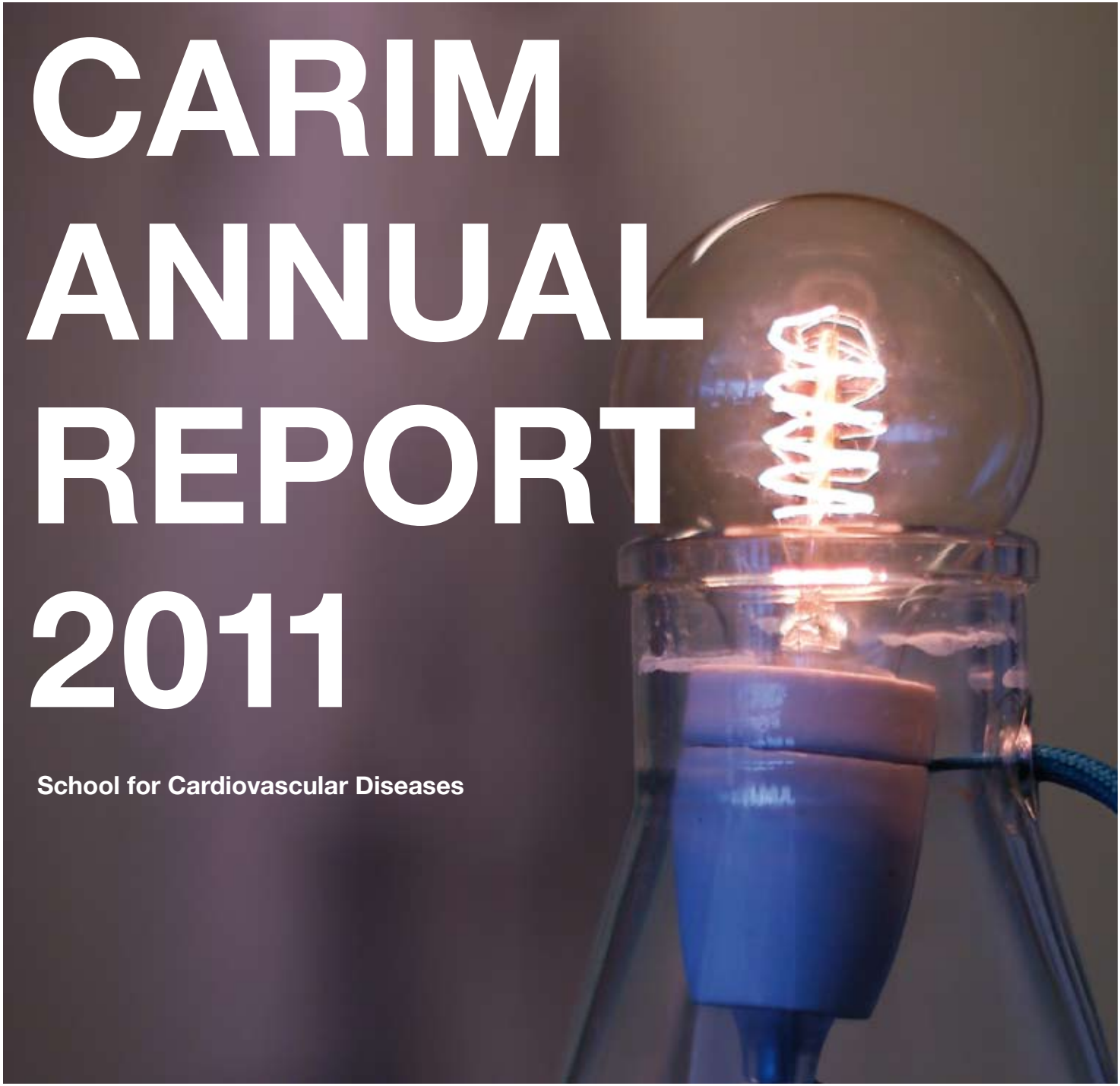
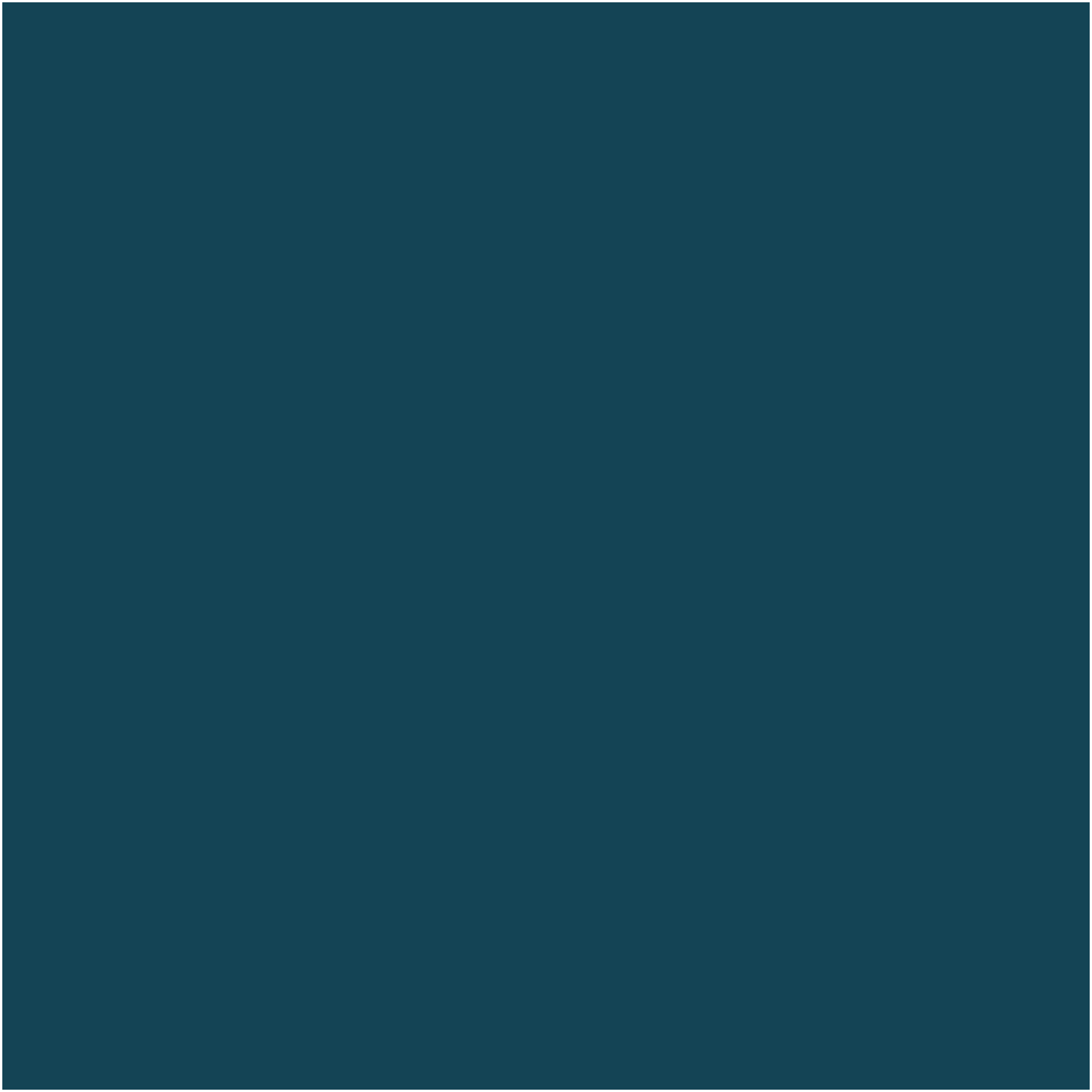
CARIM ANNUAL REPORT 2011



School for Cardiovascular Diseases

CARIM ANNUAL REPORT 2011

School for Cardiovascular Diseases



CONTENTS

PREFACE

Having started in April 2012 as the new Scientific Director of CARIM, it is a pleasure to present the CARIM Annual Report 2011. Being a new inhabitant of Maastricht and the CARIM community, it is not that easy to introduce the institute's highlights of a year that is already lying behind us. Especially since my job is to look forward and help the institute to develop itself into a next phase, in which a more focused research strategy will help us to survive in the competitive field of cardiovascular research.
On the other hand, real highlights speak for themselves. Also in the 2011 edition of our annual report, several of our researchers have been interviewed about their successes in the last year. Within this year's theme, 'cooperation', they will tell their story of how they work together in networks, both internal and external. Let their stories guide you through the institute's dynamic environment of research activity.

As you might notice, the light bulbs that are on the cover of this report will appear in all the portraits of these CARIM researchers. The light bulb symbolizes the eureka-moment, that most of us experience when an important discovery is done, or when we celebrate a scientific breakthrough after many years of hard work. This 'Aha! Effect' also known as eureka effect, refers to the common human experience of suddenly understanding a previously incomprehensible problem or concept. For me the first months at this new research institute have been such an eureka-moment.

First one might think a new organization is too complex to understand. But soon one will recognize patterns, structures and human behavior which are universal in nature.

I really hope to bring new insights in this wonderful world of CARIM. I would like to thank all CARIM staff members, technicians and other colleagues for their warm hearted welcome and openness. I hope that all together we will succeed to bring our institute to a higher level in the upcoming years.

I wish you lots of pleasure reading,

Professor Thomas Unger
Scientific Director CARIM
School for Cardiovascular Diseases

PROFILE

PROFILE

CARIM is one of the top research institutes in translational cardiovascular research in Europe. It has been a world leader in the fields of atherosclerosis research and atrial fibrillation. It has also made important international contributions to molecular imaging.

Cardiovascular scientists from around the world join CARIM because it values open communication, close cooperation, high ambitions, good facilities and a critical learning environment. Our 27 Principal Investigators form the foundation of our research environment and educational programs. Our interdisciplinary research is divided into 8 clusters:

1 Coagulation: Protein synthesis, modeling and function
2 Atherothrombosis
3 Atherosclerosis
4 Metabolism
5 Vascular Regeneration
6 Cardiac Hypertrophy and Heart Failure
7 Atrial Fibrillation
8 Imaging

CARIM 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+). CARIM is recognized by the KNAW as a research school and as an international training site for Early Stage Researchers in the framework of the Marie Curie Program.

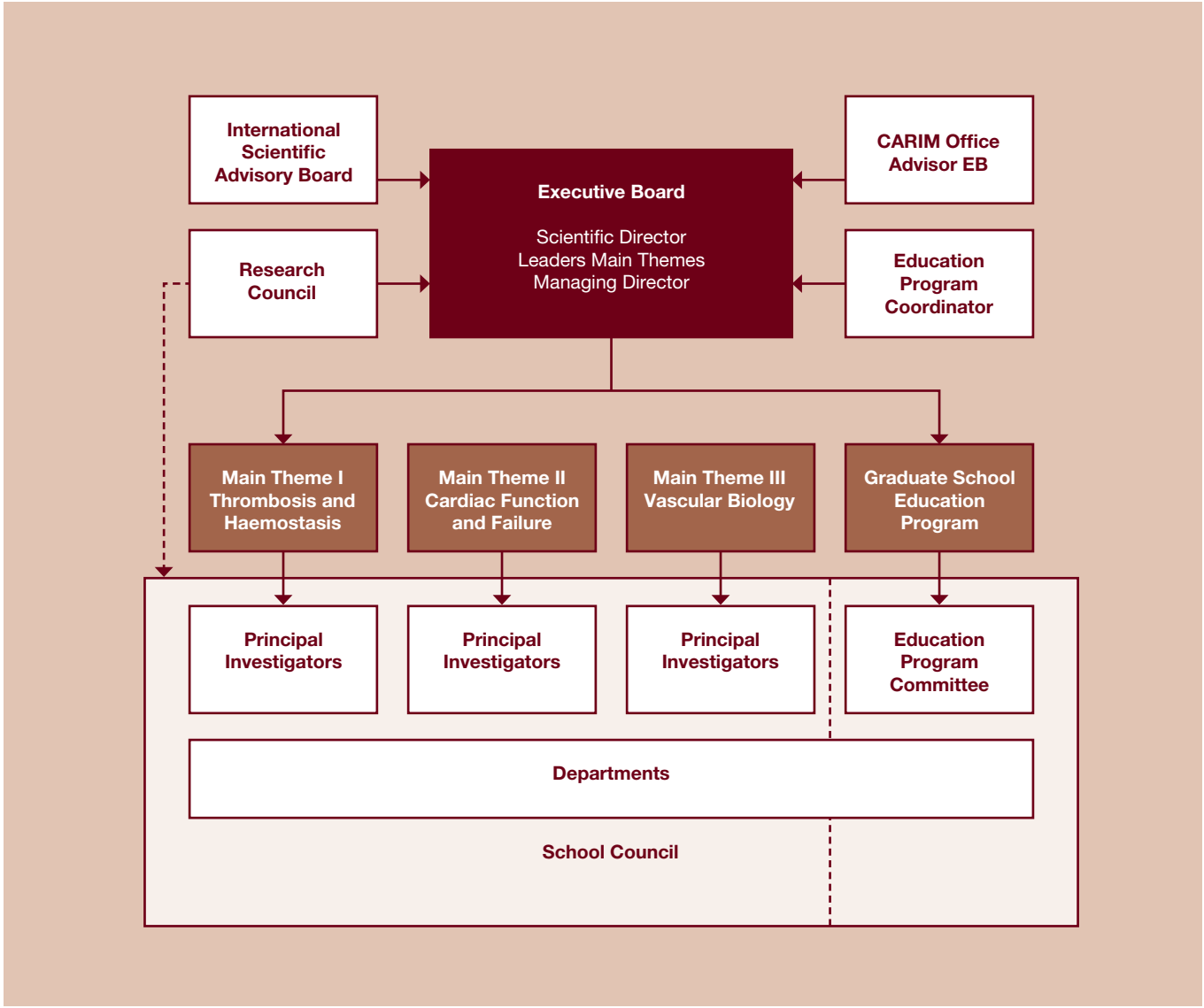
KEY FIGURES 2011

Annual budget: 15.567 K€
Researchers: 197 fte
Technical and supporting staff: 70 fte
Departments/disciplines: 13
Scientific articles: 569 (Wi-1 495)
PhD Thesis: 33
Patents: 4

International cooperation and public-private research partnerships
CARIM plays an important role in public-private research partnerships as main author and project manager of 6 out of 7 cardiovascular projects of the Center for Translational Molecular Medicine (CTMM) in the Netherlands. CTMM is a public-private consortium that comprises universities, academic medical centers, medical technology enterprises and chemical and pharmaceutical companies. Other public-private research partnerships in which our researchers participate are: the BioMedical Materials program (BMM) and Top Institute Pharma. In addition, CARIM is a member of several international networks, including the EU seventh Framework Programme (FP7) and the Leducq Transatlantic Network.

ORGANIZATION

ORGANIZATION



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, Baylor College of Medicine, Houston, USA
- Professor Anthony Ware, Lilly Corporate Center Indianapolis, USA
- Professor John Yudkin, University College London, UK

Executive Board

- Professor Thomas Unger, Scientific Director (from April 2012)
- Professor Tilman Hackeng, Leader Main Theme I
- Professor Harry Crijns, Leader Main Theme II
- Professor Coen Stehouwer, Leader Main Theme III
- Professor Mark Post, Leader Main Theme III (Scientific Director a.i. till April 2012)
- Rob van der Zander, Managing Director
- Petra Uittenbogaard, advisor and project manager

Principle Investigators

- Professor Erik Biessen, dept. of Pathology
- Professor Matthijs Blankesteijn, dept. of Pharmacology
- Professor Hans Peter Brunner-La Rocca, dept. of Cardiology
- Professor Harry Crijns, dept. of Cardiology
- Professor Hugo ten Cate, dept. of Biochemistry
- Professor Tammo Delhaas, dept. of Biomedical Technology
- Professor Jo De Mey, dept. of Pharmacology
- Professor Tilman Hackeng, dept. of Biochemistry
- Professor Johan Heemskerk, dept. of Biochemistry
- Professor Stephane Heymans, dept. of Cardiology
- Professor Leo Koole, dept. of Biomedical Technology
- Professor Peter de Leeuw, dept. of Internal Medicine
- Dr Joost Luiken, dept. of Genetics and Cell Biology
- Professor Jos Maessen, dept. of Cardiothoracic Surgery
- Dr An Moens, dept. of Cardiology
- Professor Mark Post, dept. of Physiology
- Professor Frits Prinzen, dept. of Physiology
- Professor Chris Reutelingsperger, dept. of Biochemistry
- Professor Harald Schmidt, dept. of Pharmacology
- Professor Uli Schotten, dept. of Physiology
- Professor Bert Smeets, dept. of Genetics and Cell Biology
- Professor Coen Stehouwer, dept. of Internal Medicine
- Professor Hans Vink, dept. of Physiology
- Dr Paul Volders, dept. of Cardiology
- Professor Christian Weber, dept. of Pathology
- Professor Joachim Wildberger, dept. of Radiology
- Professor Leon de Windt, dept. of Cardiology

Education Program Committee

- Dr Marc van Bilsen, PhD Coordinator, chairman (from January 2011)
- Dr Adriaan Duijvestijn, Coordinator Research Master
- Dr Matthijs Blankesteijn, staff member
- Dr Vanessa van Empel, MD
- Dr Eline Kooi, staff member
- Professor Hans Vink, staff member
- Ellen Dirkx, PhD student (till April 2011)
- Romy Kremers, master student (till September 2011)
- Timo Rademakers, PhD student
- Michael Rutjens, master student
- Emiel van der Vorst, PhD student (since April 2011)

Research Council

- Professor Thomas Unger, chairman
- Professor Harry Crijns
- Professor Tilman Hackeng
- Professor Johan Heemskerk (deputy member: Prof Hugo ten Cate)
- Professor Jo de Mey (deputy member: Professor Hans Vink)
- Professor Mark Post
- Professor Frits Prinzen (deputy member: Professor Stephane Heymans)
- Professor Chris Reutelingsperger (deputy member: Dr Gerry Nicolaes)
- Professor Uli Schotten
- Professor Leo Koole
- Professor Leon de Windt (deputy member: Dr Matthijs Blankesteijn)
- Professor Joachim Wildberger
- Professor Erik Biessen

CARIM Office

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

HR-support

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

Administrative support

The administrative department of Maastricht University (Finance) provides accounting support for the CARIM research projects on a part-time basis. The administrative staff consists of: Esther van Heel, Henny Kerckhoffs, Joost von Weersch and Jan-Willem Janssen.

Participating departments and disciplines

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

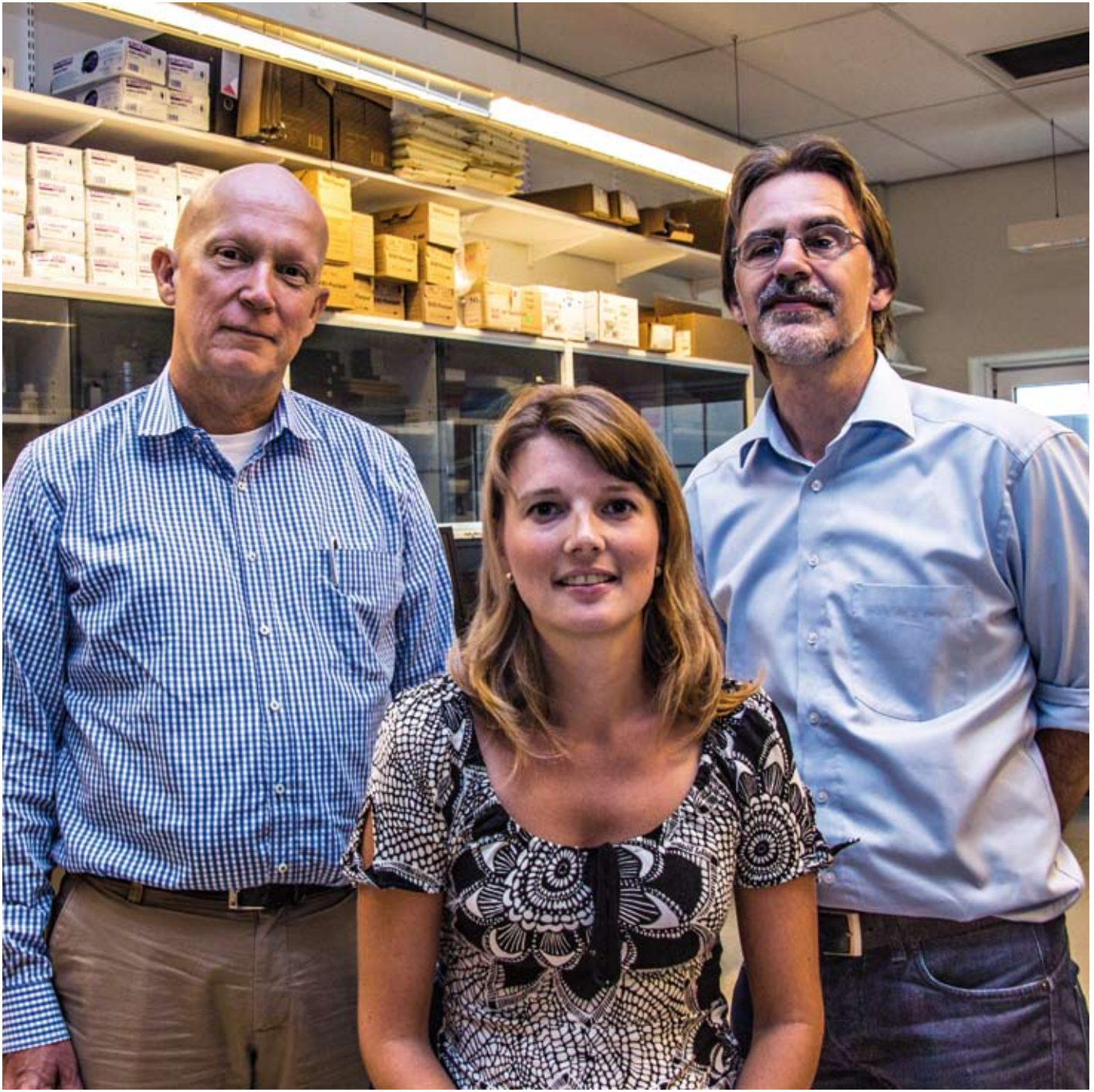
Basic Research Departments

Biochemistry
Biomedical Engineering
Genetics and Cell Biology*
Pharmacology
Physiology

Clinical Departments

Cardiology
Cardio-thoracic Surgery
Clinical Chemistry
Internal Medicine, including Immunology
Neurology
Pathology
Radiology
Surgery

* Consisting of the dept. of Clinical Genetics, dept. of Molecular Cell Biology, dept. of Clinical Genomics & Bioinformatica, and the dept. of Molecular Genetics.



Thrombosis Expertise Center aims for tailor-made therapy

‘CARIM houses all the resources and expertise that the center will need’

Hugo ten Cate, Johan Heemskerk and Judith Cosemans are scientists with a ‘can do’ attitude. They have initiated a Thrombosis Expertise Center (TEC) to facilitate closer collaboration between the lab and the clinic. Their strife for excellence is remarkable, judging by the awards and grants that came their way in 2011.

Hugo ten Cate, Professor of Internal Medicine, Clinical Thrombosis and Hemostasis, is in charge of the new center. “My hope is that we will be able to prevent secondary heart attacks by providing tailor-made therapy,” he says. “Currently, every person receives the same medication, even though we know that in about 25 percent of the cases this therapy doesn’t even work.”

Another aim for the center is to share knowledge and expertise with hospitals in the region, and to provide support in the treatment of complex cases.
In addition, Ten Cate believes the center has a role to play in patient safety. “The use, or lack of use, of certain medications can lead either to thrombosis or to bleeding complications,” he says. “We can play a role in developing and monitoring hospital policies to help prevent such complications.”

To the clinic

Facilitating translational research within TEC will be instrumental in achieving the center’s goals. The basic researchers within CARIM are eager to collaborate.
“There comes a point when you need to dare take your findings to the clinic,” says Johan Heemskerk, Professor of

▸▸

Cell Biochemistry of Thrombosis and Hemostasis. “We have established the roles of many of the proteins and protein receptors that play a role in the disease. Moreover, about 200 genes that affect thrombosis in mice have now been identified,” he says. In his view, it is because of these kinds of rapid advancements that the time has come for a Thrombosis Expertise Center.

His colleague, Assistant Professor in Biochemistry Judith Cosemans has optimized an important tool to assist in translational research. Needing just a few drops of blood, her ‘flow chamber’ enables scientists to measure the activity of blood platelets and blood coagulation in an artificial environment similar to the walls of veins or arteries. The device helps them to detect risk factors for thrombosis or haemorrhaging and to study the effects of medication, Cosemans explains. Currently, the device is only used in research labs, but it has the potential to become an important instrument for diagnosis and treatment of patients in the clinic.

Recognition

“CARIM houses all the resources and expertise that the center will need,” says Ten Cate. About 87 people within the institute are in some way involved in thrombosis and hemostasis research. In fact, CARIM’s thrombosis and hemostasis research group is one of the largest in Europe. And very successful too: in 2011 both Cosemans and Heemskerk received recognition for their work on the flow chamber and for other contributions to their field.
Cosemans won the Manucci Award for young investigators while Heemskerk received the Biennial Award for Contributions to Hemostasis (BACH). In addition, Cosemans won the Dr. E. Dekker Postdoc grant from the Dutch Heart Foundation.
Cosemans: “The Manucci Award was important to me because it meant recognition for the work I had been doing. The Dekker grant is for the future. It gives me the opportunity to create my own niche within CARIM and TEC,” says Cosemans, who intends to focus more closely on the role of platelets in vascular remodeling.

Professor Heemskerk was also awarded the Willy van Heumen Prize for furthering the restriction of animal testing for medical reasons. Heemskerk: “The development of the flow chamber means that we no longer have to anaesthetise mice in order to study the activity of blood platelets in vivo. And because we have succeeded in reducing the amount of blood we need to use in the flow chamber, we also need fewer mice.”

There is no need to worry that any of these successes will lead to complacency: “An award is an encouragement to continue your work in the area in which your peers consider you to be outstanding,” Heemskerk says reassuringly. ■

‘An award is an encouragement to continue your work in the area in which your peers consider you to be outstanding’

Johan Heemskerk

01_ FACTS AND FIGURES

Funding and expenditure at institutional level 2006-2011

K€	2006		2007		2008		2009		2010		2011	
Direct funding	7.807	46%	8.055	40%	8.239	45%	8.653	45%	8.411	41%	8.242	36%
Research Funds	1.572	9%	1.751	9%	1.411	8%	1.201	6%	2.140	10%	1.284	6%
Contracts	7.766	45%	10.426	51%	8.812	47%	9.384	49%	9.967	49%	13.202	58%
Total	**17.145**	**100%**	**20.232**	**100%**	**18.462**	**100%**	**19.238**	**100%**	**20.518**	**100%**	**22.728**	**100%**
Personnel	11.163	66%	13.401	68%	13.534	77%	14.656	83%	15.032	79%	15.984	76%
Other costs	5.827	34%	6.361	32%	4.100	23%	2.862	17%	3.957	21%	5.0424	24%
Total	**16.990**	**100%**	**19.762**	**100%**	**17.634**	**100%**	**17.518**	**100%**	**18.989**	**100%**	**21.008**	**100%**
Result	**155**		**470**		**828**		**1.720**		**1.529**		**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.

CARIM receives its basic funding from Maastricht University, through the Faculty of Health, Medicine and Life Sciences 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 funding by university and hospital, a significant part of our research program is supported by non-profit organizations and industry.

Research output in 2006-2011

	2006	2007	2008	2009	2010	2011
PhD theses	35	37	29	29	33	33
Scientific publications	490	497	465	509	523	569
Other publications	42	49	54	46	60	52
Total (I)	**567**	**583**	**548**	**584**	**616**	**654**
Academic staff in fte (II)*	35,7	35,9	37,4	37,0	38,3	34,3
Ratio I en II	15,9	16,2	14,7	15,8	16,1	19,1

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

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)

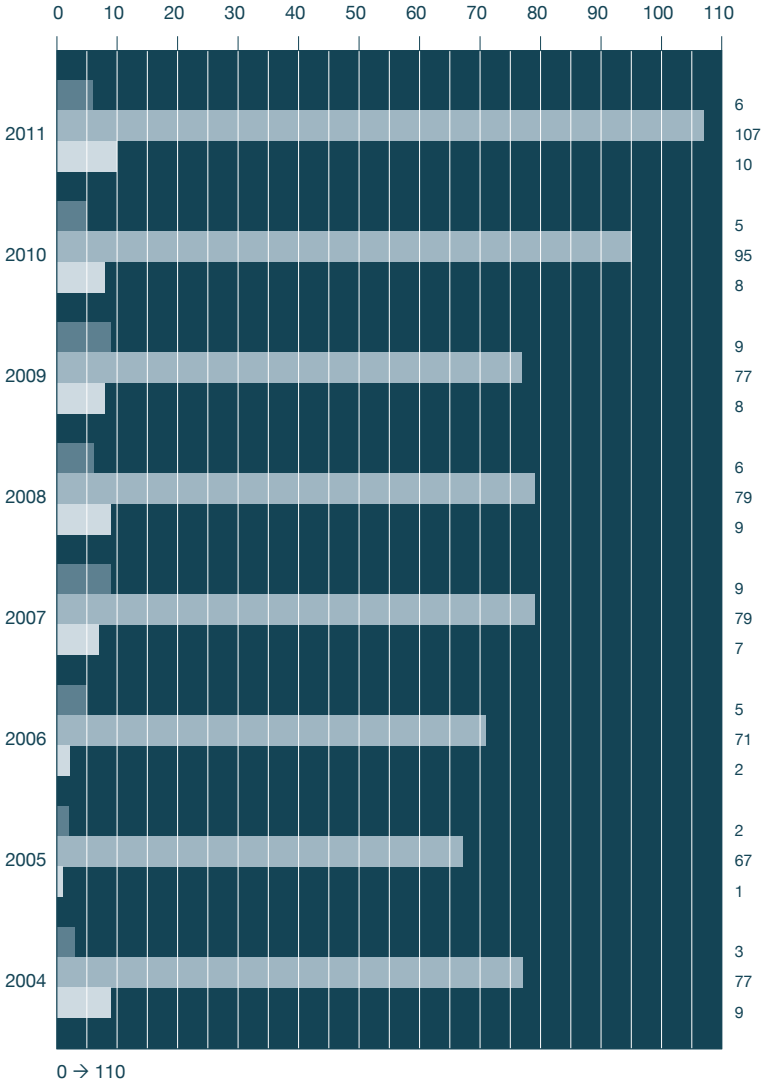
Wi-1
scientific publication
in refereed SCI-SSCI indexed journals

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)

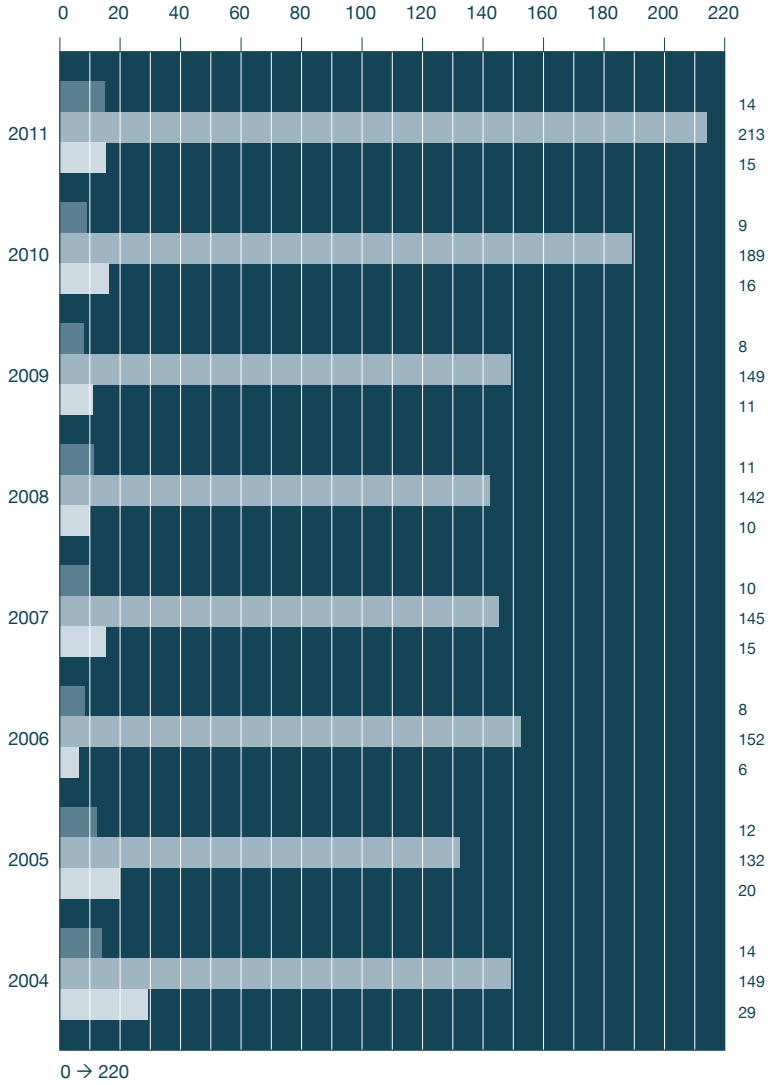
Wi-1
scientific publication
in refereed SCI-SSCI indexed journals

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)

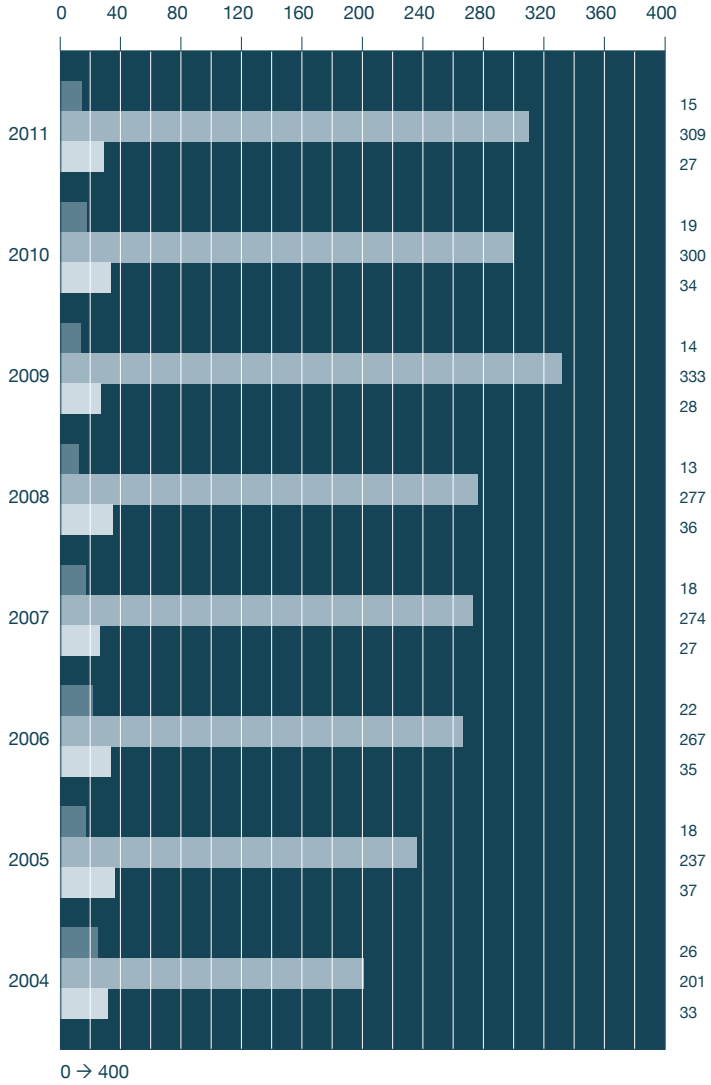
Wi-1
scientific publication
in refereed SCI-SSCI indexed journals

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



New contracts and grants concluded in 2011

Funding	Theme I	Theme II	Theme III	Total Support K€
Type 2	200.000	960.000	345.000	1.505.000
Type 3	2.994.760	3.800.000	5.637.740	12.432.500
Type 4	166.000	413.500	300.000	879.500
Type 5	250.000	250.000	250.000	750.000
Total	**3.610.760**	**5.423.500**	**6.782.740**	**15.567.000**

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

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

Type 4 = Industry, excl. CTCM (turn over in 2011: 3.131 K€)

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

Summary of scientific and technical staff CARIM 2011 (in fte)

Research Area	WP1			WP2			WP3			WP4			azM	TOTAL
	Faculty	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	fte
Thrombosis and haemostasis	7.5	6.4	1.5	0.8	0.6	0.0	0.0	12.6	4.8	2.2	4.8	5.1	0.6	46.8
Cardiac function and failure	12.1	10.2	4.5	0.8	4.6	0.8	0.5	13.8	11.7	-	4.9	1.1	1.8	66.8
Vascular biology	14.7	10.6	5.0	0.6	1.2	1.2	0.7	30.8	11.4	-	0.4	2.9	4.9	84.3
Total	**34.3**	**27.2**	**11.0**	**2.2**	**6.4**	**2.0**	**1.2**	**57.2**	**27.9**	**2.2**	**10.1**	**9.1**	**7.3**	**197.9**

	OBP 1	OBP 2	OBP 3	OBP 4	OBP azM	TOTAL
Thrombosis and haemostasis	6.4	-	4.6	2.3	1.3	14.6
Cardiac function and failure	16.2	0.9	5.4	0.0	0.2	22.7
Vacular biology	16.3	0.0	12.5	0.6	3.9	33.2
Total	**38.9**	**0.9**	**22.5**	**2.9**	**5.4**	**70.5**

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

RNA rather than DNA

‘We have brought together the country’s best researchers’

It is not every day that a budget of five million euros is allocated to so-called ‘high-risk’ research. But then CARIM’s Leon de Windt makes a convincing case for taking heart failure research into a new direction. And seven professors from five Dutch universities are bundling their expertise to make it happen.

“Ninety-nine percent of all research into heart failure focuses on just one percent of the chromosomes. Everyone, including drug companies, is looking at proteins and the DNA that encodes them. The rest is ignored, even though only one percent of our DNA encodes proteins,” states Professor of Molecular Cardiology De Windt.

To him, the results of this DNA research are simply not good enough. “Heart failure is a horrible disease. Despite our best research efforts and our best care, about 50 percent of patients die within five years. Moreover, all heart failure medications are currently protein based, causing all kinds of nasty side effects,” he says.

International efforts

Consequently, De Windt has shifted his scientific focus from DNA to RNA molecules, known to be involved in protein synthesis and the transmission of genetic information. He is convinced that RNA research will result in ‘high gain’: new insights into fundamental issues, and lead to new diagnostic tools and more efficient therapeutics.

In 2008 he joined an international research consortium of five like-minded scientists to explore the possibilities of RNA. Their work, funded by a five million euro grant of the Leducq Foundation, was so successful, that the foundation ▶▶

CardioVasculair Onderzoek Nederland (CVON), funded by the Netherlands Heart Foundation (NHF), decided to finance a follow up study, according to De Windt. It granted five million euros to the ARENA project (Approaching Heart Failure By Translational Research of RNA Mechanisms).

The country's best

De Windt and Professor Pinto of the University of Amsterdam are leading this 5-year study. "We have brought together the country's best researchers in the area of heart failure," says De Windt. "Seven Principal Investigators from five Dutch universities will take part. About half of the work will be conducted in Maastricht."

"The Leducq project generated a lot of data that will help our work," De Windt continues. "While Leducq was specifically aimed at identifying RNA molecules that play a role in heart failure and at finding ways to intervene, the ARENA project has a broader scope: We will identify RNA molecules, look at their possible function as biomarkers, try to explain inter-individual differences via RNA genetics and develop RNA based therapeutics."

"CARIM's role will be to identify RNA molecules that play a role in heart failure and to find out why an older heart is more affected by stress than a younger one. In addition, CARIM will investigate why type 2 diabetics are more susceptible to heart failure, and try to identify new biomarkers."

About ten people at CARIM will be working on the project on a daily basis, according to the Windt. "The large role of CARIM in this project is a reflection of our strength in this field. Professor Stephane Heymans, who also participates in the project, has made a name for himself in identifying RNA biomarkers and my group was the first to publish an RNA-based heart failure therapy."

Common goal

So how will CARIM benefit from the collaboration? "Using each others' expertise makes research less time-consuming and less expensive," De Windt explains. In addition, a strong international reputation of research in the Netherlands is good for CARIM. De Windt: "Internationally, it is not a matter of how CARIM compares to, say, Cambridge. No, the question is how well the Netherlands compete with the UK or Germany, for example."

To stay competitive, the current trend is towards regional collaboration between universities. De Windt is not worried that CARIM will miss the boat due to its peripheral location in the Netherlands.
"For us, Aachen, Liege and Louvain are natural partners. These large cities give us a competitive edge over other regions in Holland," he argues. "I believe that we will soon see two top cardiovascular research centers in this country: one in the Randstad and one in Maastricht. Both are strong in studying cardiovascular disease, but in Maastricht fundamental and clinical research are better integrated. So perhaps in five years time, Maastricht will be the main base for the entire country!"

‘The large role of CARIM in this project is a reflection of our strength in this field’

Leon de Windt

02_
EVENTS AND HIGHLIGHTS

SCIENTIFIC HIGHLIGHTS 2011

In 2011 the hard work of our researchers paid off in **569 scientific publications** in peer refereed journals (495 Wi-1 publications, excluding abstracts, and 47 Letters to the editor), **33 PhD theses, 4 patents,** 1.505 million Euros funding received in competition from national and international science foundations and 14.062 million Euros funding from third parties, charities, EU-framework programs, industry, etc.
In 2011 the overall average Impact Factor is 5.5 and remained at the same level compared to 2010.

TOP PUBLICATIONS

with the highest Impact Factor in 2011*
(* with CARIM researcher as first and/or last author)

Borissoff JI, Spronk HMH, ten Cate, H -
Mechanisms of Disease. The Hemostatic System as a Modulator of Atherosclerosis.
New England Journal of Medicine 2011; 364: 18: 1746-1760 IF 53.486

Stolarz-Skrzypek K, Kuznetsova T, Thijs L, Tikhonoff V, Seidlerova J, Richart T, Jin Y, Olszanecka A, Malyutina S, Casiglia E, Filipovsky J, Kawecka-Jaszcz K, Nikitin Y, Staessen JA -
Fatal and Nonfatal Outcomes, Incidence of Hypertension, and Blood Pressure Changes in Relation to Urinary Sodium Excretion.
Jama-Journal of the American Medical Association 2011; 305: 17: 1777-1785 IF 30.011

Schotten U, Verheule S, Kirchhof P, Goette A -
Pathophysiological Mechanisms of Atrial Fibrillation: A Translational Appraisal Physiological Reviews
2011; 91: 1: 265-325 IF 28.417

Weber C, Noels H –
Atherosclerosis: current pathogenesis and therapeutic options
Nature Medicine 2011; 17: 11: 1410-1422 IF 25.430

De Jager SCA, Bermudez B, Bot I, Koenen RR, Bot M, Kavelaars A, de Waard V, Heijnen CJ, Muriana FJG, Weber C, van Berkel TJC, Kuiper J, Lee SJ, Abia R, Biessen EAL -
Growth differentiation factor 15 deficiency protects against atherosclerosis by attenuating CCR2-mediated macrophage chemotaxis -
Journal of Experimental Medicine 2011; 208: 2: 217-225 IF 14.776

►►

TOP PUBLICATIONS

with the highest Impact Factor in 2011*
(* with CARIM researcher as first and/or last author)

Laeremans H, Hackeng TM, van Zandvoort M, Thijssen V, Janssen BJA, Ottenheijm HCJ, Smits JFM, Blankesteijn WM -
Blocking of Frizzled Signaling With a Homologous Peptide Fragment of Wnt3a/Wnt5a Reduces Infarct Expansion and Prevents the Development of Heart Failure After Myocardial Infarction
Circulation 2011; 124: 15: 1626-U107 IF 14.432

Van Veldhuisen DJ, Braunschweig F, Conraads V, Ford I, Cowie MR, Jondeau G, Kautzner J, Aguilera RM, Lunati M, Yu CM, Gerritse B, Borggrefe M, Investigators D-H -
Intrathoracic Impedance Monitoring, Audible Patient Alerts, and Outcome in Patients With Heart Failure
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REMARKABLE

High citation score of VitaK Research
The publication of VitaK, showing the beneficial effects of vitamin K2 on bone strength in postmenopausal women, was one of the five mostly cited papers as measured over a 3-year period. The study was published in Osteoporosis International, a well-reputed journal with an impact factor of 5.0. In 2011 VitaK has established a long-term collaboration with GenoGla at the University of Algarve (Portugal) on research concerning the newly discovered vitamin K-dependent protein Gla-rich protein (GRP). VitaK BV is a research company with a long expertise in all aspects of vitamin K and vitamin K-dependent proteins and originated from the University vitamin K-research group at the University of Maastricht. VitaK is still closely associated with CARIM.

The effect of the site of ventricular pacing on cardiac function in children
In 2011 the first part of the results of a multicenter study investigating the effect of the site of ventricular pacing on cardiac function in children has been published by **Delhaas, Prinzen and Van Geldorp** (Dept. of BMT and Dept. of Physiology) in Heart. This study, containing almost 300 children from 30 centers worldwide, has become the largest study on pacing in pediatric cardiology ever. The data clearly showed that pacing the left ventricle is considerably better than pacing the right ventricle, the left ventricular appearing to be the best site. The study therefore provides strong recommendations for where to implant pacing electrodes in children.

A new and radical approach

‘Personalized medicine is the next major leap forward’

Prof. Dr. Harald Schmidt is remarkably modest about having received a 2.3 million euro grant from the Europe Research Council (ERC). His ambitions, however, are far from unassuming. Benefitting from the broad range of expertise within CARIM, he aims for a complete overhaul of the treatment of stroke patients, and those at risk.

As a Professor of Pharmacology and Personalized Medicine, Schmidt works in a young and exciting research field in which medical therapies are developed for individual patients, based on their own genes.
“Personalized medicine is the next major leap forward in medicine,” Schmidt explains. ‘It is already used to some degree in oncology. Now it needs to enter all other major disease areas, including cardiovascular.”

“We have been content with 19th/20th century disease definitions and treatment of the masses for too long,” he continues. “Currently there is only one therapy available for stroke patients, and it is administered to just ten percent of the patients. The drug that is used dissolves blood clots and is considered too risky for many patients, because it can cause bleeding. So there is a huge need for new therapy.”

Reducing brain damage

Schmidt’s research efforts focus on protecting neurons and repairing damage after a stroke. “Our hottest new drug target is a mechanism that seems to be neuroprotective after a stroke,” says Schmidt. In 2010, he discovered that by inhibiting the production of hydrogen peroxide, also known as bleach, in the brains of mice with a new drug, brain damage was reduced considerably, even when the medicine was administered hours after the stroke.

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‘I spent a lot of time talking to other colleagues, it slows you down in the short term, but I believe I will benefit from it in the long run’

Harald Schmidt

"We concentrate a lot of our energy on validating whether this drug is really feasible and we are aiming to conduct clinical trials as soon as possible," Schmidt states. He is hopeful that his newfound drug and similar therapeutics will help many patients who suffer from a stroke, other cardiovascular conditions, and perhaps even those with cancer, Parkinson's or Alzheimer's.

He emphasizes that the medicine is not an antioxidant. "Many people take antioxidants, but we don't believe in them. While oxyradicals are found to be harmful in some parts of the body, they also have benefits. We seek to stop them from causing damage without inhibiting their positive role," he explains.

Nutriceuticals

While the drug development is a major aspect of their work, Schmidt and his team are also developing new biomarkers and conducting a clinical study on so-called nutriceuticals. Schmidt: "These are not drugs, but nutritional additives of compounds that are part of a normal diet – but then in slightly higher amounts than normal. These seem to have beneficial effects in peripheral artery disease." One example Schmidt mentions is a type of amino acid that is naturally found in watermelons.

Support

Although there is still no guarantee, Schmidt hopes that the work will eventually lead to new therapies consisting of either drugs or nutriceuticals, or both, depending on the patients needs. It is this kind of 'frontier research' the ERC wants the best and brightest scientists in Europe to engage in. Schmidt: "I guess the grant from the European Research Council is a statement that you belong to a top percentile of researchers in Europe and gives me some degree of freedom to conduct high risk / high potential benefit research for five years without worrying too much about funding."

To achieve his ambitions, he can count on the support of a broad range of experts within CARIM. It is this availability of almost every method or know-how needed to address every cardiovascular research problem that makes CARIM a great place to work, according to the German native, who joined CARIM in 2010 from a professorial and associate dean position at the Australian Monash University, which is among the top 30 in the world.
He has purposely invested time to get acquainted with his colleagues in order to build a personalized medicine platform at Maastricht University. "The first year, I spent a lot of time talking to other colleagues", he says. "It slows you down in the short term, but I believe I will benefit from it in the long run."

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.

EUROPEAN RESEARCH COUNCIL GRANTS

Professor **Harald Schmidt**, chairman of the dept. of Pharmacology and PI, received a prestigious Advanced Investigator Grant from the European Research Council. ERC Advanced Grants allow exceptional established researchers leaders to pursue ground-breaking, high-risk projects that open new directions in their respective research fields or other domains. The next five years Schmidt will receive about 2.3 million Euros to conduct his 'RadMed' project: Radical Medicine: Redefining Oxidative Stress. (Read the full interview on page 38).

Professor **Jan Staessen** (dept. of Epidemiology) received an Advanced Research Grant from the European Research Council for his project: "Subclinical left ventrikel dysfunction in the general population."

NWO VENI

In July 2011 the Netherlands Organization for Scientific Research (NWO) granted a VENI fellowship to **Kristiaan Wouters** (dept. of Internal Medicine, supervisor Prof. Casper Schalkwijk). Kristiaan received this 250 K€ grant to conduct his fundamental research project on "The obesity-induced macrophage: a new player in atherosclerotic development." Obesity is an independent risk factor for atherosclerosis, but the exact mechanistic link between these conditions is unknown. Parallel to atherogenesis, obesity induces the recruitment of pro-inflammatory macrophages from bone marrow to adipose tissue (AT). In his project, Wouters hypothesizes that obesity-induced macrophages, through interactions with AT-derived free fatty acids (FFAs), are important players in atherosclerosis development and thereby represent the key link between these conditions. By determining the effects of obesity-induced macrophages on the development of atherosclerosis and thus unravel the mechanistic link between these conditions. The results will identify new clinical markers that indicate which obese patients are at particular risk to develop atherosclerosis and can identify new therapeutic targets.

ZonMW Clinical Fellowship

In June 2011 the Netherlands Organisation for Health Research and Development (ZonMW) has granted Dr **Kevin Vernooy** (dept. of Cardiology) a Clinical Fellowship for his project proposal entitled "Synchronous ventricular pacing using novel left ventricular septum pacing site." The Clinical Fellows program is intended for physicians who have completed the AGIKO route (MD clinical research trainee) or a similar route to build and further expand their clinical research career. The Clinical Fellowship is an individual grant with a prestigious character, tailored to the specific situation of the clinician. For a period of 3-5 years, Vernooy is partly exempted from clinical responsibilities so that he can carry out scientific research on a part-time basis and set up his own line of research.

NWO Mosaic Scholarship

FHML Iranian student **Siamack Sabrkhany** was one of the nineteen winners to receive a 200,000 Euro PhD research scholarship. In his research project Sabrkhany will examine the role platelets play in tumor growth. In total, 156 students and graduates responded to the NWO's call for research proposals. The committee decided to subsidize 19 of the 44 nominated and submitted proposals. Siamack Sabrkhany was born in Iran and moved to the Netherlands at the age of twelve. Sabrkhany obtained his pre-medicine bachelor's degree in Orlando, Florida and graduated at Maastricht University with a FHML Bachelor in Molecular Life Sciences. He is currently busy completing the Physician-Clinical Investigator master's program.

NHS E. Dekker Program
In the framework of the E. Dekker program of the Dutch Heart Foundation, Dr **Judith Cosemans** (dept. of Biochemistry, program Clinical Aspects of Atherotrombosis) obtained a personal Post-doc grant. This grant will enable Cosemans' study of the roles of platelet-derived matrix metalloproteinase on vascular remodeling. (Read the full interview on page 13).
The 2006-Dekker Grant of **Isabel Ferreira** (dept. of Epidemiology/KEMTA) was extended with another two years to a Senior Post-doc position.
Bas de Laat (dept. of Biochemistry/SYNAPSE BV) also got an extension of his NHS Post-doc stipendium.

CVON
Just before the end of 2011 Professor **Leon de Windt** and Professor **Stephane Heymans** (both dept. of Cardiology) received a confirmation of their successful CVON (Cardiovasculair Onderzoek Nederland) grant application on the ARENA study. CVON is a mutual initiative of the NHS, KNAW, NWO/ZonMW and NFU officially started in 2011, which aims to improve the national and international position of cardiovascular research in the Netherlands by supporting large and strong research themes. The ARENA project, acronym of Approaching Heart Failure By Translational Research of RNA Mechanisms, is a cooperation between principal investigators of five University Medical Centers in the Netherlands; AMC Amsterdam, Maastricht UMC+, UMCG Groningen, VUMC Amsterdam, and Erasmus MC Rotterdam. Professor De Windt and Professor Pinto (AMC) will be the research coordinators of this consortium. (Read the full interview on page 25).

Kootstra Fellowships
June 2011, in the first round of the Kootstra Talent Fellowships 2011, three out of four fellowships were granted to young CARIM researchers. The Kootstra Talent Fellowships are granted to young scientific talents by the Board of Maastricht UMC+ with the aim to support developing their scientific careers.
In the category 'Talented future Postdocs' the FHML Research Council (COB) granted **Julian Ilcheff Borisoff** (applicant Prof. Hugo ten Cate, dept. of Biochemistry).
In the category 'Talented student/future PhD' **Bart Spronck** (applicant Prof. Tammo Delhaas, dept. of Biomedical Engineering) and **Siamack Sabrkhany** (applicant Dr Mirjam Oude Egbrink, dept. of Physiology) both received a fellowship.
In the second round of the Kootstra Talent Fellowships 2011, three fellowships were granted to CARIM researchers; Yanti Octavia, Katrien Gaens and Petra Erkens.
Katrien Gaens (applicant Prof. Casper Schalkwijk, dept. of Internal Medicine) was rewarded in the category 'Talented future Post-docs'. In the category 'Talented student/future PhD' **Yanti Octavia** (applicant Dr An Moens, dept. of Cardiology) received a fellowship/pre-PhD grant.
Petra Erkens (applicants Prof. Martin Prins, CAPHRI and Prof. Hugo ten Cate, CARIM) has a double appointment at CAPHRI and CARIM.

OTHER AWARDS, PRIZES AND GRANTS

In 2011 many CARIM researchers were awarded with prizes and travel grants. Below some of them will be highlighted.

Dutch Thrombosis Foundation
Dr **Elisabetta Castoldi** received a research grant from the Dutch Thrombosis Foundation for the project 'Modulation of thrombin generation and activity by total fibrinogen and fibrinogen γ. Amount: € 140.000.

Folkow Award for Hypertension Research
May 2011, Professor **Peter de Leeuw** (dept. of Internal Medicine) received the Folkow Award 2011. The award is an annual prize for a clinical scientist who distinguished himself in the field of hypertension research. The Folkow Award is the most prestigious European award in this research field.

Willy van Heumen Prize and BACH Award
August 25 2011, Professor **Johan Heemskerk** accepted the Willy van Heumen Prize from the 'Fund for the Promotion of Animal Testing Alternatives Foundation'. The Willy van Heumen-prize is awarded every two years to a person or institution who or which 'has especially deserved it for further restricting animal testing for medical reasons to strictly necessary experimentation, and that alternatives to the use of animal testing are utilized as well as possible.' Heemskerk has been awarded the prize, consisting of 25,000 Euros, for his research into in-vitro models for detecting risk factors for heart attacks and hemorrhages. The prize has been presented during the eighth World Congress on Alternatives and Animal Use in the Life Sciences in Montreal, by Professor Bert van Zutphen. Again in August, **Johan Heemskerk** was awarded the Investigator Recognition Award of the Biennial Awards for Contributions to Hemostasis, in recognition for his significant contribution to research and education in blood coagulation.

The Pier Mannucci Award
From the same research group, post-doc Dr **Judith Cosemans** was given a Mannucci award for her paper 'Potentiating role of Gas6 and Tyro3, Axl and Mer (TAM) receptors in human and murine platelet activation and thrombus stabilization.' The Pier Mannucci prize is awarded in honour of Pier M. Mannucci, the first Editor-in-Chief of the Journal of Thrombosis and Hemostasis, for the best articles by Young Investigators under 35 years. In the paper, using several approaches including flow chamber technology Dr. Cosemans has shown that plasma Gas6, by signaling via the three TAM receptors on the platelet surface, enhances thrombus stabilization. Herein, the Gas6-TAM activation pathway synergizes with ADP-P2Y12 activation by signaling via hosphoinositide 3-kinase and Akt.
(Read the full interview with Johan Heemskerk, Judith Cosemans and their colleagues on page 13).

LNVH Jubilee Prize
In September 2011 Professor **Esther Lutgens** (dept. of Pathology) received the jubilee prize of the Dutch Network of Women Professors LNVH. Lutgens, extraordinary professor of Immunopathology of the vessel wall, received the 5.000 Euro prize because she is an "absolutely outstanding scientist" within the cohort of young and female professors in the Netherlands. The LNVH aims to promote the proportionate representation of women within the university community and celebrates its tenth anniversary this year.
Unfortunately, Lutgens left Maastricht in October, to find new research challenges at the University of Amsterdam/AMC.

EVENTS AND HIGHLIGHTS

Between Lab and Life: CARIM in the community
On Saturday November 5, 2011 CARIM, together with the Netherlands Heart Foundation, organized an open day entitled “Between Lab and Life”. This thematic public meeting is part of a national series about scientific research into cardiovascular diseases. With these public meetings the NHS aims to introduce a large public into the world of scientists and their work. Around 175 visitors came to Maastricht UMC+, where they could walk through a gigantic heart (eight meters wide and six feet high), meet the researchers in the CARIM labs and attend a public lecture of Professor Tammo Delhaas on ‘the mirrored heart’.

People and Acknowledgements
In 2011 several colleagues made a step in their scientific careers, were awarded with a Royal distinction or left our institute.

On January 1, 2011 Dr **Uli Schotten** (Dept. of Physiology) was appointed as Extraordinary Professor of Cardiac Electrophysiology. His inauguration took place on October 13. Furthermore, on January 2, Professor Schotten was formally appointed as technical field manager in the EUTRAF initiative. EUTRAF is a European multidisciplinary consortium of expert groups involved in atrial fibrillation research and consists of academic research groups and industry partners.

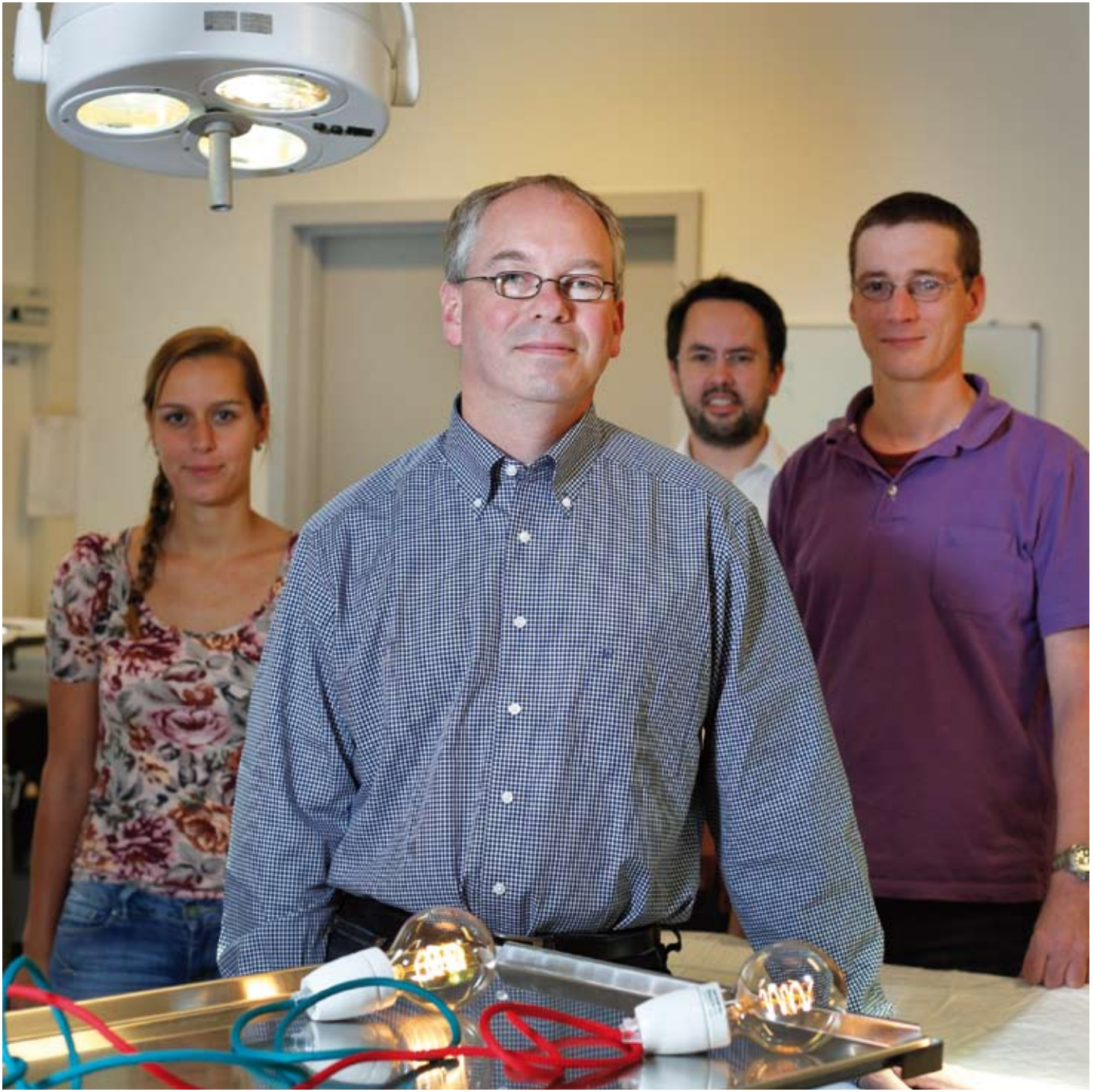
On the first of March 2011, Dr **Esther Lutgens** (Dept. of Pathology) was appointed as Extraordinary Professor Pathology, in particular Immunopathology of the Vascular Wall. Unfortunately Lutgens left our institute in October, to face new challenges at the University of Amsterdam/AMC. At the end of March, a farewell reception for Professor **Mat Daemen** took place. From April 1, 2011 Professor Daemen has been appointed staff member in the Department of Pathology of the AMC-UvA in Amsterdam. After the departure of Daemen, Professor **Mark Post** (Dept. of Physiology) took over de chair of our institute on a temporarily basis.

From April 1, 2011 VIDI laureate Dr **Dietbert Neumann** has been appointed Associate Professor in the Department of Genetics and Cell Biology. Neumann’s research is mainly focused on the integration of cellular metabolism into the protein kinase signaling work.
On April 29, 2011 one of our former PI’s and CARIM member of the first hour Professor **Maurits Allessie** has been awarded the distinction of ‘Knight of the Order of the Netherlands Lion’, an important royal order in the Netherlands, for his contributions to science.

From May 1, 2011 Dr **Gerry Nicolaes** (Dept. of Biochemistry) has been appointed as Associate Professor and on June 1, 2011 Dr **Paul Volders** (Dept. of Cardiology) received an appointment as Associatie Professor.

June 30, 2011 the official inauguration of Professor **Leon de Windt** (Dept. of Cardiology) took place.

In July 2011 Dr Ir **Walter Backes** (Dept. of Radiology) has been appointed as Associate Professor. From July 1, 2011 biochemist Professor **Casper Schalkwijk** (Dept. of Internal Medicine) has been appointed as Extraordinary Professor ‘Experimental Internal Medicine’. Dr **Mirjam Oude Egbrink** (Dept. of Physiology) was appointed acting Scientific Director of the Institute for Education of the FHML.



CARIM prominent in European study on atrial fibrillation

‘CARIM has the capacity to perform high quality translational research’

Atrial Fibrillation (AF) is on the rise in Europe because of its ageing population. Therefore, the European Union has allocated 12 million euros for integrated research into the disease mechanisms and to develop better diagnostic tools and new therapies for AF patients. Professor Uli Schotten has secured a leading role for CARIM in this international project.

Together with Professor John Camm (University of London) and Professor Stephane Hatem (INSERM, Paris), Schotten has been instrumental in forming the European Network for Translational Research in Atrial Fibrillation (EUTRAF) in order to submit a competitive, joint research proposal to the EU. “Ahead of the EU call for proposals, we noticed the development of a number of potential consortia. We thought it would be better to combine these in one joint application,” says Schotten.

They managed to convince their colleagues of their idea and EUTRAF was subsequently successful in securing the EU funding. About seventy representatives from fifteen academic institutions and three commercial enterprises are involved in the project. The work is split up in eight work packages, each focusing on a particular aspect of AF. Camm, Hatem and Schotten coordinate the research activities within the consortium.

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‘It is very important to be part of such large networks’

Uli Schotten

"We are responsible for the scientific quality of the research," explains Schotten, who has been appointed as Technical Field Manager. "I monitor progress, make sure that there is sufficient scientific coherence within the network, and that we take advantage of synergy effects. Flexibility is important. You need to have a plan, but you also need to be prepared to make adjustments."

Strong contribution

In addition to his coordinating duties, Schotten is in charge of the work package that has been allocated to CARIM. It entails studies into finding new diagnostic tools for AF. "Atrial fibrillation is heterogeneous disease," Schotten says. "There are many mechanisms that can lead to AF. We are looking at a large number of diagnostic tools, including electrophysiological techniques and imaging, but also biochemical and genetic markers, in order to detect the prevailing disease mechanism in an individual patient. And we are studying how these findings can be translated into a strategy to treat atrial fibrillation using a patient-tailored approach."

About ten scientists, with a wide range of expertise, are involved in CARIM's work for the EUTRAF project. Professor of Cardiac Electrophysiology Schotten and his team have a reputation for excellent basic research. With professor and cardiologist Harry Crijns on board, the other end of the spectrum, clinical research, is represented at the highest level, according to Schotten.
In his view, it is this vast experience and know how regarding anything from imaging and biomarkers to animal models and clinical studies that make CARIM such a strong contributor to the network. "CARIM undoubtedly has the capacity to perform high quality translational research," he states.

International visibility

Schotten is convinced that it is vital for CARIM to participate in consortia such as EUTRAF. The project does not only provide funding, but also enhances the institute's reputation by giving it international visibility. "It is very important to be part of such large networks, because science has become more multidisciplinary and is currently performed on a larger scale. Small, individual projects no longer have much chance of receiving any funding. As it is simply impossible for a single organization to have all the expertise on board that is necessary for innovative research, alliances with other partners have become essential," Schotten concludes.

03_
TRAINING AND EDUCATION

DEVELOPMENTS

Start of a new CARIM PhD program

In 2010 a new PhD program was developed. The plan was extensively discussed in the Education Program Committee and presented to the School Council. After approval by the CARIM Board the new plan was implemented in 2011.
The cornerstone of the new program is to offer a more structured and transparent training program, that is attractive and challenging for CARIM's next generation researchers. It focuses on both the research component and the acquisition of (cardiovascular) knowledge, skills and competencies. This also includes competencies and skills that are of use in the next step in the career of the PhD, the so-called transferrable skills.

CaRES Plan launched

The PhD training program is formalized in the **Ca**RIM **R**esearch, **E**ducation and **S**upervision plan. This CaRES plan encompasses;
a general part describing the rights, duties, and tasks of the PhD and the supervisors. This part has to be signed by all parties, including the human resource manager;
the **Research plan,** in which the research aims, experimental approach, work plan and timeline of the project are specified;
the **Education plan,** which demands that the PhD will invest in his training. In the Education plan, all courses and activities, including the participation in scientific meetings, the supervision of interns, teaching activities, that will be followed to meet this goal, are specified;
the **Supervision plan,** describing how the supervision of the PhD is organized, specifying the role of each (co) supervisor. Also, the members of the mentoring committee are appointed. The mentoring committee meets with the PhD student on an annual basis to assess the progress of the research and the scientific performance of the PhD.

The CaRES plan has to be drafted in the first months after the start of the appointment and is designed to be a tailored and flexible plan, allowing adjustment during the course of the PhD trajectory. An important additional goal of the CaRES plan is to increase the transparency among all stakeholders, which is the PhD, his supervisor(s) and CARIM.

National guidelines for PhD programs

In the second half of 2011 two guidelines for PhD programs were issued, one by the Netherlands Federation of University Medical Centers (NFU) and the other by ORPHEUS (Organization for PhD Education in Biomedicine and Health Sciences in the European System). It is of note that the CaRES PhD program turns out to be in line with their recommendations, both in terms of total load of the education program (25 ECTS), the attention for transferrable skills, and the transparency and flexibility of the PhD training program. This strengthens us in our feeling that the new CARIM PhD program is up to date and meets the current criteria for a high quality PhD training program.

First CARIM Summer Course

Along with the shaping of our new PhD training program, the set-up and contents of CARIM's cardiovascular courses were drastically renewed. As a collaborative effort from many of our PI's and with the valuable input of various members from the Department of Educational Development & Research, the first CARIM Summer Course was organized in the first week of July 2011. The course week consisted of six parallel courses, covering all aspects of CARIM's research, alternated with a combined scientific program and a social program organized in part by I'MCARIM, the organization of CARIM's PhD's. Nearly 60 PhD's and Research Master students participated and highly appreciated the quality and instructiveness of the courses and the ability to interact with fellow PhD's and staff members. The success of the first CARIM course week is a big stimulus to continue with this new format. ■

RESEARCH MASTER

In 2011, the Faculty of Health, Medicine and Life Sciences (FHML) has decided to end the individual school research master programs and to integrate these programs in a newly designed FHML Master 'Biomedical Sciences'. However, this new master still allows specialization in the research disciplines of the several FHML Schools. As a consequence in September 2011, no new first year students could enroll the CARIM research master 'Cardiovascular Biology and Medicine' (CBM). Students then entering the second year of the CBM master program were allowed to accomplish their CBM master.

In the new Biomedical Sciences program, Master students are informed about the FHML research school programs in the first half year by attending school-specific lectures and parallel programs. In the second half year students are offered a 2 week elective course program organized by the schools. This allows them to make up their mind about the school of choice to specialize their practical research training. When students choose for CARIM, a notification of cardiovascular specialization will be mentioned on their Master's certificate.

August 2011 eight students received their Research Master's degree, and four of them continued in a PhD-program within our institute. ■

Graduates CARIM Research Master's in CBM in 2011

Pranali Buch
Sophie Deckx
Kevin Hermans
Robin Hermans
Linda Korthout
Romy Kremers
Victor Lamin
Yanti Octavia

PhD PROGRAM

Our PhD program is accessible for students of the UM Research Master Molecular Life Sciences, or for excellent students from other national or international biomedical Masters. At the end of 2011, 141 PhD students attended our PhD program.

Number of PhD students at 31.12.2011

Funding source	PhD students 2008	PhD students 2009	PhD students 2010	PhD students 2011
University	28	28	31	48
NWO	7	6	8	14
Non-profit + Industry	58	62	78	79
TOTAL	**93**	**96**	**117**	**141**

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 14 PhD students who are labeled as EuCAR PhD. Each PhD project is supervised by at least one investigator from IMCAR, Aachen and one from CARIM, Maastricht. EuCAR students will obtain a PhD in Aachen as well as in Maastricht. For an interview with one of our EuCAR PhD's, Annette Christ, see page 65. ■

PhD DELIVERABLES

In 2011 27 PhD students finished their theses within our institute, and 6 theses were externally prepared. The table below illustrates the numbers of PhD students in the years 2006-2011, related to the period in which they obtained their degree. The graphics on pages 19-21 present the number of PhD theses on the level of our research themes.

PhD student careers from 2006 till 2011

Year intake	2006	2007	2008	2009	2010	2011
Cohort volume (annual intake)	23	28	26	41	38	40
Male	8	16	14	23	15	24
Female	15	12	12	18	23	16
PhD from abroad	6	7	9	19	16	13
Thesis completed	15	1	0	0	-	0
Drop out	4	1	4	5	-	1
Drop out > 1 year	3	0	2	2	2	0
Average duration (in months)	50	45	-	-	-	-
Ongoing	6	26	22	36	36	39

CARIM THESES IN 2011

Moret K –
The role of technological advances in sodium prescription and adequacy assessment during hemodialysis
Promotor: Prof Dr K Leunissen
Co-promotor: Dr J Kooman
Maastricht University, January 21, 2011

Kubben N –
Lamin interA/Ctors: from the premature to senescence
Promotor: Prof Dr Y Pinto
Promotores: Dr J Voncken, Dr T Mistelli (Bethesda, USA)
Maastricht University, January 26, 2011

Verkaar F –
Pharmacological characterization of wnt/frizzled signaling
Promotor: Prof Dr J Smits
Co-promotores: Dr M Blankesteijn, Dr G Zaman
Maastricht University, February 10, 2011

Dennert R –
Idiopathic cardiomyopathies: the role of virus persistence and immune-mediated disease
Promotores: Prof Dr S Heymans, Prof Dr H Crijns
Co-promotor: Prof Dr J Cohen Tervaert
Maastricht University, February 25, 2011

Verstraeten V –
Nuclear structure at the crossroad of premature aging and lipodystrophy
Promotor: Prof Dr FCS Ramaekers
Co-promotores: Dr JLV Broers, Dr MAM van Steensel
Maastricht University, March 3, 2011

Cranenburg E –
Circulating Matrix Fla-protein: a biomarker for vascular disease
Promotor: Prof Dr J Rosing
Co-promotores: Dr C Vermeer, Dr L Schurgers
Maastricht University, March 17, 2011

Duckers C –
Modulators of bleeding tendency in severe factore V deficiency
Promotor: Prof Dr J Rosing
Co-promotor: Dr E Castoldi
Maastricht University, March 24ζε, 2011

Gaens K –
The Nε- (Carboxymethyl)lysine-RAGE axis; Implications for the pathogenesis of obesity-related complications
Promotor: Prof Dr C Stehouwer
Co-promotor: Dr C Schalkwijk
Maastricht University, April 1, 2011

Nabben M –
Uncoupling protein 3 and the protection of skeletal muscle mitochondrial function; a transgenic approach
Promotores: Prof Dr LP Schrauwen, Prof Dr J Glatz
Co-promotor: Dr J Hoeks
Maastricht University, April 20, 2011

Caolo V -
VEGF and NOTCH in Blood Vessels, an Intricate and Fascinating Interplay
Promotor: Prof Dr M Post
Co-promotor: Dr D Molin
Maastricht University, May 11, 2011

CARIM THESES IN 2011

Brouwers O -
Intracellular glycation and endothelial dysfunction; role of methylglyoxal
Promotores: Prof Dr CDA Stehouwer, Prof Dr JGR De Mey
Co-promotor: Dr CG Schalkwijk
Maastricht University, May 18, 2011

Groeneweg HM -
Macrophages and modified lipoproteins: modulation of inflammation?
Promotor: Prof Dr MH Hofker
Co-promotor: Dr MPJ de Winther
Maastricht University, May 20, 2011

Loon van MM –
Cannulation practise and complications in hemodialysis vascular access
Promotor: Prof Dr PJEHM Kitslaar
Co-promotores: Dr J Tordoir, Dr F van der Sande
Maastricht University, May 26, 2011

Bekkers SCAM -
Assessment of injury in reperfused acute myocardial infarction using cardiovascular magnetic resonance imaging
Promotores: Prof Dr APM Gorgels, Prof Dr J Waltenberger
Maastricht University, June 1, 2011

Nergiz-Unal R -
Platelets in atherothrombosis - roles of CD36 and P2Y12 receptors
Promotor: Prof Dr JWM Heemskerk
Co-promotor: Dr J Cosemans
Maastricht University, June 23, 2011

Rennenberg R -
Vascular Calcifications and Matrix Gla Protein in Hypertensive Subjects
Promotor: Prof Dr PW de Leeuw
Co-promotores: Dr AA Kroon, Dr LJ Schurgers
Maastricht University, July 6, 2011

Martherus SRM -
Pulsing response of the cardiac transcriptome
Promotores: Prof Dr HJM Smeets, Prof Dr JPM Geraedts
Co-promotor: Dr TAY Ayoubi
Maastricht University, September 7, 2011

Jaspers K -
MRI of the therapeutic neovascularization: morphology & function
Promotor: Prof Dr MJ Post
Co-promotores: Dr Ir WH Backes, Dr T Leiner
Maastricht University, September 9, 2011

Jacobs M -
The Metabolic Syndrome and Cardiovascular Disease: The CODAM study
Promotor: Prof Dr CDA Stehouwer
Co-promotores: Dr MM van Greevenbroek, Dr CJ van der Kallen
Maastricht University, September 29, 2011

Hanssen SJP -
Hemolysis, microcirculatory changes and organ injury induced by cardiovascular surgery
Promotores: Prof Dr MJHM Jacobs, Prof Dr WA Buurman
Maastricht University, September 30, 2011

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CARIM THESES IN 2011

Steinbusch LKM –
CD 36; a target to restore cardiac function in type 2 diabetes
Promotores: Prof Dr JFC Glatz, Prof Dr M. Diamant, VUA
Co-promotores: Dr JFP Luiken, Dr DW Ouwens
Maastricht University, October 13, 2011

Meens MJPMT –
Interactions between ET-1 and CGRP in resistance arteries
Promotor: Prof Dr JGR De Mey
Maastricht University, October 19, 2011

Verjans JWH –
Molecular imaging of acute and healing myocardial infarction
Promotor: Prof Dr L Hofstra
Maastricht University, December 14, 2011

Stevens KNJ –
Blood-contacting biomaterials for critical clinical applications
Promotores: Prof Dr JG Maessen, Prof Dr LH Koole
Maastricht University, December 15, 2011

Jonk AM –
Microvascular actions of insulin: studies on the interaction with angiotensin II and on the postprandial state
Promotores: Prof Dr CDA Stehouwer, Prof Dr P de Leeuw
Co-promotor: Dr AJHM Houben
Maastricht University, December 15, 2011

Houben F –
Nucleo-cytoskeletal interactions in the mechanical functioning of the cell
Promotores: Prof Dr FCS Ramaekers, Prof Dr LH Snoeckx
Co-promotor: Dr JLV Broers
Maastricht University, December 20, 2011

Kilinc E –
Effects of air pollution on haemostasis and atherosclerosis
Promotor: Prof Dr H ten Cate
Co-promotor: Dr H Spronk
Maastricht University, December 22, 2011

PHD THESES EXTERNALLY PREPARED

Soliman Hamad M –
Surgical revascularization in patients with left ventricular dysfunction, management and predictors of outcome
Promotores: Prof Dr O Penn, Prof Dr O Zundert
Co-promotor: Dr A van Straten
Catharina Hospital, January 21, 2011

Sarabi A –
Structural and functional characterization of the interactions of platelet-derived chemokines CCL5, CXCL4 and CXCL4L1
Promotores: Prof Dr C Weber, Prof Dr R Fischer
Co-promotor: Dr R Koenen
RWTH Aachen, January 31, 2011

Warringer J –
Automatische intrathorakale Impedanzmessung bei Patienten mit Herzinsuffizienz und biventrikulärer ICD-Therapie – Behandlungsalgorithmus
Promotor: Prof Dr K. Leonhardt
Co-promoteres: Dr G. Muehlenbruch, Dr Ch. Knackstedt
RWTH Aachen, March 29, 2011

Busch J –
Die Auswirkung von Kraft- und Gleichgewichtstraining bei sehr alten Patienten nach Bypass-Operation auf die funktionale Kapazität, die Lebnsqualität und die Aktivitäten des täglichen Lebens
Promotor: Prof Dr B. Bjarnason-Wehrens
Co-promotores: Dr D. Willemsen, Dr C. Knackstedt
Deutsche Sporthochschule Köln, July 12, 2011

Klem TMAL –
Venous cry surgery of the leg
Promotor: Prof Dr CHA Wittens
Co-promotor: Dr A van der Ham
Maastricht University, September 29

Kats S –
Alkaline phosphatase. An old enzyme newly discovered. Implications in cardiac surgery
Promotores: Prof Dr W Seinen, Prof Dr JG Maessen
Co-promotores: Dr JPAM Schönberger, Dr W van Oeveren
University of Utrecht, November 25, 2011

PhD AWARD 2011

June 22, 2011 four students of the CARIM Research Master Cardiovascular Biology and Medicine defended their project ideas to compete for a CARIM-funded PhD position. Sophie Deckx, Yanti Octavia, Kevin Hermans and Robin Hermans all defended their project proposal. The jury ranked the presentation of Sophie Deckx “Increased WARP causes heart failure. Unravel its biological role to target ischemic and hypertensive heart disease” as the winning project (Supervisors: Prof. Stephane Heymans and Dr Anna Papageorgiou, Dept. of Cardiology). ■

Sophie Deckx winner of the CARIM PhD Award 2011

CARIM THESIS AWARD 2009-2010

Dr Susanne van den Borne received the CARIM Thesis Award 2009-2010 at the CARIM Symposium on Wednesday November 9. This award is given biannually for the best thesis written by a CARIM PhD student. Suzanne conducted her research in the department of Pharmacology under the supervision of promotor Prof. Jos Smits, and co-promotores Prof. Mat Daemen and Prof. Matthijs Blankesteijn. In her thesis ‘Myocard infarct healing – rupture and remodeling’, Susanne studied the process of myocardial infarct healing which sometimes is complicated by infarct rupture and/or heart failure. She discovered that alterations in the cadherin/catenin cell adhesion complex and the subsequent excessive inflammation may result in post-infarct rupture. Furthermore she found that myofibroblasts (cells that have characteristics of both fibroblast and smooth muscle cells) are essential for development of heart failure and can be visualized by molecular imaging. The project of Susanne resulted in three publications in the Journal of American College of Cardiology, one in Cardiovascular Research, one in Cardiovascular Pathology, and a review in Nature Reviews Cardiology. ■

Professor Jan Willem Cohen Tervaert, chairman of the jury, hands over the CARIM Thesis Award 2009-2010 to Dr Susanne van den Borne

KNOWLEDGE TRANSFER

CARIM Lecture Series, Cardiovascular Grand Rounds and symposia

The CARIM Lecture series, the Cardiovascular Grand Rounds Maastricht and the yearly CARIM Symposium are means to update the knowledge of our graduate students, our researchers and other external people with interest in the field of cardiovascular research. In 2011 eight lectures were organized in the CARIM Lecture Series. The successful Cardiovascular Grand Rounds Maastricht initiative that started October 2009 has been given follow-up in 2011. Three lecture series were organized, with cardiovascular lectures on a weekly basis. For the full programs please visit www.carimmaastricht.nl, 'CARIM Lectures' in the 'Education' section.

On June 17, 2011 Dr Eline Kooi (Dept. of Radiology) organized a mini-symposium on micro-MRI entitled "A non-invasive window in tissue morphology, function and metabolism".

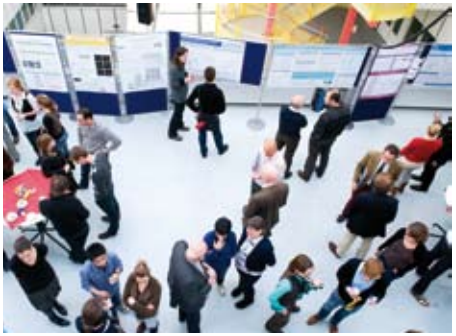
On june 30, 2011 Prof dr Leon de Windt (dept. of Cardiology) organized a mini-symposium on microRNA entitled "microRNAs in Cardiovascular Disease".

CARIM SYMPOSIUM 2011

On November 9, the nineteenth annual scientific symposium was held in Maastricht. Prof. Dr W. Ouwehand from the University of Cambridge joined us to speak out the Robert Reneman Lecture 2011: 'From a reductionism to a systems view of the formation and function of platelets'. Professor Ouwehand is professor of Experimental Hematology and leads a group studying megakaryocyte and platelet biology in thrombus formation and arterial haemostasis. Professor Ouwehand also holds an honorary Consultant Haematologist appointment at NHS Blood and Transplant in Cambridge. Besides the traditional poster sessions during lunch time, several CARIM researchers presented their current research project; CARIM PhD Award winner 2011, Sophie Deckx, presented her 'WARP-project' and VIDI laureate Dr Dietbert Neumann (Dept. of Genetics and Cell biology) explained glycogen-targeting of AMP-activated protein kinase in a lecture entitled 'Regulated sugar for my sweetheart'. Post-doc and pediatrician Dr Ward Vanagt presented a lecture on the reduction of ischemia/reperfusion injury by pre- and post conditioning, Dr Judith Cosemans (Dept. of Biochemistry) gave a lecture on the role of platelets in vascular remodeling, and Dr Jan Bucerius (Dept. of Radiology/Nuclear Medicine) explained the audience something about PET/CT imaging of vessel wall changes and identifying patients at risk.

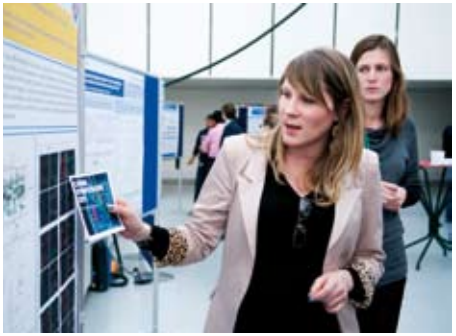









CARIM
SYMPOSIUM
2011




CARIM LECTURE SERIES 2011

DATE: 04.01.2011
LECTURER: Dr D Fuchs, Visual Sonics, The Netherlands
LECTURE TITLE: High-frequency ultrasound for imaging cardiovascular disease in mice and rats
Organizer: Dr Ben Janssen, Dept. of Pharmacology

DATE: 19.01.12
LECTURER: Prof. Dr P Leenen, University of Rotterdam, The Netherlands
LECTURE TITLE: Development of macrophages and DC in inflammation: regulation of M-CSF receptor expression
Organizer: Dr Menno de Winther, Dept. of Molecular Genetics

DATE: 01.06.2010
LECTURER: Dr K Hoebe, College of Medicine, University of Cincinnati, USA
LECTURE TITLE: Colitis development in Gimap5-deficient mice; a crash course towards loss of immunological tolerance
Organizer: Prof. Erik Biessen, Dept. of Pathology

DATE: 09.06.2011
LECTURER: Dr J Lindeman, Leiden University Medical Center, The Netherlands
LECTURE TITLE: The natural history of atherosclerosis in man: a systematic evaluation on aorta patches from donated kidneys
Organizer: : Prof. Erik Biessen, Dept. of Pathology

DATE: 22.08.11
LECTURER: Dr R Boon, Goethe Universitätsklinikum, Germany
LECTURE TITLE: The role of age-regulated microRNAs in cardiovascular diseases
Organizer: Prof Erik Biessen, Dept. of Pathology

DATE: 26.10.11
LECTURER: Dr J van Gils, New York University School of Medicine, USA
LECTURE TITLE: Netrin-1: a novel immune cell modulator that promotes atherosclerosis
Organizer: Prof Erik Biessen, Dept. of Pathology

DATE: 29.11.11
LECTURER: Prof. GRY De Meyer, University of Antwerp, Belgium
LECTURE TITLE: A novel plaque rupture model in mice
Organizers: Dr Judith Sluimer and Prof. Erik Biessen, Dept. of Pathology

DATE: 20.12.11
LECTURER: Prof S Ylä-Herttuala, University of Eastern Finland
LECTURE TITLE: VEFG gene transfers: from basic science to clinical applications
Organizers: Dr Judith Sluimer and Prof. Erik Biessen, Dept. of Pathology

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Impression of the CARIM Symposium 2011

CARIM provides solid career foundation

‘Gaining international experience is an integral part of our program’

Maastricht may be known for its easy pace of life, but earning a PhD at CARIM is far from a walk in the park. Doctoral students Yvonne Oligschläger (see picture page 62) and Anette Christ (see picture page 64) are not complaining though. The two young scientists are confident that their scientific careers will benefit from the solid foundation CARIM is providing.

First-year student Yvonne was surprised she had to hand in a detailed 4-year research, education and supervision plan within her first six weeks at CARIM. “I had never even heard of such a plan,” Yvonne recalls. “It is unique to CARIM. The CaRES-plan forces you to clarify what you are going to do, when, and how. I like the structure it provides. When you go to the lab, for example, you know exactly what and how you are going to investigate.”

The CaRES-plan also urges PhD students to plan ahead for the 25 ECTS points they need to earn through coursework, attending conferences and lectures, teaching, and supervising interns. Yvonne: “Some students may be taken aback by this requirement - not all programs have it. But in my view, it helps us to become independent researchers. To me, working on a PhD is all about preparing for the rest of my scientific career. So it has to involve more than just sitting in a lab and doing my research.”

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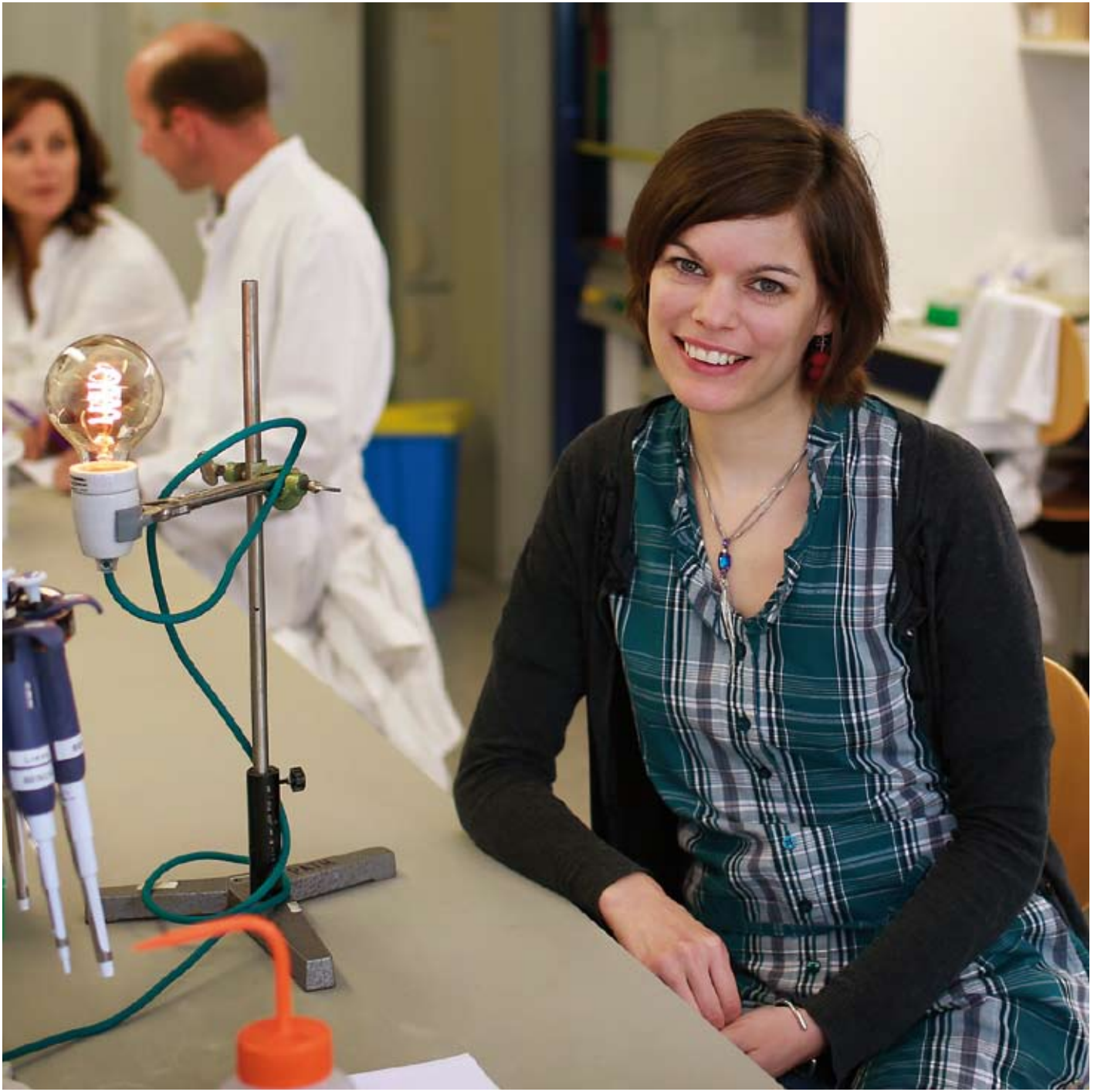


Support

"CARIM offers a very dynamic learning environment," she continues. "There is a lot of interaction between the different disciplines and many opportunities to exchange knowledge, such as the CARIM Lecture Series and Symposium, and seminars."
Yvonne, whose research focuses on understanding the physiological impact of interfering with myocellular AMPK-glycogen shuttling in the context of type 2 diabetes, is making the most of such events and actively building her network. "As a scientist, you want to be competitive. For that, you also need others to help you," she says.

Networking will also help Yvonne to complete the third section of her CaRES plan: supervision. "My network here, at Maastricht University, was just too small to select a mentoring committee within my first six weeks at CARIM," she explains. "But the great thing is that once I have selected my committee, I will have a group of people to support me in the coming years."

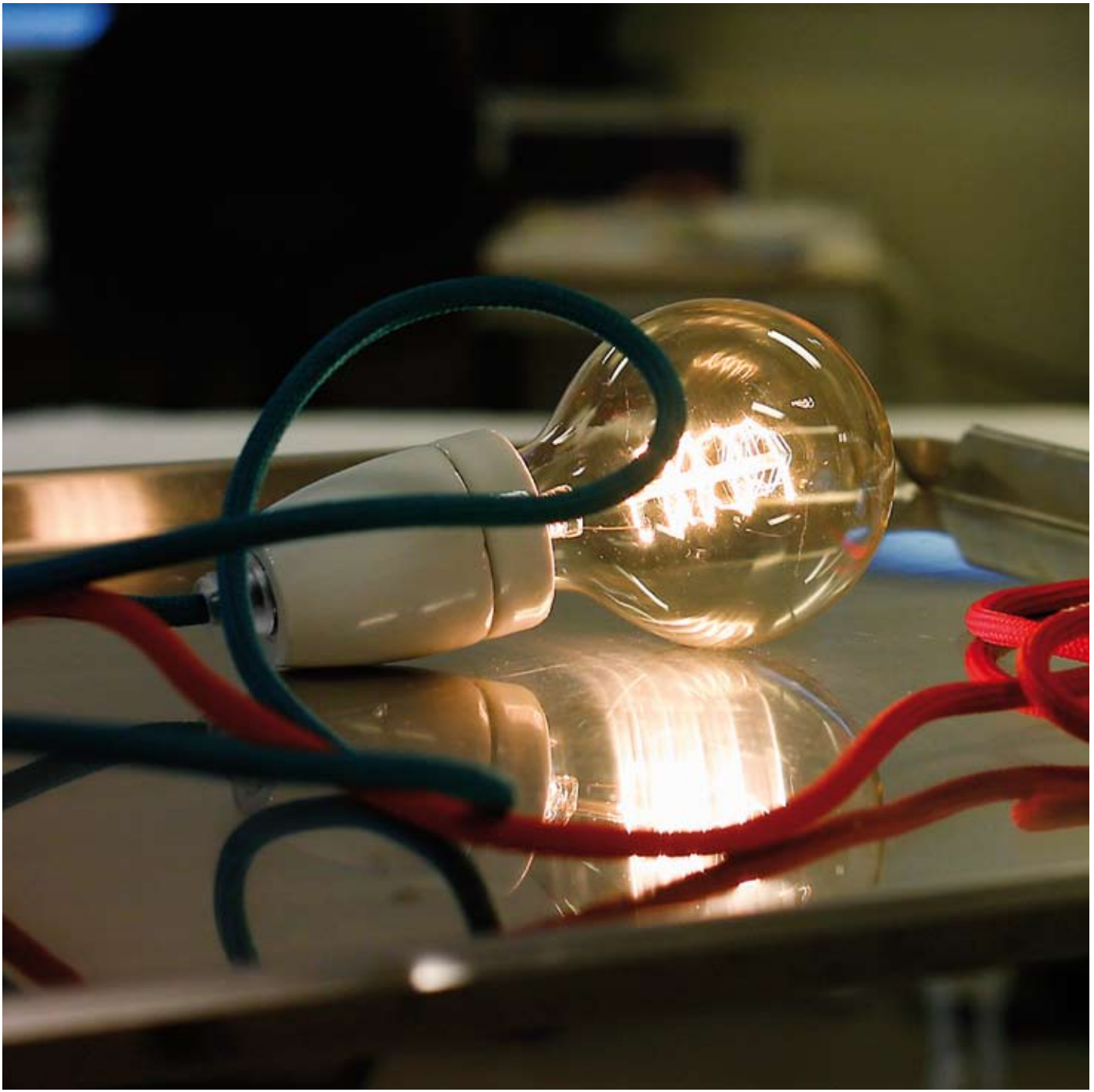
EuCAR fellowship

While Yvonne has only just plunged into life as a PhD student, Anette Christ is making preparations to present and defend her dissertation…twice!
It is because Anette belongs to the first group of fourteen PhD students who were awarded EuCAR fellowships in 2008. EuCAR is a collaborative between CARIM and its German counterpart IMCAR in Aachen.
It allows students to work towards a PhD from both the RWTH Aachen University and the University of Maastricht. They have the opportunity to become acquainted with science at the participating institutes and to follow courses and seminars offered at both universities. In addition, EuCAR students organize their own get-togethers to discuss their work.

International experience

Speaking from experience, Anette says that exposure to more than one scientific culture is one of the great advantages of the EuCAR program, along with the opportunity to build a network at multiple locations. "We benefit from the input of two different departments, at two different universities, in two different countries," she points out. "Gaining international experience is an integral part of our program. And even though you would expect the working environments in Aachen and Maastricht to be quite similar because of their proximity, there is a world of difference: in Germany a more hierarchical structure exists compared to CARIM, where I can work quite independently."

Anette has devoted her PhD years to studying the function of plasmacytoid dendritic cells in atherosclerosis. Dendritic cells are known as mediators of adaptive immune responses as well as inducers of tolerance. She is co-author of a CARIM-led study on this subject published in the Journal of the American Heart Association in 2011.
"To stay in research, the most important thing is to have your research published," concludes Anette, who hopes to become a postdoc. She believes that her professional networks at CARIM and the institutes at the RWTH Aachen will help advance her scientific career.



LIST OF ABBREVIATIONS

ARENA	Approaching Heart Failure by Translational Research of RNA Mechanisms (CVON project)
AF	Atrial Fibrillation
azM	University hospital Maastricht
BMM	BioMedical Materials program
CaRES Plan	CARIM Research, Education and Supervision Plan
CARIM	Cardiovascular Research Institute Maastricht
CBM	Research Master's in Cardiovascular Biology and Medicine
CTMM	Center for Translational Molecular Medicine
CVON	CardioVasculair Onderzoek Nederland
EB	Executive Board
ECTS	European Credit Transfer and Accumulation System
EPC	Education Program Committee
ERC	European Research Council
EuCAR	Euregio Cardiovascular International Research Training Group
EUTRAF	European Network for Translational Research in Atrial Fibrillation
FHML	Faculty of Health Medicine and Life Sciences (Maastricht University)
FP6, FP7	Sixth and Seventh European Framework Programme
IMCAR	Institute for Molecular Cardiovascular Research, Aachen, Germany
INSERM	Institut national de la santé et de la recherche médicale (France)
ISAB	International Scientific Advisory Board
KNAW	Royal Netherlands Academy of Arts and Sciences
Maastricht UMC+	Maastricht University Medical Center+
MD	Doctor of Medicine
NFU	Netherlands Federation of University Medical Centers
NHF	Netherlands Heart Foundation (see also NHS)
NHS	Dutch Heart Foundation
NWO	Netherlands Organisation for Scientific Research
OBP	Technical staff
ORPHEUS	Organization for PhD Education in Biomedicine and Health Sciences in the European System
PI	Principal Investigator
SCI-SSCI	Science Citation Index-Social Science Citation Index
UM	Maastricht University
WP	Scientific staff
ZonMw	Netherlands Organisation for Health Research and Development

COLOPHON

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