Aachen University in Germany.

In May 2009, Rory Koenen (34) was appointed to the position of part-time researcher at CARIM. In addition, he is one of six team leaders at the institute for cardiovascular disease in Aachen. Here, the qualified biochemist studies the roles of chemokines and adhesion molecules in atherosclerosis. This means that he works at the world-renowned institute of professor Christian Weber, trying to understand the interactions between proteins that enable cells of the immune system to bind to blood vessel cells. “Depending on the physiological context, interactions between these cells can either prevent or cause diseases”, Koenen explains while sitting in his Maastricht lab. From here, he coordinates Weber’s work while also sharing the knowledge he obtains in Aachen with his Maastricht colleagues. “The ten people in my research team all work on biochemical projects that specifically focus on these protein interactions.” The German-Dutch cooperation resulted in a paper in Nature Medicine.*

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* Koenen RR, von Hundelshausen P, Nesmelova IV, Zerneck A, Liehn EA, Sarabi A, Kramp BK, Piccinini AM, Pauldan SR, Kowalska MA, Kungl AJ, Hackeng TM, Mayo KH, Weber C –

Disrupting functional interactions between platelet chemokines inhibits atherosclerosis in hyperlipidemic mice.

Nature Medicine 2009; 15: 97-103

TRANSMITTING SIGNALS

Transmitting signals

In recent years, Rory Koenen has done a lot of research on chemokines, small proteins that can be described as signal transmitters to cells in the immune system. "There are a lot of these chemokines, about fifty in total", Koenen explains. "This fact alone raises the question among scientists why so many are needed."

They're asking the wrong question, according to Koenen, who suspects that the question is the result of typical laboratory science methodology. "Researchers have treated all kinds of immune cells with these chemokines in test tubes and have consequently noticed that many cells react to chemokines. But of course it's a different story within the body", Koenen says. "Most of these cells won't encounter any chemokines. Therefore, I regard them much more as a system with an infinite number of combinations. Different chemokines in different combinations will transmit different 'commands'. My greatest achievement so far has been describing the pairing of these chemokines. When different chemokines pair up, they are also able to transmit specific signals to immune cells. In my work, I've been describing the role these paired chemokines possibly play in atherosclerosis in mice and I'm adding a new dimension to the language of chemokines."

The Deutsche Gesellschaft für Kardiologie agreed that this was a remarkable discovery. Therefore, the organisation awarded Koenen during its annual conference in Mannheim with the Oskar Lapp-Preis, which has a value of 12,000 Euros.

Inevitable wear and tear

The young Limburg scientist Esther Lutgens (34) has been working for years on finding the key to inhibiting atherosclerosis. Like Koenen, she not only works in the research lab at CARIM, but also at professor Weber's IMCAR institute in Aachen. Even though many regard atherosclerosis to be an

SOFJA KOVALEVSKAJA GRANT

inevitable process of wear and tear on the arteries, there is, according to Lutgens definitely a solution that will help prevent the severe effects of the disease. "My research is all about the formation of plaque in the arteries", she explains. "When such a plaque bursts, it causes an acute blockage of the blood vessel." Her PhD research, which she conducted a few years ago, already showed that when you inhibit molecule CD40, the plaques remain smaller and more stable. "However, this discovery also had a downside", Lutgens says. "Because, when you inhibit the entire molecule, this will over time have a negative impact on our immune system. We now know how to block the route of the molecule within the cell without affecting the way the immune system functions."

Sofja Kovalevskaja grant

In 2009, Lutgens received the Sofja Kovalevskaja grant for her work. This grant from the German Alexander von Humboldt Foundation has a value of 1.65 million euros. Esther Lutgens was the third Dutch scientist to receive the grant. Due to the grant, she has been leading a research team since the beginning of 2009, consisting of five people who are entirely focused on inhibiting atherosclerosis. "The grant has made it possible to double the size of the research team that I was already leading in Maastricht at CARIM", she says. "As a result, a growing number of people are working together in this field and their cooperation is no longer restricted by national borders. With ten of us, we'll be able to get results much more quickly, which hopefully means that my research will also move along more quickly." In 2009, Lutgens also received an Established Investigatorship from the Netherlands Heart Foundation. "This was again a significant amount of money: half a million euros. It enables me to continue with my research in Maastricht and in Aachen for another five years."

▶▶



Rory Koenen

TWO SPARRING PARTNERS

More money available

The fact that Rory Koenen and Esther Lutgens have ties to a Dutch as well as a German university, greatly increases their chances to obtain subsidies and research grants. Koenen: "Our position enables us to apply for subsidies in either country. It's easier in Germany than in The Netherlands where research grants are limited. In Germany, there is more money available, there are more foundations to approach and the selection criteria are less strict, which increases the chance to succeed."

Two sparring partners

Although there are a lot differences in the way the research institutes work, cooperation between the two is definitely very valuable, according to the scientists. Esther Lutgens: "We exchange a lot of knowledge and research techniques. The institutes benefit from each other's strengths. That's great. In my experience, both CARIM and IMCAR approach their field of research in their own particular way. For example, IMCAR strongly focuses on the specific characteristics of individual cells, while at CARIM we take the total picture of atherosclerosis into perspective, while also focusing on the entire immune system. Having those differences are definitely beneficial. It means that you have two sparring partners to discuss your findings and interpretations with."

EuCAR-project and M-CAR

Another example of cooperation between Germany and The Netherlands is the EuCAR-initiative. The initiative is partly financed by the Deutsche Forschungsgemeinschaft in Germany and partly by the NWO in The Netherlands and comprises an international bilateral cardiovascular graduate school. PhD students receive guidance from two professors at once: one professor from the university in Aachen, the other one from Maastricht University. Koenen: "Because of

CULTURAL DIFFERENCES

EuCAR, the students' research projects can be regarded as projects of international cooperation between the professors involved.

The staff members working for these professors are responsible for providing personal guidance to the PhD students." Within EuCAR, Koenen and Lutgens are also in charge of coordinating research projects and supporting students who are working in Aachen as well as Maastricht. "PhD students can earn both a Dutch and a German PhD title."

A second initiative aimed at strengthening the link between CARIM and IMCAR, is the establishment of M-CAR, the 'Maastricht Center for Atherosclerosis Research' within CARIM in 2010. The research team of Esther Lutgens and Menno de Winther will be one of the teams that are part of this centre, which will be lead by Prof. Christian Weber, who received an NWO VICI grant in the beginning of 2010. M-CAR will function as a 'centre of excellence' with an emphasis on de basic research questions regarding the blood vessel wall.

Cultural differences

In the years they've worked in The Netherlands and Germany, Koenen and Lutgens have noticed some very obvious cultural differences between the two countries. Koenen: "It's interesting to see how different the cultures are, even though the institutes are only about 30 kilometres apart." Most noticeable is the difference in hierarchy. "When I look at the structure and organisation of both research teams, I can only say that there is much more of a hierarchy in Germany. The boss is in charge and the employees do as they are told." That's unheard of in Maastricht, Lutgens adds. "Here, people tend to speak up, let you know when you're wrong or if they don't agree with you. This is also the case for the technical lab employees. In The Netherlands they are much more part of the group, clearly contributing to it. This is definitely different from Aachen."

■

PASSPORTS



Name:

Esther Lutgens

Age:

34

Esther Lutgens is a senior lecturer and works in the Pathology department. In 2009, she received an Established Investigatorship from the Netherlands Heart Foundation, while also winning the German Sofja Kovalevskaja Award (1.6 million euros). Her research focuses on atherosclerosis: the formation of plaques in arteries. Esther Lutgens works both at CARIM and at the IMCAR-institute of Prof. Christian Weber in Aachen.



Name:

Rory Koenen

Age:

34

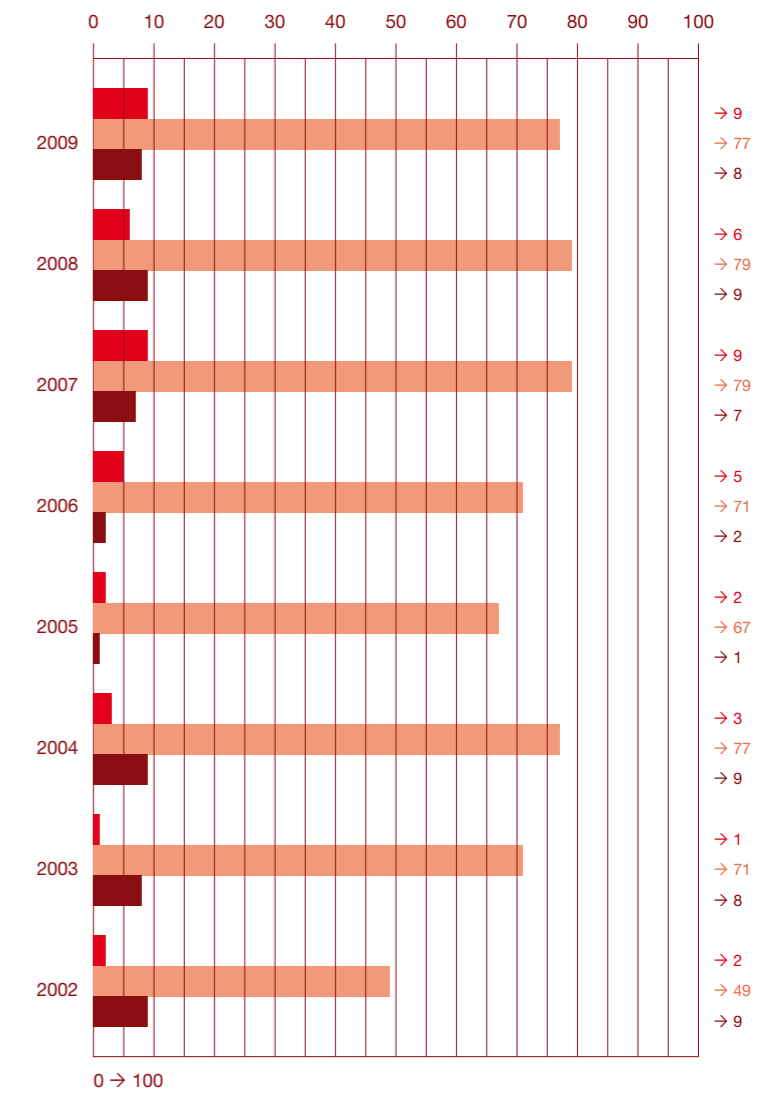
Rory Koenen studied biochemistry at Radboud University Nijmegen and joined CARIM in 1999, conducting his PhD research within the Biochemistry department. In 2003, he exchanged CARIM for the RWTH Aachen, taking the opportunity to work with Prof. Weber on his postdoctoral studies. After having earned his PhD, he was appointed to the position of team leader in Aachen. Since May 2009, he works part-time for CARIM studying the roles of chemokines en adhesion molecules in atherosclerosis.

03_ SUMMARY SCIENTIFIC OUTPUT

MAIN THEME I THROMBOSIS AND HAEMOSTASIS

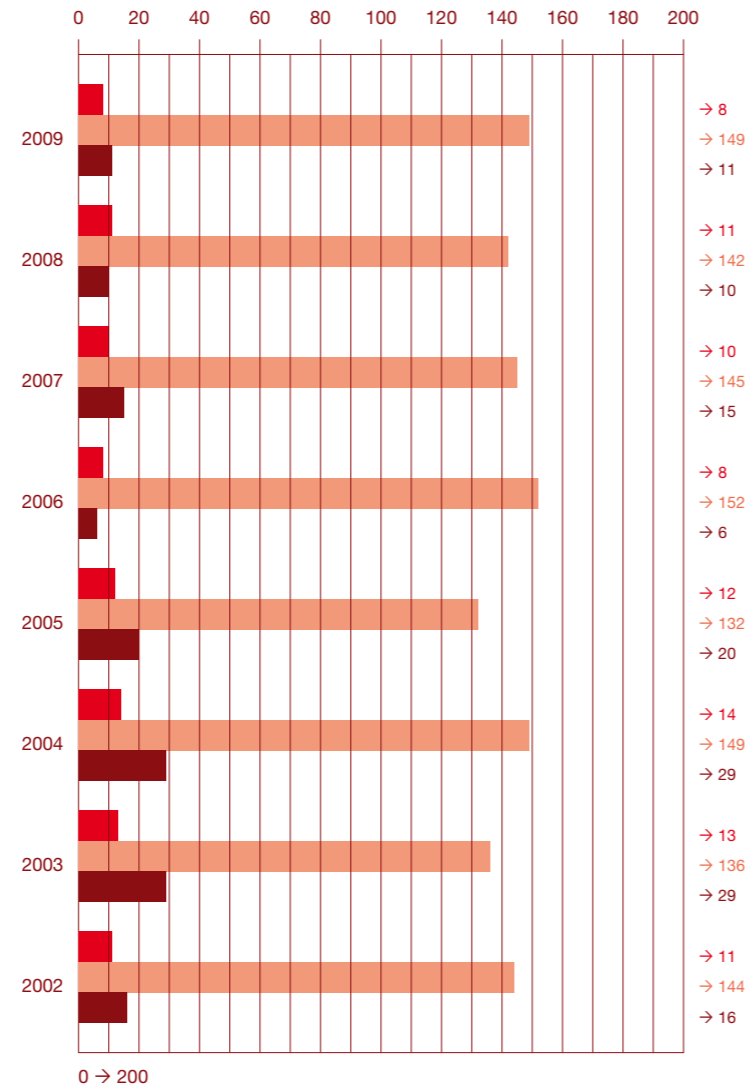
■ PhD theses
■ Scientific publications (Wi-1, Wi-2 and Letters to the Editor)
■ Other publications (Wn, Wb/conference papers, Vp)

Wi-1 = scientific publication in refereed SCI-SSCI indexed journals
 Wi-2 = scientific publication in refereed non SCI-SSCI indexed journals
 Wn = scientific publication in national journal
 Wb = book, or contribution to book, conference papers/proceedings
 Vp = professional publication in national or international periodical



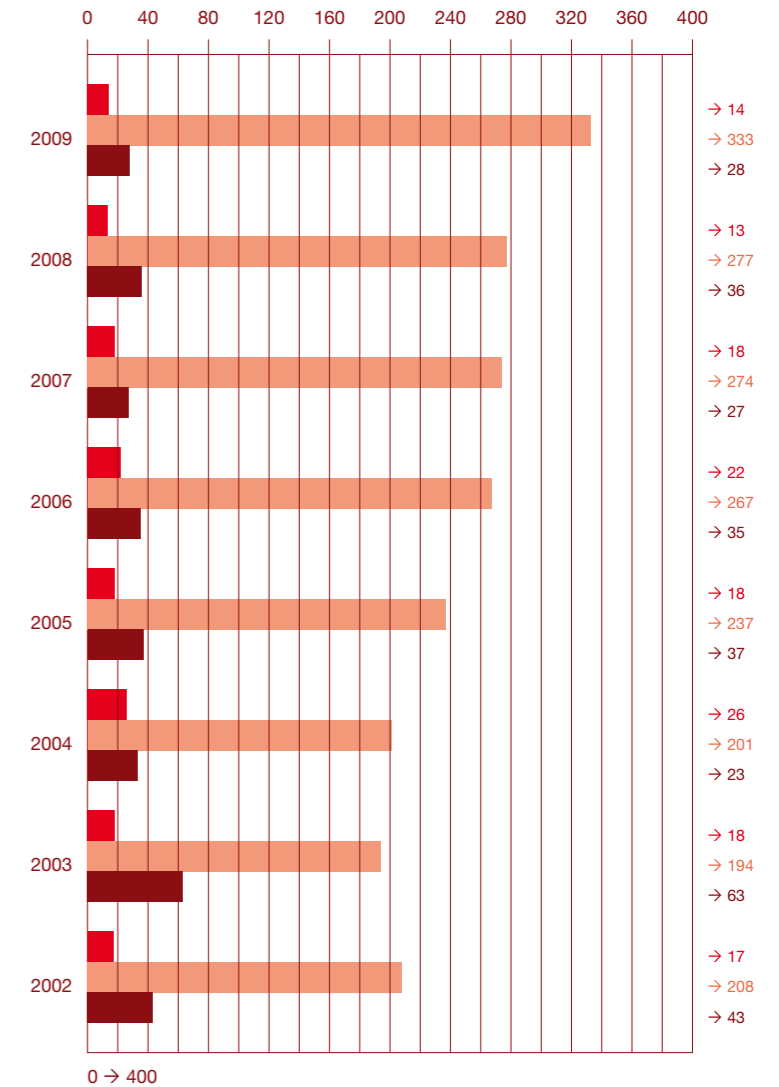
MAIN THEME II CARDIAC FUNCTION AND FAILURE

- **PhD theses**
 - **Scientific publications** (Wi-1, Wi-2 and Letters to the Editor)
 - **Other publications** (Wn, Wb/conference papers, Vp)
- Wi-1 = scientific publication in refereed SCI-SSCI indexed journals
 Wi-2 = scientific publication in refereed non SCI-SSCI indexed journals
 Wn = scientific publication in national journal
 Wb = book, or contribution to book, conference papers/proceedings
 Vp = professional publication in national or international periodical



MAIN THEME III VASCULAR BIOLOGY

- **PhD theses**
 - **Scientific publications** (Wi-1, Wi-2 and Letters to the Editor)
 - **Other publications** (Wn, Wb/conference papers, Vp)
- Wi-1 = scientific publication in refereed SCI-SSCI indexed journals
 Wi-2 = scientific publication in refereed non SCI-SSCI indexed journals
 Wn = scientific publication in national journal
 Wb = book, or contribution to book, conference papers/proceedings
 Vp = professional publication in national or international periodical



04_

EVENTS AND

HIGHLIGHTS

2009

SCIENTIFIC HIGHLIGHTS 2009

In 2009 the researchers of CARIM have been very productive, resulting in **509 scientific publications** in peer refereed journals (Wi1 publications, excluding abstracts), **29 PhD theses, 7 patents**, 1.98 million Euros funding received in competition from national and international science foundations and 24.4 million Euros funding from third parties, charities, EU-framework programs, industry, etc. Compared with 2008 the quantity of our scientific output in 2009 went up; however there has been a further rise in quality too. The overall average Impact Factor increased from 4.9 in 2008 to 5.8 in 2009. Bibliometric analyses (1997-2008) illustrate that publications from CARIM have been cited 1.61 times more often than the world mean for the cardiovascular field.

TOP PUBLICATIONS

Top publications with the highest Impact Factor in 2009*

* with CARIM researcher as first and/or last author

Koenen RR, von Hundelshausen P, Nesmelova IV, Zerneck A, Liehn EA, Sarabi A, Kramp BK, Piccinini AM, Paludan SR, Kowalska MA, Kungl AJ, Hackeng TM, Mayo KH, Weber C –

Disrupting functional interactions between platelet chemokines inhibits atherosclerosis in hyperlipidemic mice.

Nature Medicine 2009; 15: 97-103 IF 27.553

Schellings MW, Vanhoutte D, Swinnen M, Cleutjens JP, Debets J, van Leeuwen RE, d'Hooge J, Van de Werf F, Carmeliet P, Pinto YM, Sage EH, Heymans S –

Absence of SPARC results in increased cardiac rupture and dysfunction after acute myocardial infarction.

J Exp Med 2009; 206: 113-123 IF 15.219

Kwee RM, Schreuder FHB, Mess WH, van Oostenbrugge R, Triebels VHJM, van den Akker L, Heeneman S, Hofman PAM, van Engelshoven J, Wildberger J, Kooi ME –

Carotid intraplaque hemorrhage: a possible cause of stroke.

Circulation 2009; 120: 1637-1639 IF 14.595

Tchaikovski V, Olieslagers SJF, Böhmer FD, Waltenberger J –

Diabetes mellitus activates signal transduction pathways resulting in VEGF resistance of human monocytes.

Circulation 2009; 120: 150-159 IF 14.595

▶▶

TOP PUBLICATIONS

Swinnen M, Vanhoutte D, Van Almen GC, Hamdani N, Schellings MW, D'Hooge J, Van der Velden J, Weaver MS, Sage EH, Bornstein P, Verheyen FK, VandenDriesche T, Chuah MK, Westermann D, Paulus WJ, Van de Werf F, Schroen B, Carmeliet P, Pinto YM, Heymans S – Absence of thrombospondin-2 causes age-related dilated cardiomyopathy.

Circulation 2009; 120: 1585-1597 IF 14.595

Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, van Oostenbrugge R –

Surgical decompression for space-occupying cerebral infarction (the Hemispherectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomized ...

Lancet Neurol 2009; 8: 326-33 IF 14.27

Tikhonoff V, Zhang H, Richart T, Staessen JAH –

Blood pressure as a prognostic factor after acute stroke.

Lancet Neurol 2009; 8: 938-948 IF 14.27

Cohen Tervaert J, van Hoek B, Koek GH –

Antineutrophil Cytoplasmic Antibodies in Small-Duct Primary Sclerosing Cholangitis.

Gastroenterology 2009; 136: 364-368 IF 12.591

Van Kimmenade R, Januzzi JL, Bakker JA, Houben AJHM, Rennenberg RJ, Kroon AA, Crijns HJGM, van Dieijen-Visser M, de Leeuw PW, Pinto, YM –

Renal clearance of B-type natriuretic peptide and amino terminal pro-B-type natriuretic peptide a mechanistic study in hypertensive subjects.

J Am Coll Cardiol 2009; 53: 884-90 IF 11.438

Sluimer JC, Kolodgie FD, Bijmens AP, Maxfield K, Pacheco E, Kutys B, Duimel H, Frederik PM, van Hinsbergh V, Virmani R, Daemen MJAP –

Thin-walled microvessels in human coronary atherosclerotic plaques show incomplete endothelial junctions relevance of compromised structural integrity for intraplaque microvascular leakage.

J Am Coll Cardiol 2009; 53(17): 1517-27 IF 11.438

Nieuwlaat R, Eurlings LW, Cleland JG, Cobbe SM, Vardas PE, Capucci A, López-Sendón J, Meeder JG, Pinto YM, Crijns HJGM –

Atrial fibrillation and heart failure in cardiology practice: reciprocal impact and combined management from the perspective of atrial fibrillation: results of the Euro Heart Survey on atrial fibrillation.

J Am Coll Cardiol 2009; 53(18): 1690-8 IF 11.438

Top publications with the highest Impact Factor in 2009*

* with CARIM researcher as co-author

RE-COVER study group: Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Hamulyák K, Vrooman PS jr –

Dabigatran versus warfarin in the treatment of acute venous thromboembolism.

New Engl J Med 2009; 361(24): 2342-52 IF 50.017

Hohnloser SH, Crijns HJGM, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ –

Effect of dronedarone on cardiovascular events in atrial fibrillation.

New Engl J Med 2009; 360(7): 668-78 IF 50.017

PLATO Investigators: Wallentin L, Becker Budaj A, Cannon Emanuelsson H, Horrow J, Husted Katus H, Mahaffey Scirica BM, Skene Steg PG, Storey Harrington RA, Waltenberger J, Freij A, Thorsén M –

Ticagrelor versus clopidogrel in patients with acute coronary syndromes.

New Engl J Med 2009; 361: 1045-57 IF 50.017

Drazen JM, van der Weyden, Sahni P, Rosenberg J, Marusic A, Laine C, Kotzin S, Horton R, Hébert PC, Haug C, Godlee F, Frizelle FA, de Leeuw PW, DeAngelis CD –

Uniform format for disclosure of competing interests in ICMJE journals.

New Engl J Med 2009; 361(19): 1896-7 IF 50.017

Emerging Risk Factors Collaboration: Tipping RW, Ford CE, Stehouwer CD, Erqou S, Kaptoge –

Lipoprotein(a) concentration and the risk of coronary heart disease stroke and nonvascular mortality.

JAMA-J Am Med 2009; 320: 412-23 IF 31.718

PATENTS

Vermeer C –

Anti-thrombotic effects of vitamin K.

International publication date: September 17, 2009

Weber C, Koenen RR –

Gag-antagonism MCP-1 mutants.

Patent application WO 2009/015884.A1

International publication date: February 5, 2009

Weber C –

mIR-126 and tissue repair

Patent application WO 2009/073921

International publication date: June 18, 2009

Moens AL –

Protective effect of high dose folate on myocardial ischemia.

Patent application WO2009/098279.A1

Patent transfer from University of Antwerp to CARIM

International publication date: August 13, 2009

Nicolaes GAF, Rosing J, ten Cate H, Dahlbäck B –

A method for the treatment of ischemia reperfusion injury.

Patent application WO 2009/11548 A2

International publication date: September 24, 2009

Blankesteyn WM –

Antagonistic peptides for frizzled-1 and frizzled-2.

Patent application 09154475.9-2107

Application date: March 5, 2009

Ramaekers FCS, Broers JLV, Houben F, van Oostveldt PMV, de Vos WH –

Method for the prediction of the severity of nuclear envelope related diseases.

Patent application EP09163326

Application date: June 19, 2009

SCIENTIFIC GRANTS, AWARDS AND HONORS

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

The Netherlands Organization for Scientific Research (NWO) granted **VIDI fellowships** to **An Moens** and **Paul Volders** (both dept. of Cardiology) and one VICI to **Christian Weber** (dept. of Pathology). An Moens also received an Aspasia grant together with her VIDI fellowship. In October 1999 the Ministry of Education, Culture and Science, the Association of Universities in the Netherlands and NWO launched Aspasia as a scheme to increase the number of women senior lecturers at Dutch universities. As from 2005 Aspasia new-style has been linked to the Innovational Research Incentives Scheme (Vernieuwingsimpuls). Premiums will be made available for those university Boards that ensure that women VIDI and VICI laureates (round 2005 and following) are promoted to senior lecturers or professors within a year after the subsidy is awarded. In the interview on page 47, both Dr Moens and Dr Volders will tell about their research ambitions related to their VIDI-grants.

Christian Weber's 1.25 million Euros VICI grant was awarded on his project "Putting a brake on atherosclerosis". Atherosclerosis is caused by an inflammatory reaction in coronary arteries which gives rise to ulcerous patches in the vessel wall. The advance of this inflammatory reaction is mediated by specific signaling proteins that originate from the platelets. In his research he will study how these signaling proteins function, and how they can be stopped without the occurrence of harmful side effects. A NWO-VICI is one of the largest individual grants in the Netherlands, and is meant for researchers to build up their own research group over a period of five years.

In December **Christian Weber** also received an Advanced Investigator Grant of the European Research Council of 2.5 million Euros.

Esther Lutgens, Associate Professor of Pathology, has been appointed Established Investigator by the Netherlands Heart Foundation (NHS). Every two years the NHS awards a five-year stipendium to stimulate developing the research groups of established researchers. In this way the Established Investigator will be able to further strengthen his/her research. Esther works both at CARIM (Theme III, program Markers and Makers) and the Institute for Molecular Cardiovascular Research (IMCAR) in Aachen, Germany. She studies the role of co-stimulatory and co-inhibitory factors in atherosclerosis and focuses on the cell-type specific actions and signal transduction cascades that are involved in the different stages of its pathogenesis. For more details about Dr Lutgens' research work and the cooperation with IMCAR read the duo interview with Dr Koenen (page 27).

Another five project proposals were funded with large project grants. The NHS granted two projects with each 250 K€; a project of **An Moens** (Prevention of doxorubicin-induced acute cardiotoxicity and chronic ventricular dysfunction by modulating eNOS-uncoupling) and a project of **Stephane Heymans** (Implication of miRNAs in ischemic heart disease). Heymans also received a 230 K€ FWO grant from the Research Foundation Flanders for his project Role of miRNAs in cardiac transplantation. **Christian Weber** was given a 700 K€ grant by the DFG (Deutsche Forschungsgemeinschaft) on his project House Cell Adhesion at Vascular Interfaces (MTBo07). **Coen Stehouwer** and **Miranda Schram**, managed to receive funding for the Maastricht Study; total amount 11 mln Euros. For more information about the **Maastricht Study**, read the interview with Professor Stehouwer and Dr Schram (page 67).

On July 13th **Gerry Nicoales** (dept. of Biochemistry, CARIM research program Humoral aspects of Thrombosis and Haemostasis) was honored with a Special Project Award of the Bayer Hemophilia Awards Program at the XXII Congress of the International Society on Thrombosis and Haemostasis (ISTH) in Boston, Massachusetts. This unrestricted grant, amounting US\$ 200.000, was awarded for a two year period to support the project titled Application of a generic platform for the discovery and optimization of biologically active molecules that inhibit the functions of activated protein C.

Gerry Nicolaes wins Special Project Award of the Bayer Hemophilia Awards Program

(from left to right) David Lillicrap MD (Chairman Grants Review and Awards Committee), Hans Bishop (President Bayer HealthCare), Gerry Nicolaes, Mike Mathews (Vice President Global Strategic Marketing & General Manager of Hemophilia)



In October our young talented PhD student **Tom Seijkens** (dept. of Pathology) received a Kootstra Talent Fellowship of the Board of Maastricht University Medical Center+. This grant is given to young scientific talents to develop their scientific careers. Besides his PhD-position within CARIM, Tom follows both a Research Master in Medicine and a Research Master in Cardiovascular Biology and Medicine at Maastricht University. For an interview with Tom Seijkens and his colleague PhD student Laura Steinbusch go to page 17.

In 2009 many CARIM researchers were awarded with prizes and travel grants. An overview of these laureates in alphabetical order is given in the figure on page 42.

BioMedical Materials (BMM)

The BioMedical Materials program (BMM), a public private partnership, is dedicated to the development of novel BioMedical Materials and their applications. In 2009 BMM granted three project proposals in which CARIM researchers are involved. **Mark Post** is project leader of the **iVALVE** project (Instructive scaffolds for in situ tissue engineering of heart valves and arteries); project grant 639 K€. Furthermore Mark Post participates in the **PENT** project (Polymer Enabled Neovascularization Therapies, project leader Professor P. Quax, Leiden University Medical Center); project grant 531 k€. In the musculoskeletal BMM research line, CARIM PI **Leo Koole** participates in the **IdIDAS** project (New Early Therapies for Intervertebral Disc Diseases, Drug Delivery and Augmentation through Smart Polymeric Biomaterials, project leader Professor W. Dhert, University Medical Center Utrecht); project grant 427 k€.

For more details on the BMM program please visit www.bmm-program.nl

OVERVIEW AWARDS, PRIZES AND PERSONAL GRANTS

AWARDEES	DEPT.	AWARD/PRIZE	INSTITUTION
Hugo ten Cate	Internal Medicine	Runners-up price for the Third Sunstar Foundation World Perio Research Awards	Sunstar Foundation for Oral Health Promotion, Japan
Judith Cosemans	Biochemistry	Young Investigator Award	International Society on Thrombosis and Haemostasis, XXII Congress ISTH, Boston, MA, USA
Ellen Dirkx	Molecular Genetics	Poster Price	Plenary meeting of the Department of Genetics and Cell biology
Connie Duckers	Biochemistry	Young Investigator Award for the abstract: Duckers C, Simioni P, Radu C, Spiezia L, Gavasso S, Rosing J, Castoldi E. Thrombin generation in patients with severe factor V	International Society on Thrombosis and Haemostasis, XXII Congress ISTH, Boston, MA USA
Iris Knottnerus	Neurology	Young Investigator Award for the best oral presentation: "Markers of Endothelial Function in Lacunar Stroke".	International Society on Thrombosis and Haemostasis, XXII Congress ISTH, Boston, MA USA
Rory Koenen	Biochemistry	Oskar-Lapp-Preis 2009 Award: 12K€	Oskar-Lapp-Stiftung, Stuttgart, Germany. 75. Jahrestagung der Deutschen Gesellschaft für Kardiologie in Mannheim (Germany)
Esther Lutgens	Pathology	Established Investigator Grant: 500K€	NHS
An Moens	Cardiology	VIDI fellowship Grant: 800K€, including Aspasia grant: 100k€	NWO
Reyhan Nergiz-Unal	Biochemistry	Young Investigator Award	International Society on Thrombosis and Haemostasis, XXII Congress ISTH, Boston, MA USA

AWARDEES	DEPT.	AWARD/PRIZE	INSTITUTION
Gerry Nicolaes	Biochemistry	Special Project Award Award: 200.000 US\$	Bayer Hemophilia Awards Program
Koen Reesink	Biomedical Engineering	Second prize best young investigator presentation: Reesink K, Hermeling E, Vermeersch S, Rietzschel E, De Buyzere M, Reneman R, Hoeks, A, Segers P. Quantification of both systolic and diastolic local arterial stiffness improves identification of arterial stiffening with normal aging.	Artery 9, Cambridge, USA
Olivier Segers	Biochemistry	Young Investigator Award for the abstract: Segers O, van Oerle R, ten Cate H, Rosing J, Castoldi E. Functional analysis of common haemostatic gene polymorphisms using Calibrated Automated Thrombography	International Society on Thrombosis and Haemostasis, XXII Congress ISTH, Boston, MA USA
Tom Seijkens	Pathology	Kootstra Talent Fellowship	Maastricht UMC+
Laura Steinbusch	Molecular Genetics	Two conference grants	Nederlandse Vereniging voor Diabetes Onderzoek
Laura Steinbusch	Molecular Genetics	Albert Renold Travel Fellowship for Young Scientists	European Federation for the Study of Diabetes
Paul Volders	Cardiology	VIDI fellowship Grant: 720 K€	NWO
Christian Weber	Pathology/IMCAR	Galenus-von-Pergamon-Preis 2009	Internationaler Stifterverband Prix Galen, Berlin, Germany
Christian Weber	Pathology/IMCAR	VICI fellowship Grant: 1.25 M€	NWO
Christian Weber	Pathology/IMCAR	Advanced Investigator Grant Grant: 2.5 M€	European Research Council

Center for Molecular Medicine (CTMM)

Three CARIM project proposals were successful in the second call for CTMM proposals, and were rewarded with together 35 million Euros and a position as project leader (including the contribution of the Dutch Heart Foundation). All Dutch university medical centers, several universities, a broad spectrum of small and medium-sized enterprises, major industry leaders including Philips and Schering and Plough, and the Dutch Government are involved. **Hugo ten Cate** became principal investigator of the **INCOAG project (Innovative Coagulation Diagnostics)**; project grant 1,952 k€. The INCOAG project aims to develop a set of state-of-the-art diagnostic tests that can be used in near-patient settings to estimate, more easily and more sensitively than is currently possible, the risk of venous or arterial thrombosis. These same tests will also be targeted at assessment of the efficacy of preventive and curative antithrombotic medications. As a parallel exercise, the INCOAG project also aims to discover new types of thrombotic risk marker, possibly in the form of microRNA molecules. **Mat Daemen** is principal investigator of the **ParisK project (Assessment of Plaque at Risk by Non-invasive (Molecular) Imaging and Modeling)**; project grant 2,223 k€. Focusing on the carotid artery, the ParisK consortium will construct technological and translational platforms in which several novel imaging modalities will be advanced, validated and added to existing non-invasive imaging modalities to measure one or more parameters of plaque at risk. The data will be integrated to develop a novel heuristic algorithm that gives the predicted risk of rupture of an individual plaque, which will be validated in subsequent clinical studies.

The **EMINENCE project** (contract not yet concluded), of which **Mark Post** is principal investigator, aims to develop multiple diagnostic technologies to enable the early and

sensitive detection of neovascularization, and novel tools to stratify an individual patient's risk of cardiovascular disease.

For more details on the CTMM projects please visit www.ctmm.nl.

Top Institute Pharma

In October 2009 TI Pharma formed a consortium with Actelion Pharmaceuticals Ltd, Erasmus Medical Centre and Maastricht University to define new modalities for the treatment of hypertension (high blood pressure) and associated vascular complications such as heart and kidney failure, myocardial infarction and stroke. **Jo De Mey** (dept. of Pharmacology) participates in one of the cardiovascular TI Pharma projects; **Renin-angiotensin system blockade beyond angiotensin II** (contract value 917 K€). Based on novel action mechanisms, new drugs may be discovered with the potential to prevent vascular complications in patients with hypertension: an opportunity to improve the quality of life for over a billion people worldwide.

SenterNovem

For the development of a European Cardiovascular Campus (project leaders **Prof Mat Daemen** in cooperation with **Prof Michael Jacobs, director of the Cardiovascular Center**) we were granted 623 k€ by SenterNovem. The project is conducted by Maastricht UMC+ in cooperation with several strategic partners, e.g. University Hospital Aachen, Germany, Biomed Booster, Clinical Trial Center Maastricht, BioPartner Center Maastricht.

Scientific Symposium 2009

Our annual scientific symposium was held on November 25 in Maastricht. The Robert Reneman Lecture 2009, a lecture in honor of the institute's founding director, was given by Professor Kenneth Walsh, Director of the Whitaker Cardio-

vascular Institute of the Boston University School of Medicine. Professor Walsh is renowned for his studies on the signaling- and transcriptional-regulatory mechanisms that control tissue growth in the cardiovascular system.

CARIM Scientific Symposium 2009 → p. 65

People and Acknowledgements

In an extensive institute which CARIM is, people will always come and go or make a step forward in their scientific career. In 2009 we welcomed several new colleagues.

In September we welcomed VIDI and LeDucq laureate **Dr Leon de Windt** (dept. of Cardiology). Together with his researchers, De Windt is interested in gene regulation in heart failure. Their research is focused on elucidating the precise role of NFAT in the reprogramming of cardiac gene expression, and the discovery of novel partners of this transcription factor family. More recently, the researchers have gained interest in microRNAs (miRNAs), a class of endogenous, small, noncoding RNAs, which suppress protein expression by either messenger RNA degradation or translational inhibition. Each miRNA potentially targets multiple transcripts, suggesting that miRNAs, not unlike transcription factors, have a fundamental role in regulating gene expression. Overall, the laboratory integrates the use of routine molecular and cell biological approaches, transgenesis/gene knock-out technology, physiological cardiac phenotyping and non-invasive imaging techniques. In november **Dr An Moens** was appointed at the department of Cardiology.

In February **Dr Jack Cleutjens** was reappointed as Associate Professor at his department (Pathology). In April 2009 **Dr Chris Reutelingsperger** was appointed as Extraordinary

Professor Biochemistry of Apoptosis in the Faculty of Health Medicine and Life Sciences. In May 2009 **Dr Erik Biessen** was appointed as Extraordinary Professor of Experimental Vascular Pathology on behalf of Stichting Sint Annadal, as well as **Dr Frits Prinzen**, who was appointed as Extraordinary Professor of Electro Mechanics of the Heart in the Faculty of Health Medicine and Life Sciences.

In July **Dr Elisabetta Castoldi** was reappointed as Associate Professor in the department of Biochemistry. **Dr Marc van Zandvoort** was appointed as Universitätsprofessor Biophysik der Mikroskopie at the Institute of Molecular Cardiovascular Research in Aachen, Germany. In October **Dr Uli Schotten** (dept of Physiology) and in November **Dr Sylvia Heeneman** (department of Pathology) were both reappointed as Associate Professor. At the end of 2009, **Prof Coen Stehouwer** was given a Ruitinga Van Swieten visiting professorship of the Amsterdam Medical Centre-University of Amsterdam. In the context of the Spotlight European Perspective series of Circulation (Circulation 119: f37-40, 2009) **Prof Mat Daemen** was interviewed on the CARIM culture and future developments in the institute. **Dr Marc van Bilsen** was interviewed and asked to present his views on recent developments in the pre-clinical research on heart failure (Circulation 119: f64-f67, 2009). In the context of the multicentre trial ENGAGE-TIMI AF 48 (**An Moens**), CARIM was named top recruiting centre of this multicentre trial. **Prof Mat Daemen** became vice president of the NHS committee WAC2 and chairman of the Dutch Association for Pathology (NVVP).

In 2009 the following members in our research staff left our institute: **Dr Torik Ayoubi** (dept. of Genetics and Molecular Cell Biology), **Dr Peter Frederiks** (Genomics Center) retired, and **Professor Arjan Griffioen** (dept. of Pathology), accepted a position at the Department of Medical Oncology at the Free University of Amsterdam. ■



Paul Volders

INTERVIEW

VIDI SUBSIDIES FOR TWO MAASTRICHT UMC+ CARDIOLOGISTS

‘Now it’s a matter of being able to maintain our standard of excellence’

It’s like passing your driving test at the first attempt. That’s how cardiologist Paul Volders (42) describes the feeling he had when he received an e-mail on the 19th of November 2009 stating he’d won the prestigious VIDI grant for innovative research from the Netherlands Organisation for Scientific Research (NWO). At that particular moment, he was not the only researcher at CARIM who had won an award. His colleague and cardiologist An Moens (36) also had the honour of receiving a VIDI grant with a value of 800 thousand euros.

It’s not a given for young researchers – however excellent they may be in their fields – to be awarded a VIDI grant the first time they apply for one, the two UM laureates emphasize. “Therefore, the fact that two relatively young researchers from the same institute and the same department receive a VIDI in the same year, is very special - to say the least”, says Paul Volders.

Tough selection criteria

An Moens hadn’t really counted on receiving the grant so soon after transferring to a Dutch institute either. “Of course, I took the preparation of my research proposal very serious. However, at the same time I was fully aware how tough the selection criteria are and how small the theoretical chance of winning. Moreover, I am young, blond and Flemish, she says with a smile. “I believed these factors would work

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SMART ANTIOXIDANTS

against me in the world of science, which is still conservative and male dominated. I didn't have any doubts about my proposal, of course. Because I was busy with my regular clinical work during the day, I spent every night and every weekend working on the grant application. For months on end. It made the success of receiving this VIDI grant, even sweeter."

Surprise

Paul Volders agrees: "It was definitely a big surprise for both of us. However, to me it proves that the NWO has purely looked at the content of our proposals and that it chose to ignore the fact that both of us work for the same institute. We both received the support we needed from CARIM to write and defend our research proposals. For example, CARIM organised a mock interview with a committee, after we heard last summer that we had made it to the final selection round."

Smart antioxidants

In addition to the 'regular' VIDI, An Moens received an extra bonus from NWO's Aspasia programme. This premium of 300 thousand euros is awarded to female laureates who have the potential to reach the position of associate professor or professor in the not too distant future.

With these research grants – more than one million euros in total - An Moens will expand her research team and she will conduct further studies to find out which 'smart' antioxidants are powerful enough to prevent or cure heart failure. "So far, we know that administering high doses of certain specific antioxidants clearly has a number of positive effects on an ill heart. Especially those antioxidants belonging to the group of so-called eNOS modulators are expected to be very successful", Moens continues. "Folic acid is one example of an antioxidant that belongs to this group. We also expect the chemical substance BH4 – a substance which until now

INEXPENSIVE AND SAFE

has been primarily used to treat the hereditary and congenital metabolic disease phenylketonuria – to have a positive effects on the heart muscle."

Inexpensive and safe

Folic acid is an inexpensive and totally safe substance that is well known, mainly because women who want to get pregnant are advised to take folic acid supplements. "Folic acid reduces the risk of the birth defect spina bifida", Moens explains. "Within the field of cardiology the positive effects of folic acid have also been known for a while", she says. "However, its ability to limit damage caused by a heart attack had not yet been determined. Our research team has now provided evidence that treating patients who suffer from heart failure, with very specific antioxidants, can prevent the disease, stabilise it, or in some cases even stop it altogether. This is a very interesting finding for those patients who have suffered a heart attack and for people who have an enlarged heart due to high blood pressure."

Future therapies

And there is a third group of patients who could possibly benefit: these are patients whose heart muscles have weakened as a result of certain types of chemotherapy. Treatment with these smart antioxidants could contribute to improvement and recovery in these cases. Moens: "We hope that this discovery enables us to lay the foundation for future therapies that will prevent the life threatening consequences of heart failure."

The next step in An Moens' research will be to actually use this treatment on patients. "Patients are already being treated with these substances, now we will also use them for cardiovascular purposes."

Complex subject matter

Cardiologist Paul Volders will invest his grant of 800 thousand

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LIFE THREATENING ARRHYTHMIA

euro into continuing his research on sudden cardiac death (also known as cardiac arrest) after excitement or emotions. Together with the ten members of his research team, he will study the relationship between the autonomic nervous system and cardiac arrhythmia at various levels. "This field of research is positioned between those of cardiology and the autonomic nervous system, which has undergone relatively little exploration", he says. "Even though this is very complex and relatively unknown subject matter, it has been known since the 1950s that the autonomic nervous system has a determining influence on heart performance."

Life threatening arrhythmia

Volders: "In most cases sudden cardiac death is caused by coronary arteries disease: narrowing of these arteries can cause a heart attack or arrhythmia."

However, a small number of patients suffer from a totally different kind of heart problem, Volders explains. "In their case, the heart responds abnormally to tension, excitement or emotion, exhibiting life threatening arrhythmias."

Often, these patients are young, seemingly healthy people, and frequently it is discovered in hindsight that hereditary ailments played a role. Volders: "Hypertrophic cardiomyopathy is an example of such an ailment, as is the long QT syndrome, a hereditary cardiac arrhythmia that may suddenly appear. Our research is primarily aimed at seeking answers to the question why some hearts respond normally to exposure to factors such as fright or emotion, and others don't."

Cardio genetics is an area Volders and his research team focus on, also within the clinic. "We are going to use a systems biology approach for studying the influence of the autonomic nervous system on the heart. "In practice, this means that we will examine patients' hearts and autonomic nervous systems on the following five levels: organ, tissue, cellular, molecular and genetic. Thus we are seeking to answer the question what effect tension and emotions have

FINANCIAL SECURITY

on the heart. And why the effect differs from patient to patient. Once we know this, we can make a better risk assessment for our patients who are more sensitive to excitement and emotion and adjust treatment and medication accordingly."

Financial security

Both Volders and Moens find it really important that they now have the financial security to develop the research studies they are passionate about on a purely scientific basis.

Moens: "The VIDJ grants give us greater academic freedom, meaning that we will be able to conduct scientific research without any interference from the pharmaceutical industry for example."

However, winning the VIDJ grant also has a flipside, according to the two researchers. Volders: "People now have extremely high expectations of us. We have shown our excellence to the NWO. Now it's a matter of maintenance. If we succeed, that would be great."

■

PASSPORTS



Name:

Paul Volders

Age:

42

Paul Volders studied Medicine at Maastricht University. In 1993 and 1994 he spent two years conducting research at the University of Oklahoma Health Sciences Center in the United States. He earned his PhD in 1999 at the UM. Next, he combined his specialist training in cardiology with scientific research, partly funded by a NWO VENI subsidy. Volders is a registered cardiologist and his research focuses on the mechanisms of cardiac arrhythmias and sudden cardiac death. Since December 2009, he is a Principal Investigator at CARIM. In 2009 he received a VIDJ award of 800 thousand euros from NWO.



Name:

An Moens

Age:

36

An Moens studied Medicine at the University of Antwerp. After earning her PhD, she spent three years working at Johns Hopkins Medical Institutions in Baltimore, USA. Since December 2009, An Moens is a Principal Investigator at CARIM. As a cardiologist, she leads the MUMC's clinical research team. In 2009 Moens received a VIDJ award of 800 thousand euros for her research on 'smart' antioxidants that are powerful enough to prevent or cure heart failure. In addition to the 'regular' VIDJ, An Moens received an extra bonus from NWO's Aspasia programme. This premium of 300 thousand Euros is awarded to female laureates who have the potential to reach the position of associate professor or professor in the not too distant future.

05_ EDUCATION

TRAINING THE NEXT GENERATION OF SCIENTISTS

CARIM School for Cardiovascular Diseases offers a program to educate and train students in the field of cardiovascular research. The program consists of a Research Master in Cardiovascular Biology and Medicine and a contiguous PhD (doctoral) training course. The educational programs are co-organized with the Institute for Education of Maastricht UMC+/FHML and have fully integrated the concepts of 'problem-based learning' and 'tutorial group sessions', for which the UM has won a high international reputation. For more details on our Educational program please visit www.carimmaastricht.org/index.php/education. ■

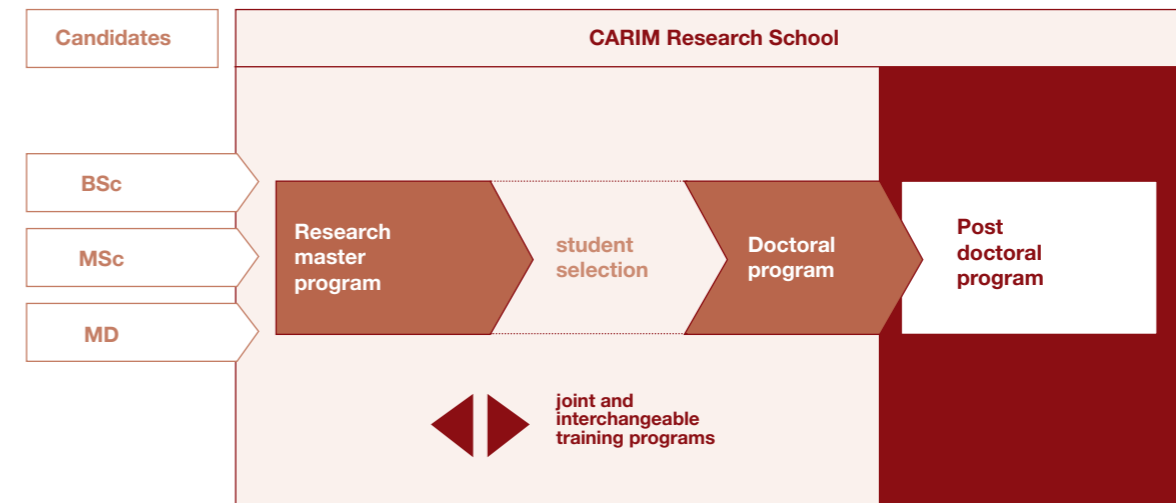
A GRADUATE TRAINING CONTINUUM

Our educational program is conceptualized in such way that there is coherence between the training and education programs for the Master's and PhD phases. Our graduate training continuum:

- deepens student's expertise as they progress from RM to PhD training: the courses in the RM program (e.g. general courses provided by Maastricht University and the FHML, and CARIM Introductory cardiovascular courses) prepare for future skills and topics in the PhD phase.
- broadens student's expertise, as PhD students are invited to acquire theoretical and practical expertise from the RM program (for instance fundamental and clinical content to test innovative methods in the research project).

- allows personalized training in the graduate program by offering RM courses to PhD students and vice versa. (see figure)

Our senior researchers conceptualize and coordinate all courses in the RM and PhD program, which ensures linkage between ongoing cutting-edge research and training activities, and guarantees top training quality from the start till the end of the graduate program. ■





RESEARCH MASTER

The Cardiovascular Biology & Medicine program (CBM) is a two-year full-time research master accredited by the Accreditation Organisation of the Netherlands and Flanders (NVAO), and offers a balanced mix of theoretical and practical courses, allowing students to develop the various competencies to become highly qualified cardiovascular scientists. In July 2009 a review committee visited our CBM Research Master's program. In 2010 the program has been re-accredited for six years by the NVAO. In 2009 11 students received their Research Master's degree in Cardiovascular Biology & Medicine (see photo), and 7 of them continued with a PhD-program at our institute. Eight new students entered the CBM Research Master's program in 2009. ■

Graduates CARIM Research Master's in CBM in 2009

Kelly van Bragt
Matthijs Compeer
Martijn Demmers
Kathinka van Hooren
Dennis Kusters
Ben Paylor
Rick Schreurs
Karin Wildhagen
Mathijs van de Vrie
Suzanne de Witt
Ine Wolfs

Photos page 54

Impression of the graduated students of the CBM Research Master's program

PhD PROGRAM

Our PhD program is accessible for graduated master students from our own Research Master or for excellent students from other national or international biomedical Masters. At the end of 2009, 96 PhD students attended our PhD program.

Besides our regular PhD program, we offer the EuCAR program, which is a joint initiative of CARIM and our German partner institute IMCAR in Aachen. This EuCAR-group involves 12 PhD students who are labeled as EuCAR PhD. Each PhD project is guided by at least one investigator from IMCAR, Aachen en one from CARIM, Maastricht. EuCAR students will obtain a PhD in both Aachen and Maastricht. ■

Number of PhD students at 31.12.2009

Funding source	PhD students 2006	PhD students 2007	PhD students 2008	PhD students 2009
University	19	23	28	28
NWO	12	9	7	6
Non-profit + Industry	49	49	58	62
TOTAL	80	81	93	96

PhD DELIVERABLES

In 2009 27 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 2001-2009, related to the period in which they obtained their degree. The graphics on pages 33-35 present the number of PhD theses on the level of our research themes. ■

Year intake	2001	2002	2003	2004	2005	2006	2007	2008	2009
Cohort volume (annual intake)	27	37	26	24	30	22	29	26	42
Male	12	19	19	13	19	8	17	14	24
Female	15	18	7	11	11	14	12	12	18
PhD from abroad	5	15	8	11	5	6	8	9	19
Thesis completed	17	29	17	9	8	1	0	0	0
Mean duration (in months)	60	61	55	56	50	-	-	-	-
Ongoing	3	5	8	18	18	17	28	24	41
Drop out	7	3	1	2	4	4	1	2	1

CARIM THESES IN 2009

Schans van de V –

Wnt signaling and Cardiac hypertrophy
Promotores: Prof Dr J Smits, Dr M Blankesteyn.
Maastricht University, January 22, 2009

Cosemans J –

Dynamic regulation of thrombus stability
Promotor: Prof Dr J Rosing.
Co-promotor: Prof Dr J Heemskerk.
Maastricht University, January 29, 2009

Maurissen L –

Characterization of anticoagulant functions of protein S
Promotores: Prof Dr J Rosing, Prof Dr T Hackeng.
Maastricht University, February 18, 2009

Joop K –

Endotoxin and microparticles as markers for inflammation and coagulation
Promotor: Prof Dr H ten Cate.
Co-promotor: Leyte AP (OLV Gasthuis, Amsterdam).
Maastricht University, February 27, 2009

Borne van den S –

Myocardial infarct healing: Rupture and remodeling
Promotores: Prof Dr J Smits, Prof Dr M Daemen.
Co-promotor: Dr M Blankesteyn.
Maastricht University, April 17, 2009

Kloppenborg G –

Role of infections on intimal hyperplasia
Promotor: Prof Dr C Bruggeman.
Co-promotor: Dr F Stassen.
Maastricht University, April 24, 2009

Gelsomino S –

New insights in the Surgical Treatment of Chronic ischemic mitral regurgitation
Promotor: Prof Dr J Maessen.
Co-promotores: Dr R Lorusso, Dr F van der Veen.
Maastricht University, April 24, 2009

Kroon JW –

Mechanocontrol of cardiac growth and remodeling
Promotor: Prof Dr T Arts.
Co-promotores: Dr T Delhaas, Dr P Bovendeerd (TU/e, Eindhoven).
Maastricht University, May 14, 2009

Plat A –

Genetics and cardiovascular risk in a primary care population.
Studies from the Hippocrates project
Promotor: Prof Dr P de Leeuw.
Co-promotor: Dr AA Kroon.
Maastricht University, May 29, 2009

Dielis A -

The hypercoagulable state in patients. Determining (hyper) coagulability and the role of thrombin generation
Promotores: Prof Dr P de Leeuw, Prof Dr H ten Cate.
Co-promotores: Dr K Hamulyák, Dr H Spronk.
Maastricht University, June 3, 2009

Hermeling E –

Local pulse wave velocity determination: the arterial distension waveform from foot to crest
Promotores: Prof Dr Hoeks A, Prof Dr RS Reneman.
Co-promotor: Dr K Reesink.
Maastricht University, June 10, 2009

Beuk R –

Experimental ischemia and reperfusion of the small bowel: focus on microvascular events
Promotores: Prof Dr G Tangelder G, Prof Dr E Heineman.
Co-promotor: Dr M Oude Egbrink.
Maastricht University, June 12, 2009

Loubele S –

Inhibition of ischemic organ damage with anti-coagulant agents
Promotor: Prof Dr H ten Cate.
Co-promotor: Dr H Spronk.
Maastricht University, June 18, 2009

Wolfs J –

Generation of procoagulant activity in blood cells
Promotores: Prof Dr J Rosing, Prof Dr R Zwaal.
Co-promotor: Dr E Bevers.
Maastricht University, September 10, 2009

Prinzen L –

Bimodal imaging of molecular targets associated with plaque vulnerability
Promotores: Prof Dr D W Slaaf, Prof Dr M van Zandvoort (RWTH, Aachen), Prof Dr C Reutelingsperger.
Maastricht University, September 17, 2009

Lobbes M –

Non-invasive assessment of cardiovascular disease
Promotores: Prof Dr J van Engelshoven, Prof Dr M Daemen.
Co-promotores: Dr E Kooi, Dr S Heeneman.
Maastricht University, September 23, 2009

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Mastricht van G –

Outcome assessment and economic evaluation of short stay intensive care for coronary artery bypass patients
 Promotores: Prof Dr Maessen J, Prof Dr M Prins, Prof Dr J Severens.
 Maastricht University, September 25, 2009

Rossi A –

Common carotid artery morphology and dynamics estimated with automatic ultrasound segmentation
 Promotor: Prof Dr A Hoeks.
 Co-promotor: Dr P Brands.
 Maastricht University, November 5, 2009

Biggelaar van den F –

New approaches to improve the evaluation of mammograms
 Promotor: Prof Dr J van Engelshoven.
 Co-promotor: Dr K Flobbe.
 Maastricht University, November 6, 2009

Douma K –

Two-photon microscopic imaging of neo-vasculature in atherosclerotic plaques and tumors
 Promotores: Dr D Slaaf, Prof Dr M Post, Prof Dr M van Zandvoort (RWTH, Aachen).
 Maastricht University, November 11, 2009

Marchetti M –

The hypercoagulable state in patients with essential Thrombocythemia and Polycythemia Vera
 Promotor: Prof Dr H ten Cate.
 Co-promotor: Dr A Falanga.
 Maastricht University, November 19, 2009

Staals J –

The role of haptoglobin phenotype and 24-hour blood pressure characteristics in cerebral small vessel disease
 Promotor: Prof Dr J Lodder.
 Co-promotor: Dr RJ van Oostenbrugge.
 Maastricht University, December 4, 2009

Speelman L –

Biomechanical analysis for abdominal aortic aneurysm risk stratification
 Promotores: Prof Dr M Jacobs, Prof Dr FN van de Vosse (TU/e, Eindhoven).
 Co-promotores: Dr Ir EMH Bosboom, Dr G Schurink.
 Maastricht University, December 10, 2009

Chi Yuen Simon Cheung –

Use of tacrolimus in Chinese renal transplant recipients
 Promotor: Prof Dr J van Hooff.
 Co-promotor: Dr M Christiaans, Mr C Li.
 Maastricht University, December 10, 2009

Sauren L –

Cerebral microembolic signals in cardiac interventions
 Promotores: Prof Dr J Maessen, Prof Dr W Mess.
 Co-promotor: Dr F van der Veen.
 Maastricht University, December 15, 2009

Tchaikovski S –

Hormone-induced changes in the coagulation system
 Promotor: Prof Dr J Rosing.
 Co-promotor: Dr G Tans.
 Maastricht University, December 16, 2009

Tchaikovski V –

VEGFR-1 function and dysfunction in monocytes
 Promotor: Prof Dr J Waltenberger.
 Maastricht University, December 16, 2009

PhD THESES EXTERNALLY PREPARED**EI Azzouzi H –**

Peroxisome proliferators-activated receptor (PPAR) regulation in cardiac metabolism and disease
 Promotor: Prof Dr HC Clevers.
 Co-promotores: Dr L de Windt, Dr M van Bilsen.
 Utrecht University, January 13, 2009

Roijers R –

Element analysis with a proton microprobe of early atherosclerotic lesions
 Promotor: Prof Dr G van der Vusse.
 Eindhoven Technical University, January 14, 2009

CARIM DISSERTATION AWARD 2007-2008

In November Ward Vanagt (Group Prinzen, Promotor Prof. G. van der Vusse) received the CARIM Dissertation Award 2007-2008 from the chairman of the jury, Professor Jan Willem Cohen Tervaert. This award is given biannually at the CARIM Symposium for the best thesis written by a CARIM PhD student, and is made possible through a grant from the Foundation for Scientific Research on Cardiovascular Diseases and Nutrition. Ward Vanagt wrote his thesis "Pacing-induced dyssynchrony, blessing or curse?" on the optimal use of pacemakers in children with heart disease. Furthermore, he identified a novel application for cardiac pacemakers by demonstrating that ventricular pacing is an effective tool to reduce cardiac ischemia and reperfusion injury. ■

Professor Jan Willem Cohen Tervaert and Ward Vanagt



DEVELOPMENTS IN CARDIOVASCULAR EDUCATION

In 2009 our Education Program Committee has been very active in further improving the CARIM training programs and the facilities for our Master and PhD students. The pilot with the Electronic Personal Portfolio, an instrument for PhD students to register progress of their education and training program, was evaluated by the students. In 2010-2011 we will, together with other Schools of the UM, further develop a more user friendly monitoring instrument. In 2010-2011 the five existing CARIM RM-PhD courses (see figure), together with two new ones, will be reorganized and clustered in a one week period. Eventually this course week has to develop into a new concept, the CARIM Summer School, which will also be accessible for interested students from other national and international institutes. Since 2009 an introductory session is organized two times a year for our new PhD students. Together with our very

active RM and PhD representatives, who are organized in I'MCARIM, our new PhDs receive general and practical information from our Education Program Coordinator about working at CARIM. Besides several lectures I'MCARIM also organizes social activities for our RM and PhD students, such as informal drinks and the I'MCARIM Weekend (every 2 years). They have also produced two very useful brochures for RM and PhD students; the "CARIM Graduate School Travel Guide" and "CARIM Graduate School in a nutshell". Their new regular newsletter I'MCARIM keeps our students informed about upcoming courses, job opportunities, social activities and other relevant information. At the end of 2009, together with a student's delegation, a web project has been started to improve the information and communication strategy of our institute, finally resulting in a new CARIM website and extranet in the autumn of 2010. ■

School-specific courses and training elements

Introductory cardiovascular courses

- Physiology of the heart and circulation
- Introduction to cardiovascular pharmacology
- Microscopy and vital imaging
- Molecular biology and genetics of the heart and blood vessels
- Clinical aspects of cardiovascular and peripheral vascular diseases
- Molecular biology and genetics of the heart and blood vessels
- Imaging
- Thrombosis and hemostasis

- Organized by CARIM
- Organized by CARIM
- Organized by CARIM/TU Eindhoven
- Organized by CARIM
- Organized by ICar/VU
- Organized by CARIM
- New CARIM course
- New CARIM course

PhD AWARD 2009

In 2009 the CARIM Board decided to stimulate talented Master students to practice designing, writing and defending a PhD project proposal by awarding a CARIM-funded PhD position to the best PhD proposal. The best proposal is selected from those of the top 2nd year Research Master's students as well as from top Master's students not involved in the CBM Research Master program, who can also write a PhD project proposal on a subject of their choice and with a supervisor of their choice. The selected students present and discuss their proposal at a meeting with the CARIM Research Council. The best student (and project) is awarded a CARIM-funded PhD position. In June 2009, Kelly van Bragt was selected as the best student, having presented and defended the best PhD project proposal titled "Atrial metabolism in a rabbit model of heart failure". ■

Kelly van Bragt wins PhD Award 2009



CARDIOVASCULAR GRAND ROUNDS MAASTRICHT

A new and very successful initiative was started in October by Dr. An Moens (dept. of Cardiology), the so called Cardiovascular Grand Rounds Maastricht; an interesting program consisting of weekly lectures for researchers and clinicians who work in the cardiovascular field. The first lecture series started in October till half December. For the full program see figure below.

Cardiovascular Grand Rounds Maastricht 2009

- 02/10 **Martin Paul, MD, PhD**
Genomics and cardiovascular diseases
Maastricht University Medical Center+
- 09/10 **Pieter Doevendans, MD, PhD**
Stemcells: from laboratory to clinic
University Medical Centre Utrecht
- 16/10 **Barbara Casadei, MD, PhD**
Atrial fibrillation and superoxide-generation
University of Oxford, UK
- 23/10 **Frits Prinzen, PhD**
How pathophysiology can improve CRT
Maastricht University Medical Center+
- 30/10 **Bart Loeys, MD, PhD**
Loeys-Dietz and Marfan syndrome: from genetics to treatment
Johns Hopkins University, USA & University of Gent, Belgium
- 06/11 **Dirk Dunker, PhD**
Regulation of coronary flow during exercise
Erasmus Medical Centre Rotterdam
- 13/11 **Sandro Gelsomino, MD, PhD**
New insights in the surgical treatment of chronic ischemic mitral regurgitation
University of Firenze, Italy
- 20/11 **Esther Lutgens, MD, PhD**
Inducing atherosclerotic plaque stability: taming the CD40-CD40L dyad
Maastricht University Medical Center+
- 27/11 **Pedro Brugada, MD, PhD**
Brugada-syndrome
Free University Brussel, Belgium
- 04/12 **Dirk Brutsaert, MD, PhD**
Why and how measure cardiac function in heart failure: recommendations for the practicing physician
Middelheim Hospital Antwerpen, Belgium
- 11/12 **Thomas Renné, MD, PhD**
Crosstalks of the plasma contact system with vascular cells
Karolinska Institute Stockholm, Sweden
- 18/12 **Leon de Windt, PhD**
MicroRNAs: bridging fundamental science and clinical treatment opportunities in heart failure
Maastricht University Medical Center+



KNOWLEDGE TRANSFER

The CARIM Lecture series and the yearly CARIM Symposium are means to update the knowledge of our graduate students, our researchers and other external people with interest in the field of cardiovascular research. In 2009 eight lectures were organized.

CARIM Lecture series 2009

DATE: 14.01.09

LECTURER: Prof. R. Krams, Department of Bioengineering, Imperial College, London, UK

TITLE LECTURE: Shear stress, inflammation and atherosclerosis
Organizer: Prof.dr. Erik Biessen, dept. of Pathology

DATE: 16.01.09

LECTURER: Dr. D. Spendlove, University of Bern, Switzerland

TITLE LECTURE: Virtopsy, Ontwikkelingen in de postmortale beeldvorming
Organizer: Prof.dr. Mat Daemen, dept. of Pathology

DATE: 11.02.09

LECTURER: Prof. Gordon Lowe, University of Glasgow, Scotland

TITLE LECTURE: Can Blood Tests Predict Thrombosis? (including a master class Biomarkers for thrombosis in clinical studies for PhD and RM students)
Moderator: Prof.dr. Hugo ten Cate, dept. of Internal Medicine

DATE: 17.03.09

LECTURER: Dr. Balz Frei, Director and Endowed Chair Linus Pauling Institute, Oregon State University, USA

TITLE LECTURE: Vascular inflammation and oxidative stress in atherosclerosis and aging: Ameliorating effects of alpha-lipoic acid
Organizer: Prof.dr. Aalt Bast, dept. of Pharmacology, section Toxicology

DATE: 09.07.09

LECTURER: Dr. Maren Roman, Virginia Polytechnic Institute and State University

TITLE LECTURE: Cellulose nanocrystals – A novel drug delivery system
Moderator: Dr. Marc van Zandvoort, dept. of BioMedical Engineering

DATE: 28.09.09

LECTURER: Prof. Y. Rudy, Cardiac Bioelectricity and Arrhythmia Center, Washington University, St. Louis
TITLE LECTURE: Theoretical concepts in cardiac conduction and imaging abnormal electrophysiological substrate
Organizer: Dr. Paul Volders, dept. of Cardiology

DATE: 06.10.09

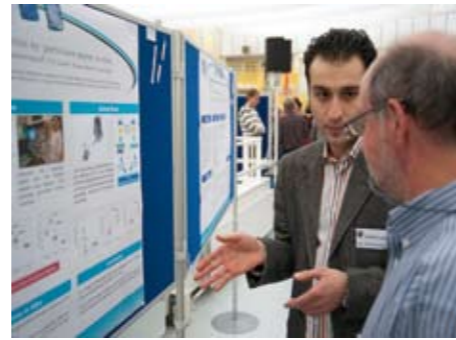
LECTURER: Prof. C. Shanahan, King College London, UK

TITLE LECTURE: Initiators and inhibitors in vascular calcification
Moderator: Dr. Leon Schurgers, dept. of Biochemistry

DATE: 08.10.09

LECTURER: Prof. John H. Griffin, The Scripps Research Institute, La Jolla, CA, USA

TITLE LECTURE: Mutagenic Dissection of Activated Protein C's Multiple Activities (including a master class)
Moderator: Prof.dr. Tilman Hackeng, dept. of Biochemistry



CARIM SYMPOSIUM 2009

CARIM's annual scientific symposium was held on November 25 in Maastricht. For several years this symposium follows the same concept. The heart of the program is a poster session, in which scientists of the institute present their recent research findings and second year Research Master's students present their own project. Our own Principal Investigators Professor Erik Biessen and Professor Hans Peter Brunner La Rocca gave lectures on respectively "Leukocyte dynamics in the advanced plaque: of mice and men" and on "Evidence based medicine – is this all we need in clinical care?"

The winner of the 2009 CARIM PhD Award, Kelly van Bragt, presented her PhD-project "Dysregulation of atrial flow and atrial metabolic remodeling due to structural heart disease". The program was concluded with the Robert Reneman Lecture 2009, a lecture in honor of CARIM's founding director. The lecture entitled "Molecular control of body composition and its impact on cardiovascular disease" was given by Professor Kenneth Walsh, Director of the Whitaker Cardiovascular Institute of the Boston University School of Medicine. Professor Walsh is renowned for his studies on the signaling- and transcriptional-regulatory mechanisms that control tissue growth in the cardiovascular system. ■

Photos page 64

Impression of the CARIM Symposium 2009



Coen Stehouwer

INTERVIEW

WORLD'S LARGEST RESEARCH STUDY ON LINK BETWEEN CHRONIC DISEASES

‘Maastricht Study will track ten thousand people over ten year period’

September 2010 will mark the start of the Maastricht Study: a large-scale scientific study by the Maastricht University Medical Center (Maastricht UMC+) on diabetes, cardiovascular diseases, other chronic diseases and mutual links between these ailments. Prof. dr. Coen Stehouwer, scientific director of the Maastricht Study and dr. Miranda Schram, project leader, hold high expectations for the research study that will be the largest of its kind in the world. “The Maastricht Study isn’t just of scientific significance, but also of social importance.”

In the coming years, about ten thousand people aged between 40 and 70 from the city of Maastricht and its neighbouring communities will participate in a large scale scientific study on the link between chronic diseases such as diabetes, cardiovascular diseases, and also intestinal and lung diseases. “Half of those ten thousand research participants are suffering from diabetes. All participants will be closely tracked for at least the next ten years”, Coen Stehouwer explains. “At the start of the study, all participants will undergo extensive medical examinations. Using the most advanced medical research methods and techniques, we will measure their physical and mental health, physical fitness while also mapping their lifestyles.

All of this will take place in a new research centre, which has been set up for this specific purpose. We will also

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HUGE DATABASE

contact all participants annually to inquire about the state of their health.”

Early warning signs

The scientific goal of the study is to research the link between diabetes and other chronic diseases and to gain greater understanding about the prevention and treatment of these diseases. “We focus on early warning signs – the so-called biomarkers – that signal the onset of these chronic diseases”, project leader and epidemiologist Miranda Schram explains. In order to trace biomarkers in the human body, researchers will use advanced medical imaging techniques, such as MRI, CT and echography. Schram: “All the data we collect by using these techniques and from blood and urine samples, we will store in a database.”

Huge database

“Every UMC invests in this type of research”, Stehouwer says. “This study allows us to create a huge database, which PhD students can use for their research projects. Thus we create many high skilled jobs. This kind of scientific infrastructure is vitally important for attracting and holding on to talented people and for competing with other universities.”

The strategic alliance that was formed several years ago between the Maastricht UMC+ and the Universitätsklinikum Aachen in Germany also fits these purposes. The two academic hospitals are planning to create a joint, international centre for top-level research and care in the field of cardiovascular disease. This Cardio Vascular Center (CVC) of Excellence will rely heavily on the knowledge infrastructure created by the Maastricht Study.

Much to be gained

Stehouwer: “Globally there are several research studies being conducted that focus on cardiovascular diseases,

STAYING PUT

diabetes or other chronic diseases, but the Maastricht Study is the only one in the world gathering data from people with and without diabetes at this large scale and with this much depth.”

This is exactly the reason why the researchers believe there is so much to gain from this study. Stehouwer: “Cardiovascular diseases, along with lung disease and diabetes constitute the highest burden of disease among patients. In addition, they are the most common diseases in the western world. And finally, it’s the chronic diseases such as diabetes and cardiovascular diseases that tend to cluster together with one disease triggering the next.”

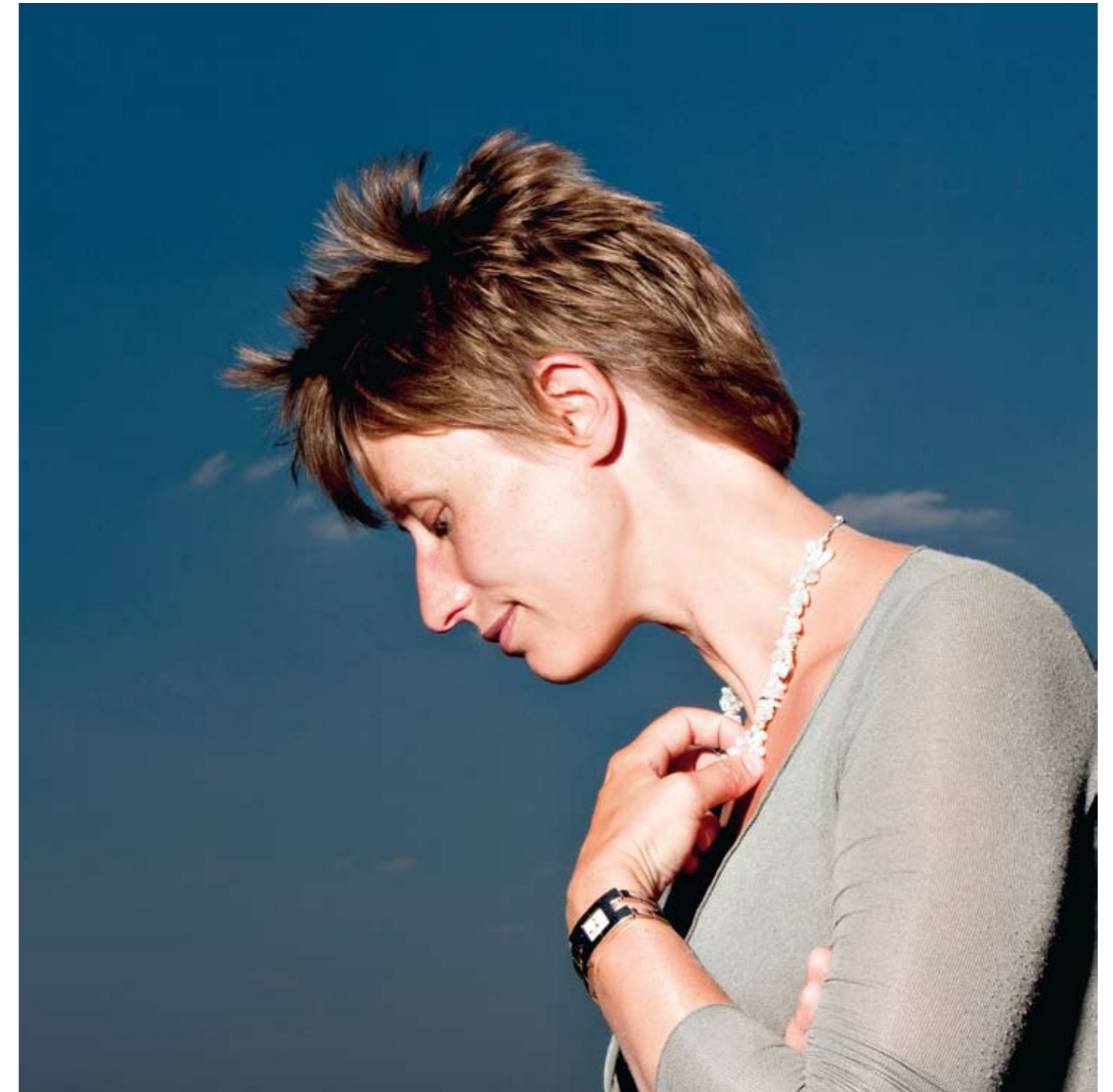
Scientists have not yet discovered which mechanism causes this to happen. Stehouwer: “That’s why this study focuses on finding out why this clustering takes place and why diabetes increases the rate of development of other chronic diseases. Only when you have answered these questions, you can work on prevention and adjust your treatment accordingly. This will help to control costs in the health care sector.”

Staying put

Maastricht and its neighbouring communities are located in the southernmost tip of the Province of Limburg, where the Dutch, German and Belgian borders come together. The area is also known as ‘South Limburg’.

“It’s a great region for conducting the Maastricht Study”, say Stehouwer and Schram. “In this region, there is a higher prevalence of chronic diseases than elsewhere in The Netherlands. This can be partly explained by the fact that the population is ageing and by a lower life expectancy due to a generally less healthy life style. The average lifespan of people in Limburg is about ten to twelve years shorter than of those living in the ‘healthiest’ parts of The Netherlands.

▶▶



Miranda Schram

PEOPLE'S HEALTH

In South Limburg the prevalence of cardiovascular diseases is above average. Therefore, this study will not only be of scientific significance, but also of social importance.” There is a practical advantage in the fact that the research population tends to stay put. Stehouwer: “This characteristic is very beneficial to our study. From an organisational point of view, it will make it easier for us to track people over a long period of time.”

People's health

Stehouwer: “The Maastricht Study is very special for CARIM, because of its emphasis on people's health in general instead of cardiovascular diseases only. Thus, it crosses natural borders between research institutes. I am very grateful to CARIM and its executive board for embracing this research project while fully realizing that parts of the study focus on research fields outside the scope of CARIM.”

Schram: “This research project requires a lot of organisation. In addition to CARIM researchers who participate in the project, there are also many researchers involved from other Maastricht University research institutes. The Maastricht Study offers an ideal structure to address a number of research questions at the same time. Choices regarding which tests and measurements we will use to assess the research population are subject to interdisciplinary discussions.”

Great benefits

Participants will benefit from their involvement in this study, Miranda Schram states. “First of all, they will undergo extensive and detailed examinations. If we notice something that is significant, high blood pressure or a high blood sugar levels for example, we will inform both the participant and his or her GP.”

And there are more benefits. “We will be able to offer each participant personal advice regarding his or her lifestyle –

ECONOMIC SPIN OFF

using an interactive computer programme that helps you improve your lifestyle – and we are currently also developing an incentive programme for participants. It will offer discounts on health related products and services, such as a fitness club membership.”

Economic spin off

With most of the finances in place, the Maastricht Study – which involves a sum of about 23 million euros in the first five years alone – will start in September 2010. The project will create jobs for about 250 people. About three quarters of these jobs will be based in the Province of Limburg. Because of the economic spin off, the Provincial Council of Limburg made 1 million euros available for the Maastricht Study. Other financial contributors are the Dutch Ministry of Economic Affairs (2 million), the European Regional Development Fund (5 million) and the Weijerhorst Foundation (3 million). The Maastricht UMC+ itself is investing 5 million euros in the Maastricht Study.

Stehouwer: “This money will keep us going until 2015. However, it's our ambition to examine all participants twice or three times during the course of this study, instead of just once at the start of the research project. This would greatly benefit the study and its results.”

■

PASSPORTS



Name:

Coen Stehouwer

Age:

50

Coen Stehouwer studied Medicine at Erasmus University Rotterdam. He is an internist and head of the department of Internal Medicine at the Maastricht UMC+. Stehouwer is an expert in the field of vascular complications in metabolic diseases, in particular in diabetes, hypertension, chronic kidney diseases and hyperhomocysteinaemia. He is the Principal Investigator of the Maastricht Study, which starts in 2010.



Name:

Miranda Schram

Age:

33

Miranda Schram studied Biomedical Sciences at Leiden University. She earned her PhD at the VUmc in Amsterdam, conducting diabetes and epidemiologic research. Since 2008, she has been working at CARIM and been involved with the Maastricht Study as project leader. In this role, she coordinates all necessary activities in preparation for the start of the Maastricht Study: specific scientific choices, fundraising, logistics, workspaces and public relations.

LIST OF ABBREVIATIONS

A-F

ASC azM	Administrative Service Center University Hospital Maastricht
BMM BSc	BioMedical Materials program Bachelor of Science
CARIM CBAC CBM COHFAR CTCM CTMM CVC	Cardiovascular Research Institute Maastricht Cardiac Bioelectricity & Arrhythmia Center (Washington University St. Louis, USA) Research Master's Cardiovascular Biology & Medicine Biomarkers to predict cardiac failure, arrhythmias and success of treatment (CTMM project) Clinical Trial Center Maastricht Center for Translational Molecular Medicine Cardio Vascular Center
DAS DFG DiMI	Dutch Atherosclerosis Society Deutsche Forschungsgemeinschaft European Network on Diagnostic Molecular Imaging
EASL EB ECCE ECOS ERC ESC ESF EuCAR EU Framework EVGN	European Association for the Study of the Liver Executive Board European Center of Cardiovascular Excellence Research School Accreditation Committee European Research Council European Society of Cardiology European Science Foundation Euregio Cardiovascular International Research Training Group European Union Framework European Vascular Genomics Network
FHML FP6, FP7	Faculty of Health Medicine and Life Sciences (Maastricht University) Sixth and Seventh European Framework Programme

I-S

ICaR	Institute for Cardiovascular Research (VU, Amsterdam)
ICIN	The Netherlands Heart Institute
IDIIDAS	New Early Therapies for Intervertebral Disc Diseases. Drug Delivery and Augmentation through Smart Polymeric Biomaterials (BMM Projects)
IMCAR	Institute for Molecular Cardiovascular Research, Aachen, Germany
INCOAG	Innovative Coagulation Diagnostics (CTMM project)
ISAB	International Scientific Advisory Board
ISTH	International Society on Thrombosis and Haemostasis
iValve	Instructive scaffolds for in situ tissue engineering of heart valves and arteries (BMM project)
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KNAW	Royal Netherlands Academy of Arts and Sciences
<hr/>	
M.Sc.	Master of Science
Maastricht UMC+	Maastricht University Medical Center+
M-CAR	Maastricht Centre for Atherosclerosis Research
MD	Doctor of Medicine
MLW	Molecular Life Sciences
MSc	Master of Science
<hr/>	
NHS	Netherlands Heart Foundation
NVAO	Accreditation Organisation of the Netherlands and Flanders
NVVP	Dutch Association for Pathology
NWO	Netherlands Organisation for Scientific Research
<hr/>	
PARISk	Assessment of Plaque at Risk by Non-invasive (Molecular) Imaging and Modeling (CTMM project)
PBL	Problem Based Learning
PENT	Polymer Enabled Neovascularization Therapies
PI	Principal Investigator
PREDICcT	Biomarkers for the Prediction and Early Diagnosis of Diabetes and Diabetes-related Cardiovascular Complications (CTMM project)
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RM Program	Research Master Program
RWTH	Rheinisch-Westfälische Technische Hochschule Aachen, Germany
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STW	Technology Foundation STW

T-Z

TRIUMPH	TRanslational Initiative on Unique and novel strategies for Management of Patients with Heart failure (CTMM project)
TU/e	Eindhoven University of Technology
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UKA	Universitätsklinikum Aachen, Germany
UM	Maastricht University
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VU	Free University, Amsterdam
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WWO	Dutch University Education Act
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ZonMw	Netherlands Organisation for Health Research and Development

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