CARIM ANNUAL REPORT 2017

SCHOOL FOR CARDIOVASCULAR DISEASES

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CONTENTS

PREFACE

OUR YOUTH IS OUR FUTURE...

Why is it that in current times more and more young talent seek jobs outside of academia? Is an adventurous life of multiple postdoc positions followed by an academic rat race not appealing anymore? Does it come from a widespread demand for instant reward? Should a PhD make you eligible for an immediate tenured position? Clearly the answer to this question is no.

Obtaining a PhD is the first major battle of competence to become an independent researcher, and let us not be fooled, although the battle may be over, the war has just begun. As with all major milestones we remember, from elementary to high school, or from graduating high school to academic freshman. We are not yet established researchers at our PhD, it merely opens a world of possibilities to become one, at your choice of subject, country, or culture, but governed by a firm determination and perseverance, and most substantially, by a profound interest in science. Do the math, and you will realise that not every MSc can become an academic professional, and although competition is perhaps fiercer than in the old days, still only the best will make it.

In spite of this and to the benefit of those who are struggling, there is a strong consensus on progressive lack of future academic career perspectives. Research grants are increasingly difficult to obtain, and mostly oriented toward senior scientist consortia. True academic careers require prestigious personal grants, and we have some of world's best programmes available through our Netherlands Organisation of Scientific Research (NWO) Innovational Research Incentives Scheme and The Netherlands Heart Foundation (NHS) Dr E. Dekker programme. The ultimate accomplishment for a young PhD is acquiring NWO's Veni or NHS' junior Dekker grant. For years CARIM has successfully assisted and coached fellows with these grant applications through its Research Council, and as of 2017, CARIM boosts its young talents' scientific resume through the Harry Struijker-Boudier Awards for Talented Academics (HS-BAFTA). These grants offer opportunities to gaining (international) scientific experience during all five junior career levels from BSc; MSc, pre-PhD; PhD and postdoc. Through early recognition of young talent and better coaching through our CARIM mentorship and fellowship approach, we believe we will better prepare our young talent for a successful academic future. And how attractive higher salaries outside academia might be, they can never compete with the gratifying experience of having a job as a scientist in an academic network.

Academic future will be shaped in large international and interactive sustainable networks that are now being generated due to the very successful participation of CARIM in many European Horizon 2020 consortia. Multidisciplinary international research teams are needed to define and solve crucial scientific questions in our current cardiovascular research field. These research teams now more and more engage young scientists in addition to Principal Investigators

(PIs) allowing them positions at the consortia tables and to participate in decision making. To better prepare CARIM for participation in such international research teams and to better showcase its talent it became a wish to present CARIM in a more outgoing and recognisable fashion in a restructured format.

As CARIM is unique in fully covering all aspects of the cardiovascular spectrum; blood, vessels and heart, these divisions remain visible in the new CARIM structure. The number of programmes has been reduced, from 22 to six, making them easier to identify and to connect with in the event of research team formation.

More room is given to young researchers, in that programme overarching research objectives will be leading in CARIMs policy, with the deployment of PI groups within the programmes as self-sustaining research entities with each their respective specialism, research track, and infrastructure.

As such CARIM is now ready for its future, thriving with talent, and will continue to perform far above par in acquiring (inter)national competitive research funding, and in delivering excellent PhDs and research output.

This is CARIM 2017.

I hope you enjoy your reading.

Professor Tilman Hackeng
Scientific Director CARIM
School for Cardiovascular Diseases

PROFILE

01

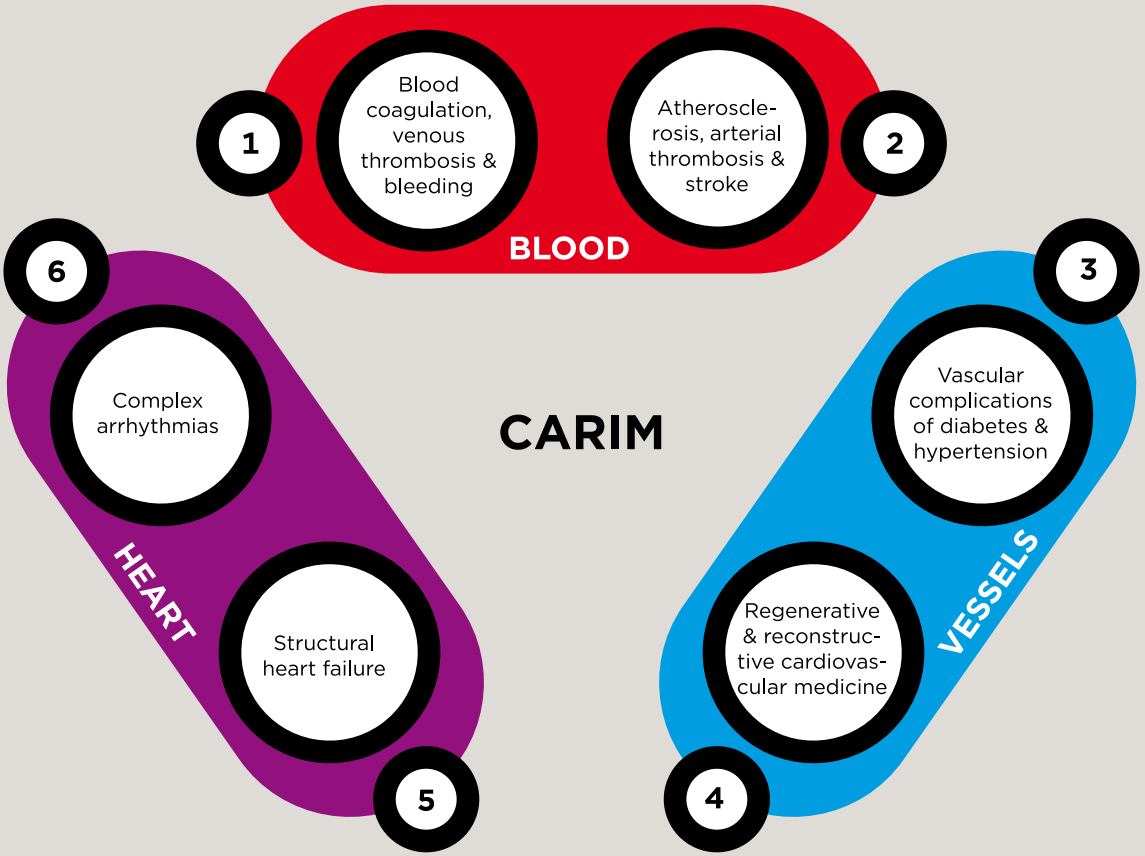
PROFILE

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

CARIM is built around three broader research divisions of 'Blood', 'Vessels' and 'Heart'. comprising six programmes; 1. Blood coagulation, venous thrombosis & bleeding; 2. Atherosclerosis, arterial thrombosis & stroke; 3. Vascular complications of diabetes & hypertension; 4. Regenerative & reconstructive cardiovascular medicine; 5. Structural heart failure and 6. Complex arrhythmias (see Figure on page 10). These six programmes together host 23 PI groups, which represent independent research, infrastructural and financial units within CARIM. CARIM applies this structure to define and address key scientific questions through application of optimal combinations of CARIM programmes, PIs, researchers, and infrastructure in an optimal team science setting combining track, expertise, and innovative content and to disseminate results to scientific communities and to society as a whole.

All three divisions involve basic and clinical programmes and will be led by a shared governance, executed by the division leader together with a basic scientist and a clinical scientist from that division. This shared governance system will be responsible for the scientific progress of their programmes, for linking activities and seeking collaborations between PIs and divisions and for mentoring of PhD students, postdocs and tenure tracks.
The PIs are responsible for the financial basis of each of their groups. Cardiovascular scientists from around the world join CARIM because it values open communication, close cooperation, stiff ambitions, good facilities and a critical learning environment. CARIM is one of the six research schools of the Faculty of Health, Medicine and Life Sciences (FHML) of Maastricht University and is embedded within the Maastricht University Medical Centre+ (MUMC+). CARIM is appointed as research school by the Royal Netherlands Academy of Arts and Sciences (KNAW) and recognised as an international training site for Early Stage Researchers by the European Union.

CARIM researchers have been very active in EU networking activities and the establishment of (inter)national alliances. In total CARIM is currently involved in about 30 European projects. CARIM is involved in nine ITN programmes with a total number of 29 Early Stage Researchers allocated to CARIM. Of two Horizon 2020 ITNs, INTRICARE (3.8 M€) and TRAIN-HEART (3.9 M€), CARIM is coordinator.


1
Blood coagulation, venous thrombosis & bleeding
Atherosclerosis, arterial thrombosis & stroke
2
BLOOD
6
Complex arrhythmias
HEART
Structural heart failure
5
CARIM
3
Vascular complications of diabetes & hypertension
VESSELS
Regenerative & reconstructive cardiovascular medicine
4

CARIM has a long-lasting tradition of executing programmes in collaboration with industry, sharing its expertise but maintaining its independence as reflected by the right to publish. Ongoing collaborations include, among others, Bayer Health Care, Roche, Medtronic Bakken Research Center BV, and Abbott. Furthermore, CARIM researchers are involved in other Public Private collaborations through Interreg programmes and the Weijerhorst Foundation, and take part in (inter)national networks such as NHF CVON, Horizon 2020, EUPlan, and Leducq Transatlantic Network.

To translate research into clinical practice, CARIM joined forces with the Heart+Vascular Center (HVC) of the MUMC+ aiming to develop into a unique internationally recognised centre of excellence in cardiovascular medicine in research (including translational research and medical care).

KEY FIGURES 2017

ANNUAL BUDGET: **23,451** K€	DEPARTMENTS/DISCIPLINES: **15**
NEW CONTRACTS AND GRANTS: **14,649** K€	SCIENTIFIC ARTICLES: **577** (Wi-1: 512)
RESEARCHERS: **156** FTE	PHD THESES: **38**
TECHNICAL AND SUPPORTING STAFF: **45** FTE	PATENTS: **5**

FACTS AND FIGURES

02

FUNDING AND EXPENDITURE AT INSTITUTIONAL LEVEL 2012-2017

	2012	2013	2014	2015	2016	2017
	K€	K€	K€	K€	K€	K€
FUNDING						
Direct Funding structural	7,391	7,419	7,500	7,443	7,096	6,995
Direct Funding specific programmes	2,717	2,272	1,309	1,492	2,751	2,344
Total Direct Funding (1)	**10,108**	**9,691**	**8,809**	**8,935**	**9,847**	**9,339**
Research grants (2)	1,566	1,730	1,481	1,850	2,053	1,899
Contract research (3)	13,464	13,456	11,117	11,612	9,176	12,213
	15,030	**15,186**	**12,598**	**13,462**	**11,229**	**14,112**
Total funding	**25,138**	**24,877**	**21,407**	**22,397**	**21,076**	**23,451**
EXPENDITURE						
Personnel costs	16,492	17,501	16,343	15,039	14,098	14,651
Other costs	8,475	8,379	6,392	5,986	6,406	6,764
Total Expenditure	**24,967**	**25,880**	**22,736**	**21,025**	**20,504**	**21,415**
RESULT	**171**	**-1,003**	**-1,328**	**1,372**	**572**	**2,036**

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

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

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

RESEARCH OUTPUT IN 2012-2017

	2012	2013	2014	2015	2016	2017
SCHOOL LEVEL						
Scientific publications	635	605	584	586	577	577
Other publications	80	50	70	48	69	65
PhD theses	50	34	35	43	55	38
Total* (I)	**765**	**689**	**689**	**677**	**701**	**680**
Academic staff** (II)	33.1	32.4	33.4	32.6	28.7	28,8
Ratio I and II	23.1	21.3	20.6	20.8	24.4	26,4
DIVISION 'BLOOD'						
Scientific publications	108	111	109	125	152	124
Other publications	12	13	19	8	13	7
PhD theses	8	7	10	10	14	6
Total	**128**	**131**	**138**	**143**	**179**	**137**
DIVISION 'VESSELS'						
Scientific publications	353	331	313	301	269	272
Other publications	45	22	32	31	26	18
PhD theses	22	12	17	12	22	20
Total	**420**	**365**	**362**	**344**	**317**	**310**
DIVISION 'HEART'						
Scientific publications	246	240	239	249	212	231
Other publications	25	20	34	13	28	41
PhD theses	20	17	10	21	23	14
Total	**291**	**277**	**283**	**283**	**263**	**286**

* Please note that the sum of the publications in the divisions exceeds the total number of publications at School level, due to a double counting of publications with authors from different divisions

** Academic staff: PhD students and postdocs not included

PhD theses: including PhD theses externally prepared

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

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

NEW CONTRACTS AND GRANTS CONCLUDED IN 2017

FUNDING	BLOOD	VESSELS	HEART	TOTAL SUPPORT
	K€	K€	K€	K€
Type 2	30	1,034	1,020	2,084
Type 3	1,879	4,330	4,196	10,405
Type 4	547	320	543	1,410
Type 5	250	250	250	750
Total	**2,706**	**5,934**	**6,009**	**14,649**

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 2017: 1,703 K€)

Type 5 Annual support MUMC+ (750 k€) Heart+Vascular Center-CARIM *'Pieken vanuit de Breedte'*

SUMMARY OF SCIENTIFIC AND TECHNICAL STAFF CARIM AT THE END OF 2017 (IN FTE)

DIVISION	WP1			WP2			WP3			WP4			MUMC+	TOTAL
	Faculty	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	FTE
Blood	5.4	1.0	1.0	1.1	3.0	1.0	0.4	17.7	4.8	-	3.5	-	2.2	41.1
Vessels	9.8	-	-	-	4.0	0.8	0.4	18.8	6.4	-	1.7	-	5.6	47.6
Heart	10.6	1.0	1.7	1.1	7.0	4.3	-	27.2	1.6	-	5.7	2.5	4.5	67.2
TOTAL	**25.8**	**2.0**	**2.7**	**2.2**	**14.0**	**6.1**	**0.8**	**63.7**	**12.8**	**-**	**10.9**	**2.5**	**12.3**	**155.9**

DIVISION	OBP 1	OBP 2	OBP 3	OBP 4	MUMC+	TOTAL
Blood	3.4	-	2.0	3.0	2.2	10.6
Vessels	8.9	-	8.7	-	-	19.1
Heart	13.1	-	2.6	-	-	15.7
TOTAL	**25.4**	**-**	**13.3**	**3.0**	**3.7**	**45.4**

WP	scientific staff
OBP	technical staff
1	University
2	NWO/KNAW
3	non-profit organisations
4	industry
MUMC+	Maastricht University Medical Centre+

HIGHLIGHT

BRIDGING THE GAP

REGRESSION OF CALCIFICATION

Barend Mees | Leon Schurgers | Harry Crijns

"If you put together two people who both think they know better, things can get a little awkward. Clinicians and scientists can be alpha males. In this case, there are three people here who also know better, but who are willing to listen to each other." This is what Leon Schurgers points out as one of the factors determining the success of his collaboration with cardiologist Harry Crijns and vascular surgeon Barend Mees. He is the 'lynchpin', which, according to the two clinicians, is why he is seated in the middle during the interview. What makes their collaboration so successful and complimentary? What barriers did they have to overcome in the past? And was there a ribbon-cutting ceremony at the start of their collaboration? "No, that's not the way it works," smiles Crijns. In an informal interview, they explain how it does work.

For five, maybe ten years, Crijns and biochemist Schurgers used to run into each other in the corridors and would say to each other: "We really should do something together some day!" For various reasons, however, it did not happen, despite these good intentions. By far the biggest problem was lack of time. As Mees explains: "If you're a doctor and you also want to do research, then it's a real challenge to keep all the balls up in the air." Crijns recognises this, but also puts it into perspective. "You have to strike while the iron is hot. And if you manage to persuade a patient to take part in a research study that will hopefully improve patient care, that's very gratifying."

CALCIFICATION AND ANEURYSM

All three obviously greatly enjoy their collaboration. Whereas 'Regression of calcification' is the formal theme of the interview, the three interviewees regard this as merely one aspect of their collaboration. Schurgers and Mees are focusing on aneurysm: severe dilations of the aorta which can rupture. Such a rupture is fatal in nearly half of the cases. Early detection, which is one of CARIM's focus areas, can save lives here. Mees: "We use molecular techniques on patient materials to try and unravel why the aorta starts to dilate, and to see whether we can counteract this. We're both interested in the smooth muscle cell and calcification, so that's one of our primary targets. We've already found that the smooth muscle cells in an aneurysm are far more stressed and calcified, and age faster than in a non-dilated aorta."

HIGHLIGHT

CALCIFICATION OF THE AORTIC VALVE

The project initiated by Crijns and Schurgers revolves around the early calcification of the aortic valve, and has already yielded a number of outstanding publications in top-rated journals. Their hypothesis is that vitamin K plays a major part in inhibiting calcification. Crijns: "We're currently engaged in a randomised clinical trial, in which we give patients vitamin K. If our hypothesis is correct, we'll have hit the jackpot. Then we'll be on the cover of both the New England Journal of Medicine and *Libelle*." "I'll do the *Libelle* one," jokes Schurgers. "You'd be just perfect for that," chuckles Crijns. The researchers are expecting their first results in the course of 2019.

GIVE OTHERS SOME CREDIT, AND MAKE GOOD ON YOUR PROMISES

Of course, coming up with a joint project, with the clinical expertise and technologies and basic research complementing each other, is important in a collaborative effort like this one. But all three emphasise that what is probably the most important factor is the willingness to cooperate. To listen to each other and to trust each other. To give the others some credit too. "I don't necessarily have to be the first author of a paper; what counts is the result. Collaboration is in our genes." Another essential aspect is making good on your promises. Schurgers: "If you promise to deliver something, you have to keep that promise. That's how trust and enthusiasm develop." And mind you, if all a surgeon does is provide the basic researcher with some tissue, they would not regard that translational research. Mees: "It goes much further than that. I share a PhD student with Leon. We work out the set-up of the experiments and papers together."

LEARNING FROM EACH OTHER

Exploring each other's field is another precondition for successful collaboration. Crijns: "In our medical training Barend and I were also taught a lot of basic science, but I've forgotten most of it. We don't really need that in our everyday practice. But we realise that we have to familiarise ourselves with the biochemical pathways. I want to know why a patient's coronary artery narrows when their vascular smooth muscle cells are overactive. If I want to start a joint project, I'll have to study the preclinical mechanisms, and Leon will have to go halfway to becoming a doctor, so to speak. He has to understand what's relevant to us, and you have to learn to speak each other's language." Schurgers remembers vividly how he drew a diagram of the coagulation cascade, while Crijns taught him about the heart's electrophysiology.

HOW CARIM INFLUENCES THE COLLABORATION

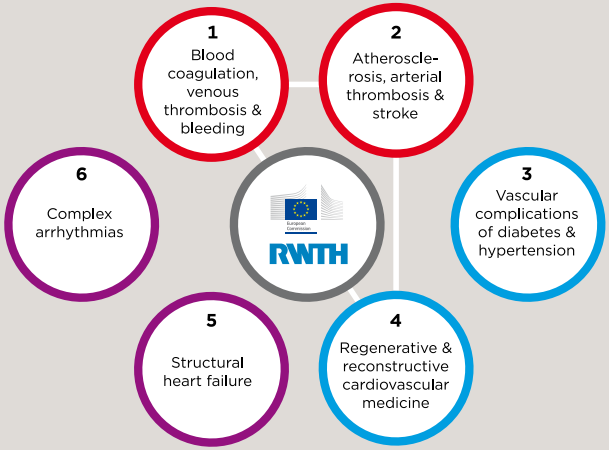
In a situation where both the clinical and preclinical aspects of a disease are highly developed within the same academic centre, it would actually be a miracle if there were no interdisciplinary collaboration, says Crijns. And yet all three think that this is not happening enough. Schurgers: "It's often easier to collaborate with people outside your own institute, perhaps because it involves less internal competition. But we're showing that you can very well collaborate with people from your own institution." In Crijns' view, a major part in this is played by the specific culture at CARIM. "For many years now, CARIM has been emphasising early detection and bridging the gap between preclinic and clinic." But how does this work out in practice? Mees jokingly gestures raising a glass. Schurgers: "We have lots of small symposia and occasionally get together for drinks. And a few years ago, when the dual presentations were introduced at the annual

CARIM day, featuring a basic researcher and a clinician, that gave me a completely different view of our research field." Other aspects that play a role are the funding of boundary-transcending projects and the Research Council, where they can pitch their grant applications in order to improve them, and where clinicians evaluate and assist pre-clinicians and vice versa.

CHECKING OUT EACH OTHER'S WORK

Mees regularly invites basic scientists to join him in the operating room. "That offer is open to all researchers with whom I collaborate. In general, vascular surgeons are more likely to exchange new interventional technologies used in the hybrid operation room with cardiologists than with basic scientists. But I have to say that we also collaborate with CARIM engineers to construct computer models for optimising the blood flow when we develop new grafts for dialysis patients." Schurgers: "If you're able to acknowledge each other's expertise and still work together, that greatly enriches your work. And the three of us represent that attitude." This is not to say that there is no blood, sweat and tears involved, if only just in formulating a joint project. Crijns: "It requires a lot of hard thinking and creativity." Mees: "It's also not easy to find a partner who's interested in collaborating with you in your field of study." Crijns: "But at some point things happen to come together. As a cardiologist you might have a PhD student who crosses into Leon's lab and comes back all excited. That's how things often start to roll." Schurgers: "Harry's PhD student spends a lot of time with me, as I'm a full-time scientist, while he also has to spend time on patient care. If you trust each other in these matters, it may be the start of something really good." Crijns: "That PhD student crossing the bridge, that's crucial in interdisciplinary collaboration."

Harry Crijns *is professor of Cardiology and member of the CARIM board*
Leon Schurgers *is professor of Biochemistry of vascular calcification and vice-chair of Biochemistry*
Barend Mees *is vascular surgeon at MUMC+*



CARIM COMMITMENT AWARD FOR A VERY COMMITTED TEAM

INTERVIEW

Together, they represent about a hundred and fifty years of experience with animal experiments, and it is for their decades of effort and their extensive expertise that the team at the CARIM Muroidean Facility (MF) received the 2017 CARIM Commitment Award.

What makes their work interesting is the whole process of carrying out efficient and responsible experiments on rats and mice, from developing a test design and doing the surgery up to and including the measurements and sometimes also reporting the results. As their story shows, various circumstances have tended to jeopardise this process in recent years.

With over forty years of experience, Helma van Essen is the doyenne of the group. She has helped build up the lab as it now exists, right from the start. But Jacques Debets, Peter Leenders and Nicole Bitsch have also clocked up over thirty years each. Decades in which they have developed their expertise to the full and have greatly enjoyed their work. Debets: "Helping researchers get good results, by correctly carrying out experiments yielding reliable results, that's our core business." Van Essen: "I feel involved in each study, so I really enjoy evaluating the results with the researchers." Leenders adds: "So that you know what you're doing it for, and it becomes more than just 'the trick of operating on ten mice' and then on to the next one."

The transition

In recent years, however, Debets, Van Essen and Leenders have seen their work gradually shifting in that direction. They see two major causes for this development. The first is that the organisational structure they are working in has changed. Previously being referred to as supporting and facilitating staff (*ondersteunend en beherend personeel*, or OBP), they were employed by a specific department, in their case that of Pharmacology & Toxicology. Researchers working in that department who wanted to do animal studies automatically consulted these experts, and the MF staff were engaged in many other places as well, since the department collaborated with departments like Biochemistry or Pathology.

This organisational structure was changed at the end of 2014. The OBPs were separated from the departments and now constitute an independent facility. Researchers who want to make use of their services now have to pay for the animal experiments by the hour. Van Essen: "For them, this often means unexpected additional expenses. So they often ask – if they ask us at all – to do only the operations, and they'll then do the rest themselves." A development which the MF team are not at all happy about. Leenders: "It affects the quality of the research, we think. Quite apart from affecting our work satisfaction." Debets: "So far, I don't see the transition as a positive development."

Bitsch has a slight different opinion about this than the others. She was previously employed by the Department of Cardiology, and much of her work is still with that department. "I still enjoy collaborating with the researchers and I still get the chance to develop myself. Plus I do try to maintain a positive view. Everyone is doing their best, including the five researchers who make up the steering committee and who coordinate the MF. It's just that a lot of things have happened at the same time."

Tightened legislation

What she is referring to is the Dutch animal research act, which was tightened around the same time as the change in the organisational structure, and is the second factor that affected their work routines. It has become a lot more difficult to get permission for an animal experiment, and even if it is granted, the application process takes the researchers a lot more time. This has led to fewer requests for the Muroidean Facility. Debets: "In the past few years, this has meant that it was sometimes necessary to look for other things for us to do, as there simply wasn't enough work. Doing histology, or other lab work. But of course that doesn't help us keep up our expertise, quite apart from the fact that I find that sort of work much less inspiring." Leenders: "When you see how extensively the researchers now have to write up their protocols for animal experiments, that makes me think: why don't you come and see us at an earlier stage? We can counsel them about all kinds of things

they have to think about, which would save them a lot of time and improve the quality of their applications." It must be emphasised here that even though the service is called the CARIM Muroidean Facility, all Maastricht University researchers can apply to them for animal research. The team members know that awareness of their existence among UM staff leaves some room for improvement. Van Essen: "Of course the PIs with whom we're already cooperating still know us. But it used to be that we taught new PhD students how to work in a lab, which now hardly happens anymore. So we do need to work on our PR."

Looking towards the future

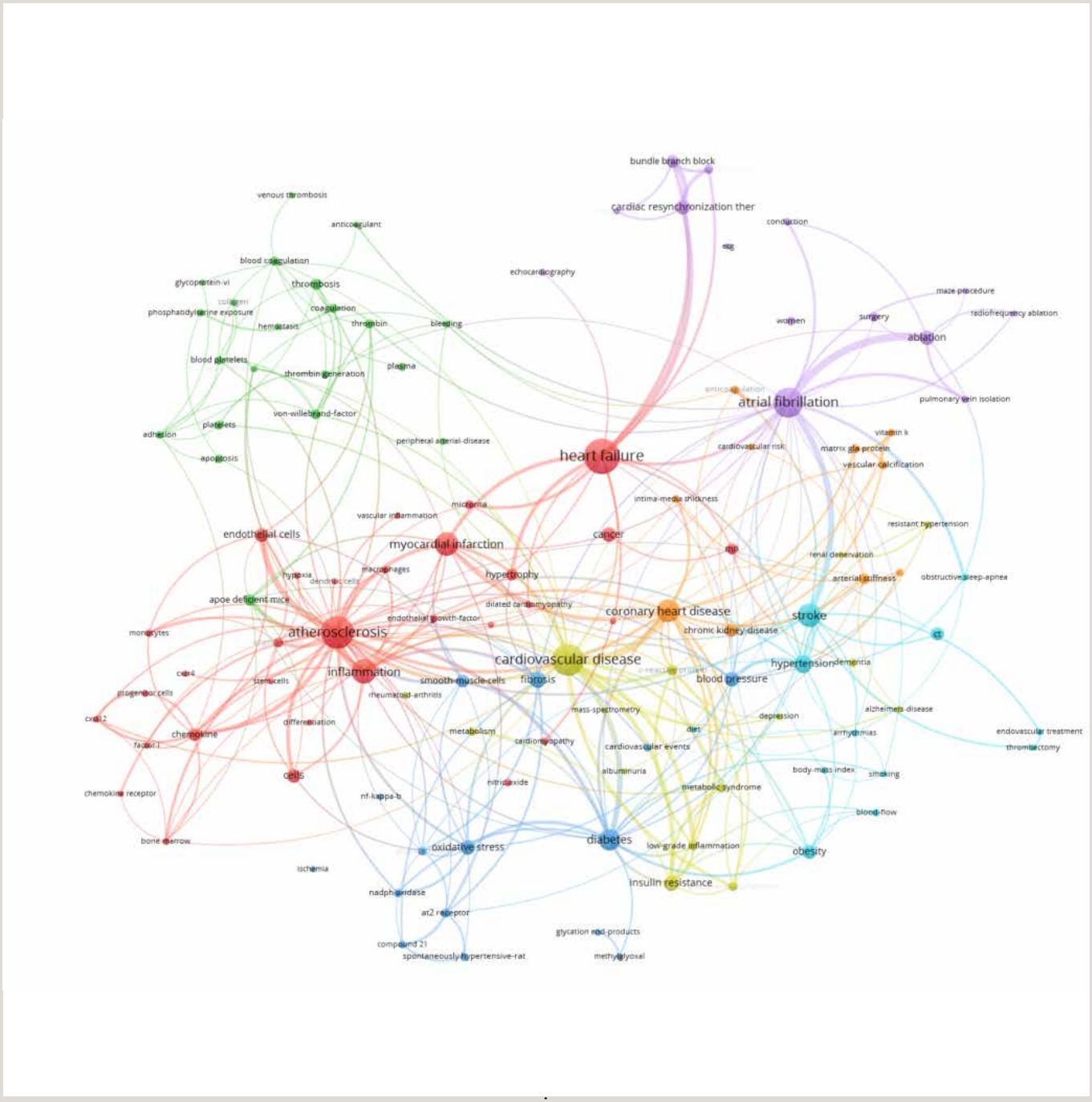
Leenders: "Recently we've been noticing that we're being engaged slightly more often by departments, like Biochemistry, for entire research programmes and larger projects. So perhaps we've just gone through a couple of difficult years and things will get better from now on." Debets: "If the researchers didn't have to pay the extra expenses because those were paid for by the university, we'd be swamped with work here." Bitsch remains optimistic: "There have just been a lot of changes over the past few years, and things need some more time to settle down."

IT HAS BECOME A LOT MORE DIFFICULT TO GET PERMISSION FOR AN ANIMAL EXPERIMENT

There is one thing they all agree upon: the award was a nice token of recognition for their expertise (and that of other support staff), which they have made available to UM researchers over the last decades. And if it is up to them, they will continue to do so for a long time.

The fifth team member, Agnieszka Brouns-Strzelecka, was not present during the interview.

www.carimmaastricht.nl/carim-muroidean-facility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body-mass-index
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cells
nitric-oxide
chemokine receptor
nf-kappa-b
metabolic syndrome
blood-flow
bone marrow
oxidative stress
diabetes
low-grade inflammation
obesity
ischemia
insulin resistance
nadph-oxidase
at2 receptor
glycation end-products
compound 21
spontaneously-hypertensive-rat
methylglyoxal

BIBLIOMETRIC ANALYSIS OF CARIM

In 2016, a review article entitled 'The joint cardiovascular research profile of the university medical centres in the Netherlands' was published in the Netherlands Heart Journal[1]. An important conclusion of the article was that Maastricht UMC+ has a very high citation score and a strong cardiovascular profile, with a means-normalised citation score (MNCS) of 1.96 in the Cardiac and Cardiovascular Systems category, the highest of all Dutch UMCs. The MNCS reflects the impact of a research unit's articles compared to the world citation average (normalised to 1.0) in the subfields in which the research unit is active. Ample empirical evidence has shown that an MNCS value between 1.5 and 2.0 for an institute as a whole is a strong indication of high research performance. The current chapter reports an analysis of recent CARIM performance and cross programme activities.

1 S.D. van Welie, T.N. van Leeuwen, C.J. Bouma, A.B.M. Klaassen. The joint cardiovascular research profile of the university medical centres in the Netherlands. Neth Heart J

General data

An analysis of all cardiovascular publications in 2016 and 2017 is shown in Table 1. CARIM is responsible for ~13% of all cardiovascular papers in the Netherlands. Approximately 0.6% of all cardiovascular articles worldwide include researchers from Maastricht among their authors (1,136 out of 199,270). Importantly, the relative share of CARIM increases progressively when going from the 25% to the 10% and 5% most-cited articles (Top 25%, Top 10% and Top 5%, respectively). Indeed, CARIM researchers are overrepresented by a factor of more than two in the Top 5% compared to all researchers in the world, and are responsible for almost 1.3% of the ~10,000 most-cited cardiovascular articles. These data suggest that CARIM produces a significant amount of high-impact research, something that is supported by the bibliometric analysis performed by CTWS.

TABLE 1 Cardiovascular publications in 2016 and 2017

	TOTAL	TOP 25%	TOP 10%	TOP 5%
World	199,270	49,818	19,927	9,964
CARIM	1,136	453	211	129
CARIM/World	**0.57%**	**0.91%**	**1.06%**	**1.29%**

Table 2 provides an overview of CARIM's bibliometric statistics as calculated by CTWS, including the number of articles (normal articles, letters, notes and reviews) published in journals processed for the Web of Science (P); the citations per publication (CPP) ratio, i.e., the average number of citations per publication during the first two years after publication, excluding self-citations (e.g., including citations from 2016 and 2017 to papers published in 2015); the impact of a research unit's article, compared to the world citation average in the subfields in which the research unit is active (MNCS); and the impact of the journals in which a research unit has published, compared to the world citation average in the subfield covered by these journals (MNJS).

These data show that CARIM's MNCS has consistently been between 1.75 and 2.0 during the last 10 years, reflecting a consistently high research performance. In addition, the MNJS is around 1.4-1.5, meaning that publications from CARIM are published in journals with a significantly above-average impact in the cardiovascular field.

Research at CARIM is highly diverse and spans the three major cardiovascular divisions: 'Blood', 'Vessels' and 'Heart'. Collaboration and integrative translational research between these areas is a major goal within CARIM. In order to obtain some initial insights into the overlap between these divisions, we investigated how CARIM publications since 2014 can be assigned to different categories and subcategories in Web of Science. The Venn diagram in

TABLE 2 Overview bibliometric statistics CARIM

	P	PP	MNCS	MNJS
2008 - 2011	1,739	13.52	1.92	1.55
2009 - 2012	1,915	14.86	1.98	1.55
2010 - 2013	2,015	15.30	1.97	1.52
2011 - 2014	2,061	13.88	1.76	1.44
2012 - 2015	2,101	13.45	1.73	1.39

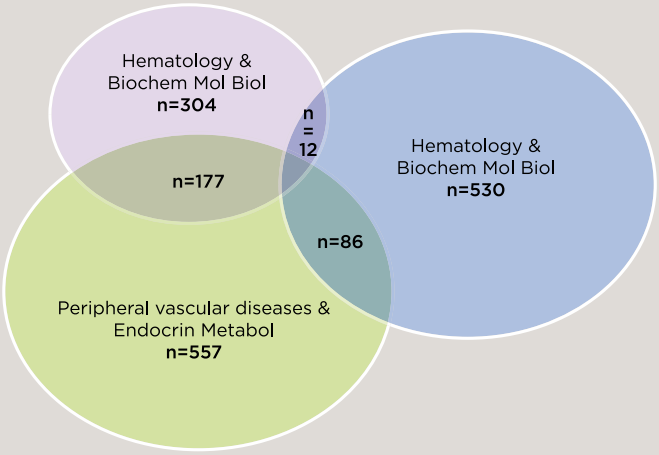

FIGURE 1 Categories of CARIM publications since 2014 in Web of Science, reflecting the three primary divisions of 'Blood', 'Vessels' and 'Heart', as well as the overlap between these divisions.

Figure 1 shows that almost 75% of CARIM publications belong to five Web of Science categories, which show some similarities to the three main divisions. The 'Hematology' and 'Biochem Mol Biol' categories primarily reflect publications on 'Blood', while the 'Cardiac Cardiovascul Systems' category primarily reflects publications on 'Heart' and the 'Peripheral Vascular Diseases' and 'Endocrin Metabol' categories correspond most closely to the 'Vessels' division. Interestingly, a substantial number of publications are classified in both the 'Blood' and 'Vessels' categories, or both the 'Heart' and 'Vessels' categories, suggesting potential topics of common interest and interactions between the divisions.

The interactions between research topics at CARIM were subsequently investigated in more detail using the VOS Viewer tool developed by CWTS. The VOS Viewer tool creates a network based on keywords identified, using a text-analysis algorithm applied to abstracts from a list of Web of Science publications. The number of abstracts in which two keywords co-occur can subsequently be visualised by the strength of the connection between two nodes. When applied to the 120 most-common keywords used in the 500 most-cited CARIM publications since 2014, the resulting network beautifully reflects CARIM's scientific landscape (Figure 2). The network consists of seven clusters (represented by different colours). At the very centre of the network lies the topic of 'cardiovascular diseases', the element which unites all CARIM researchers. In addition, the three major divisions ('Blood', 'Vessels' and 'Heart') as well as the topics of the six research programmes (including, but not limited to, thrombosis, atherosclerosis, stroke, diabetes, surgery, heart failure and atrial fibrillation) can be easily recognized in this map. Importantly, the map also highlights major connections between these topics, as derived from their co-occurrence in many abstracts. For example, diabetes is strongly linked to inflammation, atherosclerosis, stroke and atrial fibrillation (Figure 3A), whereas heart failure has important links with atherosclerosis, myocardial infarction, hypertension and atrial fibrillation (Figure 3B). In addition to connections between these major cardiovascular disease entities, the map highlights the importance of specific experimental models (e.g., ApoE-deficient mice linking the green, red and blue clusters) and biological processes (e.g., oxidative stress, inflammation and microRNA linking a number of important disease entities), among many other things. The nature of these data (common keywords in the most-cited publications) necessarily introduces a delay in the detection of new connections. However, one can already

cautiously start to identify newly emerging connections within CARIM, such as the link between hypercoagulability, coagulation enzymes and atrial fibrillation (Figure 3C). In addition, the diagram clearly illustrates that atherosclerosis is a main hub connecting most of CARIM's research disciplines (Figure 3D). In all, it is clear that CARIM's scientific landscape is highly interconnected and that the strong collaborative approach needed to tackle the topic of cardiovascular diseases is already part of our scientific DNA.

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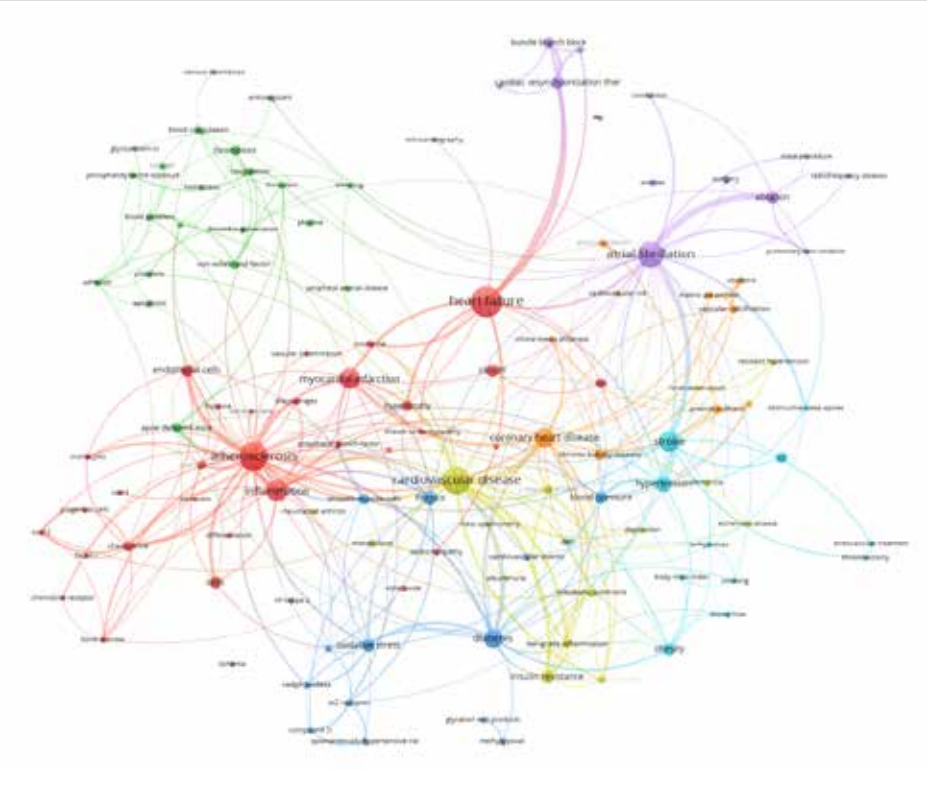

FIGURE 2
CARIM scientific landscape

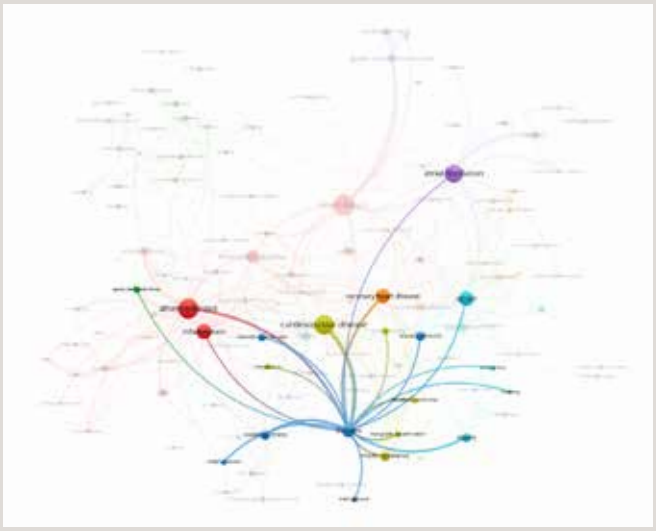

FIGURE 3A Connections between diabetes research and inflammation, atherosclerosis, stroke and atrial fibrillation research.

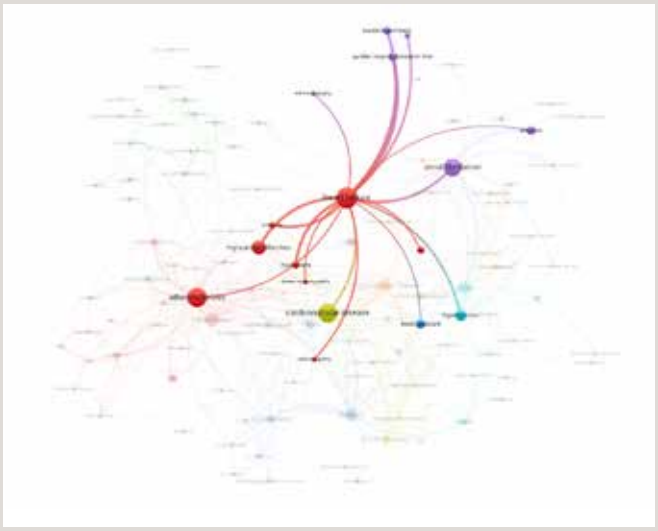

FIGURE 3B Linkage between heart failure research and atherosclerosis, myocardial infarction, hypertension and atrial fibrillation research.

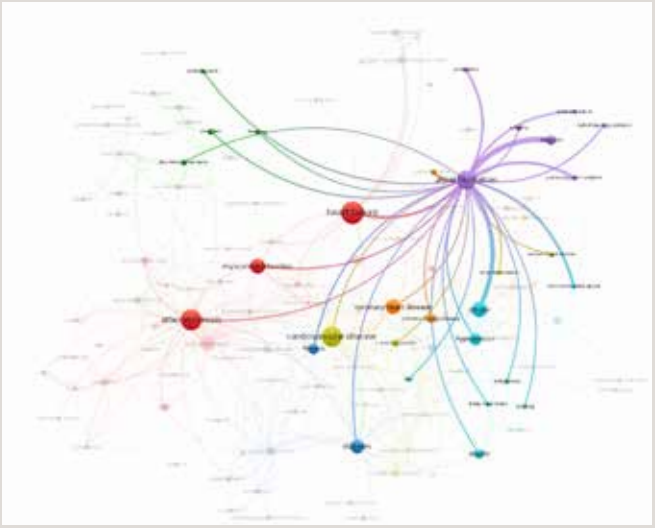

FIGURE 3C Emerging link between atrial fibrillation research and hypercoagulability/coagulation enzyme research.

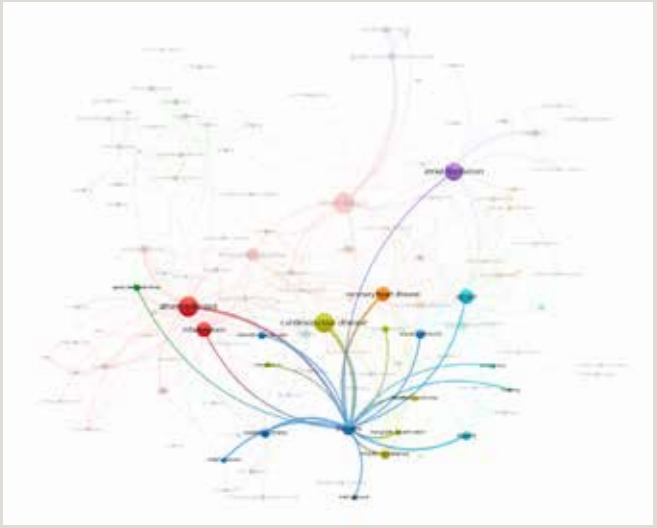

FIGURE 3D Atherosclerosis as a main connector of all CARIM disciplines.

EVENTS AND HIGHLIGHTS

03

SCIENTIFIC **HIGHLIGHTS**

In 2017, the successful work of our researchers was reflected in **577** scientific publications in peer refereed journals (**512** WI-1 publications, excluding abstracts and **29** letters to the editor), **38** PhD theses, **5** patents and **2.1** million Euros funding received in competition from national and international science foundations and **11.8** million Euros funding from third money parties, charities, EU-framework programmes, industry, etc. In 2017, the overall average Impact Factor is **5.6**.

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RESEARCHERS GRANTS AWARDED TO INDIVIDUALS

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

NWO TALENT SCHEME

Dr **Joost Lumens** (Dept. of Biomedical Engineering) has been awarded with a Vidi grant of 800 K€ to launch an innovative research line and set up his own research group. Sudden cardiac arrest following ventricular arrhythmia often arises from unrecognized cardiac tissue damage. The research group will combine common echocardiographic imaging with computer simulation to obtain an electro-mechanical 'fingerprint' of the heart. This diagnostic approach will enable early recognition and characterisation of pro-arrhythmic tissue damage and thereby improve arrhythmic risk management. See pages 59-61 for a full interview with Joost Lumens.

NWO ASPASIA JUDITH SLUIMER

Dr **Judith Sluimer** (Dept. of Pathology) received an Aspasia grant, which aims at a proportional representation of women at (higher) academic levels, and aims to promote or appoint excellent female scientists to become university lecturers or professors. This is achieved by providing 200 K€ to female Vidi candidates, who were found to be excellent or very good after the interview phase, but not honoured with a Vidi grant by lack of means.
Judith will use the Aspasia fellowship for career development, as well as for research. Together with her team, she will investigate if fibroblast-like cells in the atherosclerotic plaque are involved in connective tissue

turnover in young and aged vasculature using a new technology to study the expression profiles of individual cells. Until recently, we looked at expression in whole pieces of tissue, containing all kinds of different cells and subtypes, and it was impossible to determine the contribution of one cell type. This new technology can do this at a single cell level, and offers the possibility to recognize new subtypes. Indeed, pilot data showed that four subpopulations of fibroblast-like cells are already present in the adventitia of healthy, young arteries. These exciting findings were used to boost her Vidi proposal with new pilot data to achieve a better outcome in 2018.

NHS DR E. DEKKER PROGRAMME

Within the framework of the Dr E. Dekker programme of the Dutch Heart Foundation, Dr **Nordin Hanssen** (Dept. of Internal Medicine) received a specialist in training grant for his project 'Do methylgyoxal spikes promote cardiovascular disease?'. This grant allows Nordin to continue his research activities alongside his training as an internist-endocrinologist at the Department of Internal Medicine. The highly reactive glucose metabolite methylglyoxal has been identified as a potential key player in the development of cardiovascular disease and diabetic complications. Nordin and colleagues recently found that higher methylglyoxal levels are associated with cardiovascular disease in people with type 1 diabetes (Diabetes 2017). During his specialist training, Nordin also contributed to the discovery that

methylglyoxal levels fluctuate (spike) after a meal or oral glucose load, and that these methylglyoxal spikes increase with worsening insulin resistance. In the current proposal it will be addressed whether these methylglyoxal spikes contribute to development of cardiovascular disease, and whether pyrixodamine, a B6 vitamer with methylglyoxal quenching properties, can prevent cardiovascular disease. This work will provide new insights into the role of methylglyoxal in cardiovascular disease and will explore a potential new treatment in the form of pyridoxamine as a promising compound to reduce cardiovascular disease.

DUTCH DIABETES RESEARCH FOUNDATION

Dr **Martijn Brouwers** and Dr **Nordin Hanssen** (Dept. of Internal Medicine) have been awarded personal grants from the Dutch Diabetes Research Foundation to further their research on the development of diabetes and its complications.

Dr Martijn Brouwers has been awarded a senior fellowship for his research on nonalcoholic fatty liver disease (NAFLD). His research focuses on elucidating the relationship between NAFLD and cardiovascular complications. The current fellowship will allow him to zoom in on the role of fructose in the pathogenesis of NAFLD (and type 2 diabetes) by employing a diverse set of experiments, ranging from experimental animal and human studies to epidemiological analyses in the Maastricht Study.

Dr Nordin Hanssen has been awarded the junior postdoc grant for his research at the Department of Internal Medicine in the group of Prof. Casper Schalkwijk and Prof. Coen Stehouwer. Nordins research focuses on the role of methylglyoxal, a highly toxic glucose metabolite in cardiovascular disease. With the support of the Dutch Diabetes Research Foundation, Nordin will be able to further investigate the role of methylglyoxal in the development of diabetic complications (particularly chronic kidney disease and diabetic retinopathy). See pages 62-66 for a full interview with Martijn and Nordin.

EFSD/SANOFI GRANT MARTIJN BROUWERS

Dr **Martijn Brouwers** (Dept. of Internal Medicine) received the ‘European Foundation for the Study of Diabetes (EFSD)/Sanofi European Diabetes Research Programme in Macrovascular Complications of Diabetes’ fellowship (230 K€). Evidence is accumulating that nonalcoholic fatty liver disease predisposes to type 2 diabetes and atherosclerosis. There are, however, many different pathways that result in the accumulation of hepatic fat. This EFSD project, entitled ‘Hepatic de novo lipogenesis: the missing link between type 2 diabetes and cardiovascular disease’, will focus on the identification of a plasma biomarker of hepatic de novo lipogenesis, which will subsequently be measured in the Maastricht Study to examine whether the relationship between nonalcoholic fatty liver disease and cardiovascular complications is mediated by de novo lipogenesis.

KOOTSTRA FELLOWSHIPS

During the second round of the Kootstra Talent Fellowships 2017, Dr **Siamack Sabrkhany** was granted a fellowship in the category talented PhD students/talented future post docs. The Kootstra Talent Fellowships are granted to young scientific talents by the Board of MUMC+ with the aim to support developing their scientific career. The fellowship is meant to provide financial support for young researchers to bridge the time between the graduation of the PhD student and the start of an official contract as a postdoc.

BART SPRONCK RECEIVES RUBICON GRANT AND MARIE CURIE FELLOWSHIP

Dr **Bart Spronck** (Dept. of Biomedical Engineering) has received a Rubicon grant from the Netherlands Organisation for Scientific Research (NWO), and a Marie Sklodowska Curie Individual (Global) Fellowship from the European Commission. Both grants give young, highly promising researchers the opportunity to gain international research experience.

Using his Rubicon, Bart will start his research at the Department of BME at Yale University, United States. Subsequently, his Marie Curie Fellowship allows him to prolong his research at Yale for two years and to return to the Department of Biomedical Engineering at Maastricht University for one year to complete his project (Global Fellowship).
Bart's awarded research projects focus on arterial stiffening in the context of diabetes. Bart is developing a setup to expose diseased blood vessels to a pulsatile blood pressure, outside of the body. Using this technique, he is able to better mechanically characterise these arteries under conditions that closely mimic in vivo mechanical loading. The resulting data will be used to generate computer models to interpret and further study accelerated vessel stiffening in diabetes patients.

ERC ADVANCED GRANT FOR CHRISTIAN WEBER

Prof. **Christian Weber,** Professor at CARIM (Dept. of Biochemistry) and Chair of Vascular Medicine and Director of the Institute for Cardiovascular Prevention at the LMU Medical Center, has been awarded his second ERC Advanced Grant. This ERC Grant entitled PROVASC is an exceptional distinction for Weber, who is one of the few researchers to receive the honour of a second ERC advanced award in the course of his career to date. Atherosclerosis is a major cause of morbidity and premature death in modern societies, and the principal goal of all of Christian Weber's research is to contribute to our understanding of this condition and to identify new drug targets opening up new routes more effective and personalised treatment. Weber analyses the molecular mechanisms involved in the pathogenesis and progression of the disorder. Commonly known as hardening of the arteries, atherosclerosis is primarily characterised by the development of fatty deposits on the inner surfaces of major blood vessels, which provoke chronic inflammation that leads to obstruction of blood flow.

LSBR GRANT JOHAN HEEMSKERK AND PAOLA VAN DER MEIJDEN

Prof. **Johan Heemskerk** and Dr **Paola van der Meijden** (Dept. of Biochemistry) received a grant from the Landsteiner Foundation for Blood Transfusion Research (LSBR) of 360 K€, entitled 'Platelet subsets and priming: functional determinants of haemostasis and vascular protection'. While evidence is accumulating that circulating blood platelets are heterogeneous in structure, age and function, the causes and consequences of this heterogeneity are still markedly unclear. In this LSBR project, the investigators will systematically identify, separate and characterise subsets of platelets with regard to their functions in haemostasis and thrombosis They will further determine how the subset characteristics are changed (i) under conditions of platelet priming or dysfunction in health and disease, and (ii) in ageing platelet concentrates used for transfusion.

Furthermore, several CARIM researchers have received Young Investigator awards and poster awards on several occasions.

OTHER AWARDS, PRIZES AND GRANTS

In 2017, many CARIM researchers were awarded with other grants, prizes and awards. Below, some of them are highlighted.

CARIM POSTDOCTORAL FELLOWSHIP ROBIN VERJANS

The winner of this year's CARIM Talent Fellowship is Dr **Robin Verjans** (Dept. of Cardiology). He started a collaboration with Prof. Mauro Giacca at the International Centre for Genetic Engineering and Biotechnology, Trieste Italy. The project studies the regulatory function of miRNAs in cardiomyocyte cell cycle activity during cardiac stress. The latest techniques to modulate RNA expression and to determine cardiomyocyte cell cycle activity will be used to achieve this goal.

ERA-CVD GRANT ERIK BIESSEN

Prof. **Erik Biesen** (Dept. of Pathology) is coordinator of the project 'AtheroMacHETE' awarded by the ERA-CVD COFUND programme. AtheroMacHETE will focus on the most abundant immune cell type in the atherosclerotic plaque, the macrophage. In particular, we will dissect their transcriptional, ontogenic, and functional heterogeneity in atherosclerotic lesions in patients and in murine models of disease. The unprecedented deep characterisation will enable the researchers to identify essential gene programmes and regulatory cues, which drive adverse macrophage functions in atherosclerosis. Finally, we will design candidate drugs that target these cues and validate their efficacy in in vitro and murine models and eventually in the clinic. Thus, AtheroMacHete is expected to pave the way to more precise anti-inflammatory treatment of cardiovascular diseases.

MR CLEAN

October 14th, 2014 marked a special day in Dutch medical research: the results of the Multicentre Randomized CLinical trial on Endovascular treatment of Acute ischemic stroke in the Netherlands (MR CLEAN) were presented at the World Stroke Congress in Istanbul. The overwhelming evidence of the effectiveness of endovascular treatment provided by this landmark study not only caused a worldwide change in acute stroke treatment, but also confirmed the high scientific level of Dutch medical research. This was reflected in the publication of the main results in the New England Journal of Medicine (NEJM) on January 1st, 2015, followed by many other publications by the MR CLEAN study group in highly acclaimed medical journals like the Lancet, JAMA, BMJ, Circulation, Stroke, etc.

Two of CARIM's researchers, Prof. **Robert van Oostenbrugge,** neurologist, and Dr **Wim van Zwam,** interventional radiologist, were co-Principal Investigator of this study and contributed to all these publications, e.g. as shared last author to the NEJM paper and as last and first author respectively to the Lancet paper.

In 2017 the two-year results of the MR CLEAN trial were published in the NEJM, confirming the sustainability of the treatment effect.
Dutch and International medical societies honored the MR CLEAN study group for their achievements in the same year with two important awards:

- The Dutch Medical Specialist Federation's '*Wetenschaps- en Innovatieprijs*', and
- The Cardiovascular and Interventional Radiological Society of Europe's 'Award of Excellence and Innovation in IR'

In the meantime, the MR CLEAN study group continued their scientific endeavours with several new trials, one of them the MR CLEAN-Late trial, investigating the possible expansion of the indication for endovascular treatment, led by the two CARIM investigators. For the new trials funding came from the Dutch Heart Foundation and several industry partners. Additional funding for the MR CLEAN-Late trial was granted in 2017 by the Dutch Hersenstichting's 'the sooner the better treatment' programme.

CVON EARLIER RECOGNITION PROJECT 'VIGILANCE' GRANTED

The CVON Earlier Recognition project 'VIGILANCE' of, among others, Prof. **Paul Volders** (Dept. of Cardiology) was granted. Out-of-hospital cardiac arrest by ventricular fibrillation can occur in the absence of significant coronary artery disease, infarction or overt structural heart disease. Upon careful screening, an inherited arrhythmia syndrome or subclinical cardiomyopathy may be diagnosed, and an arrhythmogenic influence inferred, but despite all information provided by electrical phenotyping and genetic profiling it remains virtually impossible to identify in advance those individuals who will die suddenly by ventricular fibrillation. The VIGILANCE project focuses on establishing a Dutch national registry of patients with idiopathic ventricular fibrillation, i.e., individuals in whom no obvious diagnosis to explain the lethal arrhythmia can (yet) be made. In addition, the VIGILANCE investigators, with world-leading experts in the fields of cardiac electrophysiology, arrhythmogenesis, cardiogenetics, cardiovascular radiology and sudden cardiac arrest, will apply an advanced diagnostic flowchart combined with noninvasive electrocardiographic imaging (ECGI) to significantly improve the detection of arrhythmogenic substrates in patients with idiopathic VF. Ultimately, the VIGILANCE project will generate new ECGI tools for characterizing proarrhythmic substrates and provide stratification parameters with the highest clinical applicability for personalised preventive therapy for idiopathic VF.

ZONMW PTO CASPER SCHALKWIJK

The project 'AGE-less: restriction of dietary AGEs to prevent diabetes and vascular complications; a randomized controlled trial' of Prof. **Casper Schalkwijk** and his team was awarded with 600 K€ by the Programme Translation Research (PTO) of ZonMW and by the Dutch Diabetes Foundation.
The AGE-less project will determine the impact of dietary restriction of AGEs on insulin resistance and micro- and macrovascular function. In addition, the effects on biomarkers of AGEs, endothelial dysfunction, and of low-grade inflammation will be investigated. The impact of this proof-of-concept study is that food-derived AGEs might pose an important risk for insulin resistance and vascular complications.

EFSD GRANT RONALD HENRY

Dr **Ronald Henry** (Dept. of Internal Medicine) was awarded together with Dr Annemarie Koster (CAPRHI, Dept. of Social Medicine) from the European Foundation for the Study of Diabetes (EFSD), the Sanofi European Diabetes Research Programme in Macrovascular Complications of Diabetes fellowship (300 K€). The grant was awarded to study in a randomised controlled trial whether a personable wearable together with a mobile telephone app could stimulate patients with type 2 diabetes to undertake more low intensity physical activity by monitoring their physical activity/behaviour. Amongst others Ronald Henry and Annemarie Koster designed a low intensity physical activity programme and developed the app as part of the study.

MARTEN HOFKER MEMORIAL AWARD FOR MARJO DONNERS

Dr **Marjo Donners** (Dept. of Pathology) won the Marten Hofker Memorial Award during the ATVB congress that took place from May 4 until May 6, 2017. This award is in recognition of Marten Hofker, PhD, who passed away in September 2016. Prof. Hofker, previously appointed at CARIM, was renowed for his work on the molecular and genetic mechanisms underlying cardiovascular and metabolic diseases. Marjo won the award for her abstract titled 'Endothelial Murine Atherosclerosis Development'.

PAPER OF THE YEAR AWARD SSAR

The publication 'High Density Lipoproteins exert pro-inflammatory effects on macrophages via passive cholesterol depletion and PKC-NF-kB/STAT1-IRF1 signaling' in Cell metabolism 2017; 25(1):197-207 won the Paper of the Year Award, presented by the Scandinavian Society for Atherosclerosis Research (SSAR). The award was presented to the first authors, Dr **Emiel van der Vorst** and Dr **Kosta Theodorou** (Dept. of Pathology) during the annual meeting of the SSAR (April 18-21, 2017).

MCDONALD AWARD COEN STEHOUWER

Prof. **Coen Stehouwer** (Dept. of Internal Medicine) won the McDonald Award of the Artery Society 2017. The Artery Society's goal is to promote the advancement of knowledge and dissemination of information concerning the pathophysiology, pharmacology, epidemiology, detection, investigation and treatment of arterial structure and function. The McDonald Award and Lecture is Artery society's main award. It honours Donald Arthur McDonald (1917-1973), a British physiologist who established the modern approach to the study of arterial haemodynamics over a 20-year period from 1953-1973. His work established the logic of using Fourier analysis to break down pressure and flow waves, and developed the general concept of vascular impedance. His classic book on blood flow in arteries was published in 1960 and has remained a basic treatise in this field for more than 50 years. Linking with engineers and with physicians, he influenced many young physicians and physiologists. He directed work into the clinical sphere while continuing in basic physiology and haemodynamics. Donald McDonald thus is the intellectual godfather of Artery society.

VALORISATION AWARD 2016 BART SPRONCK

A jury consisting of Nick Bos, Prof. Marja van Dieijen-Visser, Prof. Jan Cobbenhagen, Theo Thuis, and Gerda Baltis-Paridaen selected Dr **Bart Spronck** (Dept. of BME) as the recipient of the Valorisation Award 2016, handed out during the Maastricht University Dinner. Bart received his PhD in 2016 for his dissertation entitled 'Stiff vessels approached in a flexible way: Advancing quantification and interpretation of arterial stiffness'.

PIETER VAN ZWIETEN AWARD PROF. THOMAS UNGER

On the occasion of the 27th Meeting of the European Society of Hypertension (ESH) in Milano, Prof. **Thomas Unger** was awarded the Pieter van Zwieten Award. This award was established in 2011 and is conferred to a scientist for his/her outstanding contribution to research on clinical pharmacology of drugs acting on the Renin-Angiotensin-Aldosterone System. Pieter van Zwieten was an Amsterdam-based pharmacologist who contributed substantially to our knowledge of the mechanisms of cardiovascular drugs. He was president of the ESH in the late nineties of the last century and a pioneer of experimental hypertension research.

DR. C.J. ROOSPRIJS DAAN VAN TWIST

On April 30, the dissertation of Dr **Daan van Twist** (Dept. of Internal Medicine) was awarded best PhD thesis in the field of Internal Medicine in 2016. The title of his thesis is 'Renin-angiotensin system in the hypertensive kidney - Clinical studies in patients with essential hypertension, fibromuscular dysplasia, and renal artery stenosis' and was supervised by Prof. Bram Kroon, Prof. Peter de Leeuw and Dr Boy Houben. The Dr C.J. Roosprijs is yearly awarded during the *Internistendagen* in Maastricht in collaboration with the *Nederlandse Internisten Vereniging.* The first prize of € 2,000 is awarded to the author of the best clinical patient-based research in internal medicine.

OTHER HIGHLIGHTS

CARIM COMMITMENT AWARD MF TECHNICIANS

The CARIM Muroidean Facility technicians, consisting of **Peter Leenders, Agnieszka Brouns-Strzelecka, Nicole Bitsch, Helma van Essen** and **Jacques Debets** received the third CARIM Commitment Award. The CARIM Commitment Award is intended for any CARIM member who has devoted his/her heart and soul to CARIM in an exceptional way, be it on an academic, managerial, service or community level. The award consists of a bronze coin of the sculptor Marina van der Kooi. The MF technicians received the award as a token of appreciation for their efforts and expertise in the field of animal experiments, and their flexibility in engaging in the new concept of a Muroidean Facility.

BLANCHE SCHROEN IN MAASTRICHT YOUNG ACADEMY

Following the KNAW example, twelve young scientists, selected from six faculties, took the initiative to start a Maastricht division of the Young Academy. Prof. **Blanche Schroen** (Dept. of Cardiology) is one of the elected members. This Maastricht Young Academy (MYA) is a dynamic and innovative platform where talented scientists from all kind of disciplines will develop visions on science, science policy, and science communication. The MYA will

function as an independent platform within Maastricht University and can function as an advisory group for the Executive Board and other relevant forums. Next to providing advice they will also organise inspiring activities for various target groups within the UM, Limburg and the Euregion.

COEN HEMKER PROFESSORSHIP PROFESSOR STEVE WATSON

Prof. **Steve Watson** has accepted the position of Coen Hemker Visiting Professorship in CARIM. Steve is a British Heart Foundation Professor in Cardiovascular Sciences and Cellular Pharmacology in the University of Birmingham, UK, and is Head of the Birmingham Platelet Group. Steve brings over thirty years of experience in platelet research. Steve identified the GPVI-FcR gamma-chain complex as the major signalling receptor for collagen in platelets in the mid 1990s, and later identified CLEC-2 and G6b-B in platelets. See pages 90-94 for a full interview with Steve Watson and Johan Heemskerk.

JOOST LUMENS RUNNER-UP IMPACT COURSE COMPETITION UM

Dr **Joost Lumens** (Dept. of. BME) has won the second prize of UM's IMPACT COURSE competition. The aim of the course is to create awareness among Maastricht researchers (MUMC+ and Zuyd Hogeschool) about the social impact of research and the opportunities of knowledge utilisation.
The subjects ranged from the effectiveness of education to refugee children to the development of environmentally friendly coatings. Joost was runner-up with his research into the virtual fingerprint of the damaged heart. He focuses on creating patient-specific computer simulations of the heart. Eighteen researchers from MUMC+ and two from Zuyd Hogeschool participated in this IMPACT COURSE. The jury consisted of Nick Bos (vice-president of the Executive Board), Prof. Jan Cobbenhagen (CEO of Brightlands Maastricht Health Campus and KTO), Jacqueline de Groot (Public Affairs officer at UM) and Margot Krijnen (UM press officer).

PROFESSORSHIPS

The following CARIM researchers were appointed to professor in 2017:
Leon Schurgers (Dept. of Biochemistry) - Professor of Biochemistry of Vascular Calcification
Blanche Schroen (Dept. of Cardiology) - Professor of Experimental Cardiology
Eline Kooi (Dept. of Radiology) - Professor of Medical Physics, especially Vascular Imaging
Marc van Zandvoort (Dept. of Radiology) - Professor of Advanced Optical Microscopy

CARIM'S HS-BAFTA TALENT PROGRAMME

Early recognition of talent is one of the key strategies of CARIM to coach and prepare gifted young academics for their future academic career. CARIM stimulates and supports talented students and staff by offering grants for research programmes at five steps in their career, be it at Bachelor, Master, post graduate, PhD or postdoc level. These grants will be enabled through our new 'Harry Struijker-Boudier award for talented academics' (HS-BAFTA). The HS-BAFTA is intended for three groups of young scientific researchers.

1. HS-BAFTA TALENTED FUTURE PHD CANDIDATES

The fellowship is intended for:

a. Talented **Bachelor students** in Health, Medicine or Life Sciences, who have demonstrated to be able to combine their studies with an active involvement in scientific research. It can be used to interrupt their study and to perform a research project within CARIM for 6-12 months during their Bachelor phase.

b. Talented **Master students** in Health, Medicine or Life Sciences, who have demonstrated to be able to combine their studies with an active involvement in scientific research. It can be used to interrupt their study and to perform a research project for 6-12 months within CARIM during their Master phase.

c. **Post graduates** to bridge the time between graduation and the start of an official contract as a PhD student within CARIM. The fellowship has to start within the first year after graduation and is open to students not yet contracted by or enrolled in a PhD programme.

The fellowship amounts to max. € 18,000 (in accordance with scale 7-0) and € 3,000 for exploitation costs and is meant for a period of max. 6 months. For Ba/Ma students the regular curriculum should be interrupted to perform the research project within CARIM. The PI concerned has to match an equal amount of money for the candidate for an equal period of max. 6 months. This brings the max. total annual amount for the HS BAFTA on € 42,000 for a total of 12 months.

2017 William van Doorn

2. HS-BAFTA TALENTED PHD CANDIDATES

The fellowship is meant to support PhD students who seek to spend time abroad during their PhD in order to gain experience and improve their chances in receiving a personal grant (i.e. Rubicon; Veni; Dr E. Dekker) after their PhD. The fellowship amounts to € 7,500 based on actual costs of max. € 1,000 for (extra) living allowance per month and travel costs, for a period of max. 6 months. The fellowship can be performed during any period within the PhD trajectory.

3. HS-BAFTA TALENTED POSTDOCS (FORMER POSTDOCTORAL TALENT FELLOWSHIP)

The fellowship is intended for recently graduated CARIM PhD students. The fellowship is meant to keep top CARIM talents connected to our institute by giving the opportunity to go abroad, thereby gaining the experience required for acquiring personal grants. Therefore, a main requirement for this fellowship is that approximately 9 months (min. 6, max. 12) shall be spent at a partner institute outside the Netherlands to acquire (further) foreign experience and strengthen the international network of the candidate and PI(s) involved. The candidate should use this year for setting up international collaborations and writing a proposal for a postdoc position (i.e. Rubicon; Veni; Dr E. Dekker) and will

be judged on his intentions of performing research of this grant from within CARIM.

The ultimate goals are to acquire and/or increase international research experience, to broaden the scientific/medical network, and to enhance the chances of obtaining prestigious grants in order to strengthen the personal and professional ties to Maastricht University and CARIM specifically.

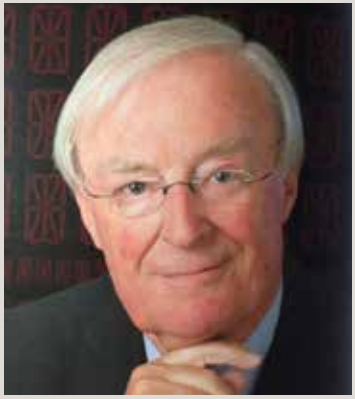
2016 Stijn Agten
2017 Robin Verjans

ROBERT RENEMAN LECTURE

The Robert Reneman Lecture takes place during the annual CARIM Scientific Symposium and is named in honour of the founding scientific director of CARIM. The Robert Reneman Lecture is given by a renowned scientist in the field of cardiovascular diseases and is awarded with a bronze sculpture of Caius Spronken.

1993	M. Verstraete	Leuven, Belgium
1994	J. Sixma	Utrecht, NL
1995	P. Vanhoutte	Courbevoie, France
1996	W. Schaper	Bad Neuheum, Germany
1997	P. Davies	Philadelphia, USA
1998	M. Pfeffer	Boston, USA
1999	Y. Nemerson	New York, USA
2000	V. Fuster	New York, USA
2001	M. Schneider	Houston, USA
2002	F. Rosendaal	Leiden, NL
2003	A. Zeiher	Frankfurt, Germany
2004	P. Poole-Wilson	London, UK
2005	D. Wagner	Boston, USA
2006	S. Wickline	St. Louis, USA
2007	J. Molkentin	Cincinnati, USA
2008	B. Furie	Boston, USA
2009	K. Walsh	Boston, USA
2010	J. Lusis	Los Angeles, USA
2011	W. Ouwehand	Cambridge, UK
2012	D. Kass	Baltimore, USA
2013	J. Yudkin	London, UK
2014	P. Reitsma	Leiden, NL
2015	S. Hatem	Paris, France
2016	S. Laurent	Paris, France
2017	J. Griffin	San Diego, USA

HEIN WELLENS VISITING PROFESSORSHIP



The Hein Wellens Visiting Professorship is endowed by the St. Annadal foundation to stimulate clinical research in the field of cardiovascular disease. The purpose of this chair is to give renowned scientists the opportunity to teach and apply their knowledge at CARIM. The chair is named after Prof. Wellens, a Dutch cardiologist who is considered to be one of the founding fathers of the cardiology subspecialty of clinical cardiac electrophysiology. From 1978 until 2002 Prof. Wellens held a chair at Maastricht University as Professor and Head of the Department of Cardiology.

2004 - 2005	J. Narula	Irvine, USA
2007 - 2008	M. Krucoff	Durham, USA
2008 - 2010	Y. Rudy	St. Louis, USA
2010 - 2011	R. Kim	Durham, USA
2011 - 2013	K. Mayo	Minneapolis, USA
2013 - 2014	M. Stoll	Münster, Germany
2016 - 2017	A. Zaza	Milano, Italy

THE H.C. HEMKER CHAIR

The H.C. Hemker Chair is founded in honour of the founder of the Department of Biochemistry, Professor Coen Hemker. The foundation encourages multiple visits to the department per year to initiate and/or maintain a scientific relation between research groups.

2014 - 2018	R. Ariëns	Leeds, UK
2017 - 2019	S. Watson	Birmingham, UK

EDMOND HUSTINX CHAIR

The Edmond Hustinx Chair, funded by the Edmond Hustinx Foundation was attached to CARIM from 1998-2008. This chair focused on research in the area of molecular and chemical aspects of cardiovascular diseases. CARIM was able to appoint internationally recognised top scientists to this chair.

1998	P. Williamson	University of Massachusetts
1999	J. Bassingthwaigthe	University of Washington
2000	M. Safar	Hôpital Broussais, Paris
2002	M. Galli	Ospedali Riuniti, Bergamo
2004	M. Kockx	University of Antwerp
2005	P. Bock Vanderbilt	University Medical School
2007 - 2008	S. Dimmeler	Molecular Cardiology, University of Frankfurt

VAN DE LAAR PROFESSORSHIPS ON BIOCHEMISTRY OF HAEMOSTASIS AND THROMBOSIS

The Van de Laar chair is endowed by a private donation from the Van de Laar Foundation, to enable renowned professors to perform work visits to the Department of Biochemistry to give lectures and to interact with researchers from the Department of Biochemistry in creating an international network for the mutual benefit of performing research on the biochemistry of thrombosis.

2016	C. Weber	Ludwig Maximilians University Munich
2017	K. Mayo	University of Minnesota at Minneapolis

COAGULATION CAUSES ATRIAL FIBRILLATION

Uli Schotten | Monika Stoll | Henri Spronk

Interdisciplinary research collaboration can make senior researchers feel like a child in a toy shop. That is the main conclusion that can be drawn after interviewing Uli Schotten, Monika Stoll and Henri Spronk. Of course there is a research question that brought them (and several other important partners, in Maastricht, Leiden and Groningen) together. Last year the RACE-V consortium received five million euros from the Netherlands Heart Foundation to investigate the risks of complications in atrial fibrillation (AF) and the role of coagulation in this phenomenon. It is a challenging scientific project, which in a way brings them child-like joy.
Schotten: "The experience of conducting a research project together with colleagues who share a passion for the same research topic contributes a lot to our enthusiasm for this programme."
"This is Toys 'R Us," Stoll smiles.
Uli Schotten, who leads the RACE-V consortium together with Isabella van Gelder from Groningen, has often been puzzled by the lack of collaboration between research groups in the past: "Here at Maastricht, there is a very strong tradition of expertise in both coagulation and in AF. But despite the fact that AF causes hypercoagulability, somehow those two research fields for a long time didn't get to the stage of actually working together. We are very glad that we have now found a way for these two research topics to work together in a fruitful way." The three representatives of the Maastricht section of the interdisciplinary consortium elaborated further on the how and why of collaborating across disciplines. But first let us start with the project itself.

How exactly did this project start?

Schotten: "Maastricht and Groningen have a long research tradition together and we were asked by the Netherlands Heart Foundation how the future of AF research could be shaped in the Netherlands. So we thought: what is actually new right now? What is a good topic to investigate at this moment in time? The entire field of anti-coagulation is currently progressing rapidly. New compounds have been discovered which are in fact among the few successful innovations in cardiovascular pharmacology in this field."
Spronk: "I remember Uli came by because he wanted to measure coagulation-related biomarkers in patients with AF, and I then asked: 'But where is this coagulation coming from?' We didn't know. So we wanted to fill that knowledge

gap. Although this was a novel idea, animal research had already demonstrated that activating coagulation leads to more arthrosclerosis and cardiovascular disease. So then we started wondering: could it be that in these patients, AF was triggered by coagulation? That's how the project started."
Stoll: "And since genetics and genomics have become more and more important in the recent years, due to the progress in technology, Many of the competitive grants require a work package on that field. That's how I came in. I had it relatively easy, because these guys had already written up everything conceptually and I only had to add my work package."

So what's your role in the project?

Stoll: "As a geneticist my main task is to present candidate genes and molecular pathways to the others, which they can study in the lab. I have some basic knowledge of the biology and of cardiovascular diseases, so I can easily recognise patterns that are similar in AF and coagulation, which they can follow up in the lab. This way we find things that I sometimes don't even know the gene name of."
Spronk: "I'm a biochemist in the field of coagulation. My task is to take basic coagulation from cellular and animal models to clinical research, by measuring biomarkers that hopefully tell us whether the therapy we come up with might be beneficial to AF patients. We have the idea that intervening in coagulation might reduce the burden of AF. The question is which parameters we can measure in human blood plasma in the end. What we learn from animal and cellular studies has to be translated into genetic models and human plasma samples. And Monika's expertise in genetics and the use of huge data sets fits in perfectly with that."
Schotten: "I'm a translational electrophysiologist and I coordinate the consortium together with Isabelle van Gelder in Groningen. The greatest challenge we're facing is that the individual disease mechanisms in patients are very different, even though the clinical presentation is relatively uniform. All kinds of different molecular diseases lead to AF, and our job is to develop strategies to identify those individual disease mechanisms in specific patients. We do that by means of a very detailed clinical characterisation of those patients and by comparing this with the molecular mechanisms leading to AF. Coagulation is one important factor that we put at the centre of this project, but of course we also look at other known mechanisms, such as fibrosis or ion channel changes, which also lead to AF."

How does the collaboration work in everyday practice?

Stoll: "We regularly meet to tell each other where we are in the work package, and that's where the scientific discussion starts. In every meeting we find something interesting that we want to follow up on. And I remember several hour-long meetings with Uli, for example, where I explained the concepts of genetics and how that could apply to what he's doing. He learned the basic concepts of complex genetics and I learned a lot about electrophysiology that I had never thought about before. So there's a huge educational aspect, even for old PIs like us."
Schotten: "Henri, for example, is analysing the coagulation factors in patients that are enrolled in our registry of patients with AF, and Monika looks at the common gene variants, to see whether they help to predict the progression of AF. And in another work package we look at atrial biopsies of patients undergoing open chest surgery, who are also very well clinically characterised. Then we ship the biopsies to Monika, to look at gene expression, genome-wide, and we do careful histology. So in the end we will be able to link all the data, from the gene expression to the histology and patient phenotypes, and then we'll be able to answer questions we weren't able to answer so far. For instance: if a patient rapidly progresses towards AF, what genes are typically

expressed in those patients and what does this mean in terms of pathophysiological mechanisms?"

What do you consider essential in this kind of cooperation?

Schotten: "You need to understand multiple scientific languages."

Spronk: "Also because the PhD students run around in various labs. They intensify and broaden established collaborations."

Schotten: "The best catalyst for collaboration is a joint project. It gives you the contractual obligation to really work on it. No matter what."

"INTERDISCIPLINARY RESEARCH COLLABORATION CAN MAKE SENIOR RESEARCHERS FEEL LIKE A CHILD IN A TOY SHOP"

Is making good on your promises indeed one of the most important factors in collaborating across disciplines?

Schotten: "As always, you are judged on what you did and not on what you promised. You have to be reliable and do your homework."

Spronk: "It's give and take. Everybody has his or her own view on doing things, such as dealing with PhD students. That sometimes makes it complicated."

Stoll: "Never boring."

Spronk: "A challenge is fun. You just have to be willing to learn. Some of us are more outspoken, like me, and others are a bit more indirect, like Uli. You have to meet each other somewhere in the middle, because there's a scientific goal. And then it's a cascade: one idea activates another, and another. The huge transfer of knowledge about models and of experiences is inspiring."

Stoll: This is something I truly enjoy when I'm in Maastricht, because in Munster, where my group is located, I don't have the same interactive research opportunities in cardiovascular research. For me, being in Maastricht is extremely productive from a scientific perspective, and I have so much fun when I'm here."

Does CARIM play a role in that?

Stoll: "I think CARIM has moved towards more interaction between the different research lines in recent years. They have realised there is an added benefit. We are starting to have more competitive grant applications, and everybody in the school has contributed a bit of money to the bioinformatics core server: things are moving together for the better."

Spronk: "Looking back, I got all the freedom and means to grow in consortia like these."

Schotten: "The strong translational focus of CARIM is pretty

special. That has grown over the past twenty years and it requires a lot of communication. The school explicitly encourages translational collaboration, by sensitising people to the opportunities it offers. I think the spirit of collaboration is the most important thing."

How do you profile your specific contribution in a large consortium like this?

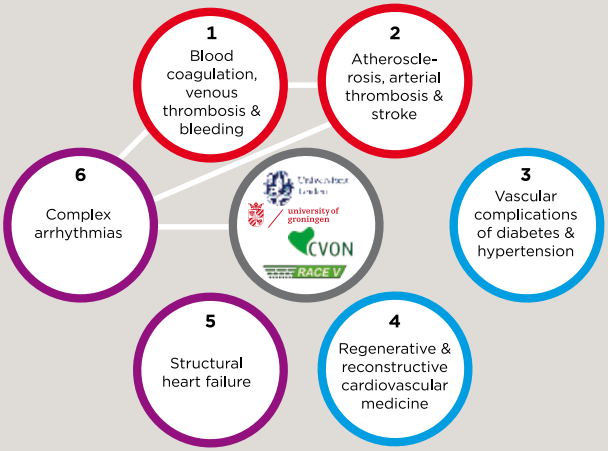
Spronk: "There is no room to say: 'This is mine'. It's the work of a group."
Stoll: "In physics and genetics, we never look at who's first or last author. You are part of the team or not. I can't even work without a clinician or someone with a model."
Schotten: "In physics a paper has hundreds of authors and we see author lists becoming longer in other fields as well, simply as a consequence of the necessity of interdisciplinary research. Still we give the first and the last authors all the credit. This needs to be corrected and it will be. We have more discussions nowadays than in the past about the impact of this development on, for example, young people's careers."

So the times they are a-changin'?

Stoll: "Since the human genome project, which was an example of how interdisciplinary research and sharing between different disciplines can accelerate knowledge development, people have started to realise: if I look a bit beyond my own territory, I might get some new impulses. Funding agencies are also specifically promoting interdisciplinary research because they see the greatest progress coming out of it."
Schotten: "People are much more open nowadays. For us it's very evident that successful research means sharing. But if I think back thirty years and look at personalities in science at that time, it wasn't always the case."

Spronk: "I remember the head of my department saying: 'This is not going outside the lab until the paper is ready.' Now I'm used to presenting new data in an abstract or poster and discussing it with people before publishing about it."
Schotten: "And the interesting thing is that this is happening despite the increasing pressure on scientists to achieve successes. Maybe it's a sign of the true added value of collaboration, or it's simply showing that collaboration is safer, in terms of predictability of success."

Uli Schotten *is professor of Cardiac Electrophysiology and chair of the Strategic Board*
Monika Stoll *is professor of Genetic Epidemiology and Statistical Genetics*
Henri Spronk *is Associate Professor of Atherothrombosis*



INTERVIEW
JOOST LUMENS

"My research is useless if I can't cooperate with a cardiologist"

If you get through to the interview stage of the application procedure for a personal research grant three times within just a few years, and you actually get it each time, people start to ask you: "How exactly do you manage to do that?" Joost Lumens is very aware of the fact that a lot of external factors play a role at that stage. "But if I have to name something, then it might be that you shouldn't be afraid to acknowledge the vulnerable spots in your research project. Show them that you've thoroughly considered those." In 2017, Lumens received a so-called Vidi grant from the Netherlands Organisation for Scientific Research, (NWO), after having previously secured the Junior and Senior postdoc Dekker grants from the Netherlands Heart Foundation.

"You haven't been frequently listed as the last author of publications, and where you have, you've shared it with others," is what Lumens was told during his interview for the Vidi grant. The interview took place in a posh building in Utrecht. "It's very intimidating and confrontational. About twenty professors sit there listening to your story for four minutes, and then four of them ask you questions for ten minutes. The other sixteen say nothing; they just watch and listen. They watch your posture, how nervous you are, how you behave. And any candidate is vulnerable and insecure at such a moment, that's for sure."

One of his 'strategies', which have resulted in his getting the grant three times, is to acknowledge vulnerabilities, both your own and those of your research project. It wasn't difficult for him to explain the issue of last authorship. "Where would I be without a cardiologist? Nowhere. My research is useless if I can't cooperate with a cardiologist to develop my method and apply it to patients. Both types of expertise are equally important. So why would I not share the last authorship? That's precisely what the new science is all about: translational research transcends disciplines. That was roughly my answer."

READING THE TELL-TALE SIGNS OF A DISEASE

Lumens' expertise centres on CircAdapt, a computer model developed at CARIM, which describes the physical and physiological principles underlying the working mechanisms of our cardiovascular system. CircAdapt can be used, for instance, to 'virtually' test the effect of pacemaker therapy before actual implantation of the device, so that the doctor has a better idea of whether the therapy will have the intended effect. He is using the Vidi grant to study a new clinical problem: sudden cardiac death. Lumens' group was already able to map the underlying disease in heart failure more accurately on the basis of the heart's tissue deformation patterns and the computer model. That is why clinical researchers from Utrecht, who had a lot of experience with measuring these so-called strain patterns of the heart, contacted him.

"When looking at the strain patterns of young people with a particular genetic heart disease called arrhythmogenic cardiomyopathy, they saw abnormalities in the way the heart muscle contracts and relaxes again. This genetic defect does not necessarily lead to heart failure, but it is associated with an elevated risk of sudden cardiac death. The subtle abnormalities in the strain patterns proved to be predictive of sudden cardiac death or the development of heart failure." Lumens will use the Vidi grant to try and find out why the deformation pattern is so different in only a small region of the heart, and why this predicts the tragic outcome in these seemingly healthy but vulnerable patients. "The regional strain patterns of the right ventricle are like a tell-tale sign of the disease. The greater the abnormality, the higher the risk of sudden cardiac death appears to become. So when is the best time to implant a defibrillator in such a patient? And are there patients for whom this treatment is not useful, whereas they are currently getting it?'

FREE MODEL, PRICELESS USER MANUAL

CircAdapt was developed at CARIM over the course of twenty years, mainly by Professor Theo Arts. Although Prof. Arts is now formally retired, he is still working steadily on the model at his desk in Lumens' office. "And we benefit hugely from his work." The model can be downloaded free of charge, and has been downloaded seven thousand times by people all over the world, for research as well as teaching purposes. "There's an increasing chance that when we do a presentation on our research, there will be someone in

the room who thinks 'I know that model'. And that can't be bad for us, I think. It's a kind of indirect valorisation of our research." Lumens is regularly asked whether it is not unwise to put the model online free of charge. "But of course we don't put the latest version online, and it's not easy to match our twenty years of expertise." He is sometimes approached, for instance by the Medtronic company, to act as a consultant in testing a new idea for cardiac devices. "They actually wanted to use CircAdapt themselves, and asked me what the manual would cost. But that isn't for sale. What I can do is see if they have any questions that would fit in our research lines. Such a public–private partnership works out well for both parties."

"BASICALLY, PROGRAMMING IS PRETTY DULL"

It is precisely this type of collaboration, with companies, clinicians and students, which drives Lumens. "Multidisciplinary collaboration and interaction are the most exciting, so I'm always looking for other disciplines to connect with. That's what makes my work interesting, as computer programming is of course basically pretty dull. It's not the method itself that gets me going; it's the implementation and application." In addition, he is very pleased with the opportunities and freedom he is given at the Department of Biomedical Engineering to investigate new topics. "Even if their nature puts them slightly beyond the Vidi project. Intrinsic curiosity can sometimes lead to some fine results, which may provide inspiration for a new grant application and concrete research lines. I hope it will always stay this way."

JUST GETTING AN INTERVIEW IS A PROOF OF QUALITY

He cannot deny that his career is on the right track. He has just heard that he has been admitted to the Top Talents programme of the Faculty of Health, Medicine and Life Sciences, a programme to prepare researchers for a future professorship at Maastricht University. Of course, his successful grant applications have played a role in this. "One grant leads to another. I actually think that's not a good system, but I wouldn't really know how it should be done otherwise." In fact, just being invited to an interview for a grant is a proof of quality, he thinks. "That should be taken into consideration when assessing researchers. Because if you don't get the grant in the end, that doesn't really mean very much. It just means that their priorities at that moment, whatever they may depend on, are not in your favour."

LETTING GO AND HOLDING ON AT THE SAME TIME

His team now consists of five PhD candidates, one postdoc and two enthusiastic students working for a Master's degree in Biomedical Engineering at Eindhoven University of Technology, where Lumens was also a student once. Three of his PhD candidates also studied in Eindhoven. Since Lumens and his colleagues teach students both in Eindhoven and Maastricht, he is in a good position to spot the talents that could be useful to his group. "In fact, the continued existence of my research depends on this teaching collaboration." He does find that supervising the five PhD candidates takes a lot of time, at least the way he does it. The challenge is to let go of some things. "It should become the candidate's own project, as that means they will put in a lot more effort. I'm gradually learning to let go, and it's wonderful to see the growing enthusiasm of the young researchers."

As long as he is able to tinker with his own research questions in the evening hours, he can keep up. "It might be something minor, but just something that's not being led by someone else, those are the fun things. I know professors who still do that too. That inspires me."

INTERVIEW

MARTIJN BROUWERS AND NORDIN HANSSEN

Physicians in science

A grant from the Dutch Diabetes Research Foundation has enabled Martijn Brouwers and Nordin Hanssen to continue their research, alongside their work as hospital doctors. Although they certainly would not be hard up for work if they did not secure research funding, they prefer to do more than just clinical work. “If we don’t do research, we’re like a kind of wizards.” A talk about hate, love, collaboration and poo.

How much time do you usually spend on research, besides your work at the hospital?

Hanssen: “I’m a trainee specialist, which is currently a full-time job. So I do most of my research in the evening hours and the weekends. I don’t regard that as problematic, and the department is quite willing to facilitate research.”

Brouwers: “I’ve been a staff member at the Department of Internal Medicine (Division Endocrinology and Metabolic Diseases) for six years now, I’m officially entitled to spend one day a week on research. That’s not enough to supervise my five PhD students, though, so I also do a lot of work outside regular working hours.”

Hanssen: “I have the benefit of doing evening shifts, for which I get compensation days. I’m happy to use them to get things done during the daytime.”

Brouwers: “But it still means you’re working mostly in your spare time. I sometimes have a kind of love–hate relationship with that. I made a very conscious decision to become a doctor, and the fact that we also do research makes our work very special. But there’s always that tension between your academic tasks: clinic, research and teaching.”

Hanssen: “It’s helpful that endocrinology is mostly about chronic disorders, which means that it’s fairly straightforward to plan our clinical work.”

Brouwers: “What also helps is that our team leaders, Professors Schaper and Stehouwer, are also clinicians who engage in scientific research and enjoy the combination.”

Hanssen: “Right: they also regard research as important. They understand what benefit it brings to patients, and so they see the importance of our doing it too.”

Brouwers: “I think the people around us are doing everything they can to facilitate our work, but certain developments in society, involving ever increasing bureaucracy, are putting pressure on things.”

But when you’re applying for a grant, do you never think: If I don’t get it I’ll just do only clinical work, which is just as much fun?

Brouwers: “I do like the clinic very much, but it’s particularly the combination with research and teaching that makes it fun. I do need the research component.”

Hanssen: “It’s the same for me. It’s often said you’re a doctor who’s doing a bit of research on the side, but for me the two go together. If we don’t practise science, we’re just a kind of wizards, aren’t we? It’s not just about generating new knowledge, but also about scrutinising existing knowledge. What you so often see in the clinic is that effects are attributed to therapies that don’t really have those effects.

IF WE DON’T PRACTISE SCIENCE, WE’RE JUST A KIND OF WIZARDS, AREN’T WE?

It's important that there are enough people in your field who are doing research."

Does applying for a grant become easier once you've been successful a few times?

Brouwers: "To some extent you find out what elements work, and how to distinguish yourself. The fact that my application covered the whole range from basic lab research to epidemiological studies like the Maastricht Study, and everything in between, did help, I suppose."
Hanssen: "I practised my pitch for the interview before the CARIM Research Council, which was really helpful. Certain types of research will always generate the same kinds of questions, as no research project is perfect. If you know how to answer those, or if you're able to indicate these limitations yourself, it says something about the quality of your application."
Brouwers: "I presented my application to researchers who are well versed in all aspects of the topic. On the whole I think that the greater the diversity of people who look at it, the better. I also think that that's what makes our group special: we cover the whole range of scientific research, from basic science to clinical studies."
Hanssen: "Yeah, we can do a lot ourselves, and if we need something new, we can easily contact pathologists or pharmacologists. If I want to do a study on myocardial infarction, we can turn to other groups for help. The field is developing rapidly, so sometimes it's not easy to decide what to focus on."

How do you relate to these developments as a researcher?

Hanssen: "When I had just started my PhD project, all you'd see at international conferences were GWAS studies. You see those less often now."
Brouwers: "Now it's all about poo. Suddenly the gut flora is responsible for everything."
Hanssen: "That's one of my problems. Should I study that subject now, for the Veni grant application I intend to write? Whereas our group is really more hypothesis-driven, rather than technology-driven. I think that's our distinguishing feature."
Brouwers: "We've set up a rather robust research line, which you'd hope will still exist in ten years' time. I could have made my grant application very topical by saying we're going to collect people's faeces, as it probably contributes to everything. I do make sure I'm up to date with the recent developments, but I then take a critical look at them to see how they fit in with my current research."
Hanssen: "I think we have a very solid approach here at Maastricht, while collaboration with other groups makes us flexible."

What do you still hope to achieve in the future?

Brouwers: "When I look back on my career later, I mostly hope to have enjoyed my work, and to have contributed something, on the one hand to patient care, and on the other hand to our knowledge about the role of (abnormal) hepatic metabolism in the development of systemic complications like cardiovascular disease and diabetes. It would be great if we could modulate that system so as to prevent diseases. Of course, if you think you're going to solve all that in the course of your own career, then you're heading for a burnout. But I would like to make a significant contribution."
Hanssen: "By 2030, 600 million people will have diabetes, and as a doctor I witness every day what an incredible burden diabetes still inflicts on some people. In the era before insulin became available, type 1 diabetes was a deadly disease; we've now left that era behind. Now we're in the era of complications. I hope we'll be able to leave that behind

us too someday; that we'll be asking ourselves in twenty or thirty years' time how these patients managed to cope for so long. So my main hope is to achieve a simpler treatment for type 2 diabetes, with fewer complications."

Martijn Brouwers
Internist/endocrinologist at Maastricht UMC+, member of CARIM's Strategic Board. Recipient of a 325 K€, Senior Fellowship grant from the Dutch Diabetes Research Fund. In addition, he received 200 K€ from the European Foundation for the Study of Diabetes in 2017.
"I'm examining the extent to which the accumulation of fat in the liver leads to cardiovascular disease. I intend to use the grant to find out how exactly hepatic fat accumulation arises, and what role nutrition plays in this process. It is especially fructose, which is currently being branded as the 'evil among sugars' by the media, whereas this has not been confirmed by all scientific studies. Our hypothesis, which we will test with the help of this grant, is that even a very small quantity of this fructose can be responsible for certain negative effects in the body. What I think is that fructose is not merely an energy substrate, but also a chemical messenger. If that is the case, then it's not much use trying to ban this type of sugar from your diet. In fact, that would be infeasible, as it's not only added to processed foods, but is also present in fruit and vegetables. I would sooner tend to consider drug therapy for people with diabetes or fat accumulation in the liver; a drug that would ensure that this specific sugar cannot cause this disadvantageous effects in the body. The ultimate goal being to prevent cardiovascular disease."

Nordin Hanssen
Fellow internist/endocrinologist at Maastricht UMC+. Recipient of a 270 K€ Junior Postdoc grant from the Dutch Diabetes Research Fund, as well as a 180 K€ grant from the Netherlands Heart Foundation (Dekker grant for trainee specialists).
"I study if and how a metabolite of blood sugar, methylglyoxal, damages the larger and smaller blood vessels and may thereby cause cardiovascular disease as well as the classic complications of diabetes, like blindness, neuropathy and kidney failure. We already found in previous research that the methylglyoxal levels in the blood closely follow the blood sugar level fluctuations, and our assumption is that this peak load is what is the most damaging. Our animal experiments have shown that such fluctuations cause higher levels of inflammation of the aorta, and activate immune cells. We hope to not only reveal such mechanisms, but also to further develop an inhibitor. Pyridoxamine resembles vitamin B6 and displays methylglyoxal lowering properties, and animal studies with this component have so far proved promising. So we're now also doing a clinical study among obese people, where we monitor the damage to small blood vessels that we think leads to the complications of diabetes."

TRAINING AND EDUCATION

04

INTRODUCTION

CARIM offers a flexible and integrated education and training programme that suits the individual ambitions of our students. Clinical and preclinical staff of CARIM is intricately involved in the development and execution of the education programmes of the FHML Master studies of Biomedical Sciences, Medicine and the Physician-Clinical Investigator Programme (MSc/MD) as well as in the design of a contiguous PhD (doctoral) training programme. The content of the PhD education programme has been developed by CARIM'S top researchers, while its framework has been created by senior educators of Maastricht University, who have earned an excellent international reputation for their didactical system that is based on problem-based learning. As from 2017, CARIM researchers have been actively and successfully involved in the education programme of the faculty of Science and Engineering.

RESEARCH MASTER

In the Biomedical Sciences programme, Master's students are informed about CARIM and the other FHML Research School programmes during the start of the master. Students can attend School-specific lectures and parallel programmes organised by School researchers. In the second semester, they may get acquainted in more detail with School-specific practical research. In this respect CARIM offers students the opportunity to do a junior research internship in the field of cardiovascular biology at one of CARIM's laboratories. In the second year, the students that are attracted to cardiovascular research can do their senior research internship and master thesis in CARIM. All too often successful Master students subsequently start their scientific career as PhD students within CARIM.

PHD PROGRAMME

Our PhD programme is accessible for talented and motivated students graduated from national and international Medical and Biomedical Masters. At the end of 2017, 105 PhD students attended our PhD programme. In 2017, 35% of our PhD candidates came from abroad, creating an exciting multicultural and international atmosphere. The translational nature of CARIM's research is exemplified by the mix of PhD students with a background in medicine or in the basic sciences. The principal goal of the 4-year PhD training programme is to support PhD candidates in developing themselves into independent and productive researchers in the cardiovascular field. To ensure high quality PhD training, CARIM offers frequent interaction of PhD candidates with skilled and experienced supervisory teams, thereby providing a stimulating and critical environment to further develop research skills. We also offer our PhD candidates a broad range of possibilities to attend general and school-specific courses, to attend seminars and master classes. PhD candidates are stimulated to visit symposia to present their own research on national and international podia.

NUMBER OF PHD STUDENTS
(date set 31-12-2017)

FUNDING SOURCE	2014	2015	2016	2017
UNIVERSITY	34	34	18	12
NWO	13	11	12	15
NON-PROFIT AND INDUSTRY	82	51	65	78
TOTAL	**129**	**96**	**95**	**105**

DAS-CAM

One of the key needs identified by the European Society of Cardiology is the training of future leaders in arrhythmia management and research. For this purpose, a new educational programme entitled 'Diploma of Advanced Studies in Cardiac Arrhythmia Management' (DAS-CAM) has been established. This initiative is a joint collaboration between MUMC+, European Heart Academy (EHA) and the European Heart Rhythm Association (EHRA), a long-standing provider of postgraduate education in arrhythmias. This unique course will train future leaders in arrhythmology to deliver state-of the-art cardiovascular services in the next decade and beyond. The programme brings together renowned experts, who will cover not only clinical cardiac electrophysiology and device technology, but also basic arrhythmogenesis and clinical epidemiology. Furthermore, topics like how to manage an arrhythmia unit and how to organize research and foster innovation will be included. Additionally, the societal impact and health economics of arrhythmias will be addressed. Thus, participants will acquire competences concerning content as well as context of cardiac arrhythmias. See pages 86-89 for an interview with **Harry Crijns** and **Pim Dassen** regarding DAS-CAM.

PHD DELIVERABLES

In 2017, 38 PhD students finished their theses within our institute and five theses were externally prepared. The table below illustrates the numbers of PhD students in the years 2008-2013, related to the period in which they obtained their degree. The table on page 14 present the number of PhD theses on the level of our research divisions.

PHD STUDENT CAREERS FROM 2008 UNTIL 2013 (date set 31-12-2017)

YEAR INTAKE	2009	2010	2011	2012	2013
COHORT VOLUME (annual intake)	34	31	37	28	22
MALE	18	12	19	12	7
FEMALE	16	19	18	16	15
PHD FROM ABROAD	12	14	15	11	8
DROP OUT	2	2	0	1	1
DROP OUT > 1 YEAR	4	3	1	4	2
THESIS COMPLETED	26	22	29	18	6
AVERAGE DURATION (in months)	64	60	59	50	50
ONGOING	2	4	7	5	13

CARIM THESES 2017

Hendrikx G -
Title: 'Spect imaging of cardiovascular neovascularization'
Promotors: Prof. F.M. Mottaghy; Prof. M.J. Post
Co-promotor: Dr M. Bauwens
January 26

Palau Cabellero G -
Title: '*In silico* mechanistic assessment of imaging-based measures of cardiac (patho) physiology'
Promotor: Prof. T. Delhaas
Co-promotors: Dr J. Lumens; Dr J. Walmsley
January 27

Van Gent W -
Title: 'Surgical treatment of venous leg ulcers'
Promotor: Prof. C.H.A. Wittens
Co-promotor: Dr E.G.J.M. Pierik, Isala Zwolle
February 2

Sallevelt S -
Title: 'Preventing the transmission of mitochondrial diseases'
Promotors: Prof. H.J.M. Smeets; Prof. C.E.M. de Die-Smulders
Co-promotor: Dr I.F.M. de Coo, EUR
February 3

Maessen D -
Title: 'Alpha-dicarbonyl stress: implications for obesity and type 2 diabetes?'
Promotors: Prof. C.G. Schalkwijk; Prof. C.D.A. Stehouwer
Co-promotor: Dr N.M.J. Hanssen
February 17

Martens R -
Title: 'Mildly reduced kidney function and albuminuria: looking beyond the kidney - the Maastricht Study -'
Promotors: Prof. J. Kooman; Prof. C.D.A. Stehouwer
Co-promotor: Dr R.M.A. Henry
March 23

Schellings D -
Title: 'Risk assessment after acute myocardial infarction; Role of novel biomarkers and implications for early discharge'
Promotor: Prof. J.C.A. Hoorntje
Co-promotors: Dr A.W.J. van 't Hof; Dr A. Adiyaman, Isala Zwolle
April 12

Juni R -
Title: 'MicroRNAs as regulators of cardiac vascular remodeling'
Promotor: Prof. L. de Windt
Co-promotor: Dr P.A. de Costa Martins
April 16

Clerx M -
Title: 'Multi-scale Modeling and Variability in Cardiac Cellular Electrophysiology'
Promotors: Prof. R.L.M. Peeters; Prof. P.G.A. Volders
Co-promotor: Dr P. Collins
April 20

Driessen A -
Title: 'Unintended effects of anti-hyperglycaemic drugs studied in population-based cohorts'
Promotor: Prof. J. van den Bergh
Co-promotors: Dr F. de Vries; Dr R.M.A. Henry; Dr H.A.W. van Onzenoort, UMC St. Radboud
April 21

Streng S -
Title: 'The path of life of cardiac troponin T; Proteomic Analysis of circulating proteoforms'
Promotor: Prof. M.P. van Dieijen-Visser
Co-promotors: Dr W.K.W.H. Wodzig; Dr D. de Boer
May 4

Yang Yu A -
Title: 'Towards understanding interchangeability of generic drugs'
Promotors: Prof. C. Neef; Prof. D. Burger, RUN
Co-promotor: Dr M. Maliepaard, Utrecht
May 19

Folkeringa R -
Title: 'Target Specific AF Management'
Promotors: Prof. H.J.G.M. Crijns; Prof. E.N. van Roon, RUG
May 24

Steinbusch J -
Title: 'In vivo ultrasound assessment of carotid artery walls and plaques: Integration morphological and mechanical characteristics'
Promotor: Prof. W.H. Mess
Co-promotor: Dr. K.D. Reesink
June 2

Van Hoof R -
Title: 'Dynamic contrast-enhanced MR imaging of Atherosclerotic plaque microvasculature'
Promotors: Prof. J.E. Wildberger; Prof. S. Heeneman
Co-promotor: Dr M.W. Kooi
June 2

CARIM THESES 2017

Scheijen J -
Title: 'The analysis of advanced glycation endproducts; A mass spectrometry-based approach and its applications'
Promotors: Prof. C.G. Schalkwijk; Prof. C.D.A. Stehouwer
June 21

Van Moorsel D -
Title: 'Insulin Sensitivity, Energy Metabolism & Cardiovascular Risk; Effects of Bcl I glucocorticoid receptor polymorphism and the biological clock'
Promotors: Prof. P. Schrauwen; Prof. N.C. Schaper
Co-promotor: Dr B. Havekes
June 23

Sabrkhany S -
Title: 'Platelets in cancer: a big role for small cells'
Promotors: Prof. M.G.A. Oude Egbrink; Prof. A.W. Griffioen, VUA
Co-promotor: Dr M.J. Kuijpers
July 3

Scheepers E -
Title: 'Uric acid, blood pressure and gout management; Beneath the surface'
Promotors: Prof. A.E.R.C.H. Boonen; Prof. I.C.W. Arts; Prof. C.D.A. Stehouwer
July 7

Van Eupen M -
Title: 'The accumulation of advanced glycation endproducts in diabetes and its relation to vascular disease'
Promotors: Prof. C.G. Schalkwijk; Prof. C.D.A. Stehouwer
September 7

Limantoro I -
Title: 'Electro-echocardiographic imaging in atrial fibrillation'
Promotors: Prof. H.J.G.M. Crijns; Prof. T. Delhaas
Co-promotors: Dr CB. de Vos, Hasselt; Dr B. Weijs
September 7

Li J -
Title: 'Macrophage stimulating protein (MSP) in the metabolic syndrome'
Promotors: Prof. R. Shiri-Sverdlov; Prof. J.F.C. Glatz
Co-promotor: Dr D. Neumann
September 8

Hazebroek M -
Title: 'Unraveling the origins of dilated cardiomyopathy: How genes, viruses, toxic, metabolic, electric and autoimmune disorders interact to cause dilated cardiomyopathy'
Promotors: Prof. S.R.B. Heymans; Prof. HP. Brunner-La Rocca
Co-promotors: Dr P. van Paassen; Dr R. Dennert
September 22

Wolters M -
Title: 'Advanced contrasts for vascular MRI'
Promotors: Prof. M.J. Post; Prof. W.H. Backes
Co-promotor: Dr M.E. Kooi
September 27

Sigterman T -
Title: 'Renal function after endovascular intervention; in patients with peripheral arterial disease'
Promotor: Prof. G. Schurink
Co-promotor: Dr L. Bouwman
September 29

Taramasso M -
Title: 'Open issues and next challenges in transcatheter mitral valve intervention'
Promotor: Prof. HP. Brunner-La Rocca
Co-promotor: Dr P. Sardari Nia
October 26

Duygu B -
Title: 'The therapeutic relevance of microRNA-199b in preclinical models of heart failure'
Promotor: Prof. L. de Windt
Co-promotor: Dr P. da Costa Martins
October 27

Duvivier B -
Title: 'Sit less or exercise more? Impact of interventions reducing sedentary behavior on cardiovascular risk factors'
Promotors: Prof. H. Savelberg; Prof. N. Schaper
Co-promotor: Dr A. Koster
October 27

Vajen T -
Title: 'Platelets and platelet extracellular vesicles as messengers in vascular inflammation'
Promotor: Prof. T.M. Hackeng
Co-promotor: Dr R. Koenen
November 9

CARIM THESES 2017

Van der Velde J -
Title: 'Sedentary behaviour, physical activity, and fitness: associations with cardio-metabolic health'
Promotors: Prof. N.C. Schaper; Prof. H.H.C.M. Savelberg
Co-promotor: Dr A. Koster
November 10

Godschalk T -
Title: 'New insights into coronary stent thrombosis'
Promotor: Prof. H. ten Cate
Co-promotors: Dr J.M. ten Berg; Dr C.M. Hackeng, St. Antoniusziekenhuis Nieuwegein
November 16

Pickwell K -
Title: 'The spectrum of diabetic foot disease: etiological considerations and prediction of outcome'
Promotor: Prof. N.C. Schaper
Co-promotors: Dr M. Kars; Dr V.D. Siersma, Copenhagen, Denmark
November 24

Willems B -
Title: 'Vascular smooth muscle cell phenotypic switching governs vascular calcification. Role of harnessing endogenous protective mechanisms'
Promotor: Prof. C.P.M. Reutelingsperger
Co-promotors: Dr L.J. Schurgers; Dr C. Vermeer
December 1

De Waard E -
Title: 'Bone microarchitecture, bone strength and fracture risk in prediabetes and type 2 diabetes melitus'
Promotors: Prof. J.P.W. van den Bergh; Prof. P.P.M.M. Geusens
Co-promotor: Dr A. de Koster
December 12

Vranken N -
Title: 'Non-invasive tissue oximetry: current and prospective applications'
Promotor: Prof. J.G. Maessen
Co-promotors: Dr P.W. Weerwind; Dr S. Teerenstra
December 18

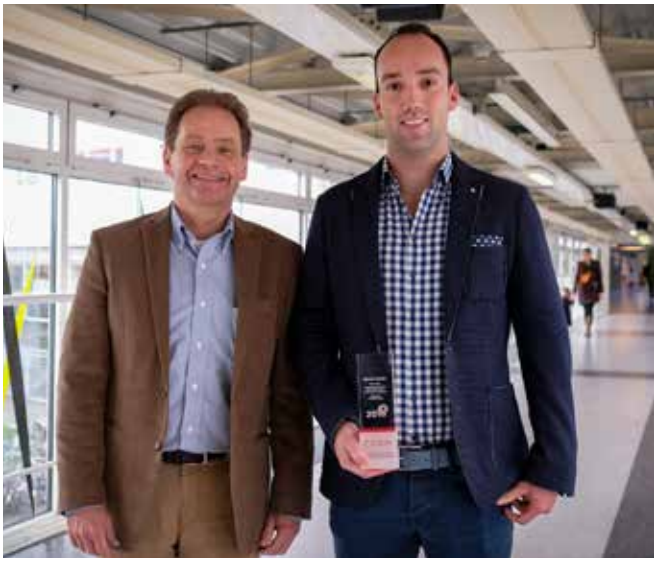
Den Biggelaar L -
Title: 'Nutrition and beta-cell function; Towards a better understanding of the effects of diet on type 2 diabetes'
Promotor: Prof. P.C. Dagnelie
Co-promotors: Dr S.J.M. Eussen; Dr S.J.S. Sep
December 19

Peeters S -
Title: 'Extracellular matrix remodeling and vascular complications in type 1 diabetes'
Promotors: Prof. C.D.A. Stehouwer; Prof. C.G. Schalkwijk
Promotors: Dr L. Engelen; Dr J. Buijs, Heerlen
December 20

De Clerck E -
Title: 'Ocular neurodegenerative changes and macular cysts in prediabetes and type 2 diabetes'
Promotors: Prof. C.A.B. Webers; Prof. C.D.A. Stehouwer
Co-promotor: Dr J.S.A.G. Schouten
December 22

DISSERTATION PRIZE 2016

Dr **Stijn Agten** (Dept. of Biochemistry) received the CARIM Dissertation Award 2016 for his thesis 'Oximation optimization and applications in cardiovascular research'.



KNOWLEDGE TRANSFER

CARIM COURSE WEEK

From June 29 until June 23, the annual CARIM Course Week took place. The week consisted of parallel courses, covering several aspects of CARIM's research, alternated with a combined scientific programme and a social programme organised by I'M CARIM, the organisation of CARIM's PhDs. In 2017, three courses were organised by CARIM researchers: 'Vascular Inflammation and Thrombosis', 'Drug Discovery and Development' and 'Advanced Microscopy and Vital Imaging'. Almost 50 PhD and Master's students participated.

CARDIOVASCULAR GRAND ROUNDS, CARIM SYMPOSIUM 2017 AND CARIM LECTURES

The Cardiovascular Grand Rounds Maastricht and the yearly CARIM Symposium are means to update the knowledge of our graduate students, our researchers and other external people with interest in the field of cardiovascular research. In the framework of the Cardiovascular Grand Rounds Maastricht, three successful lecture series were organised in 2017 by Dr **Blanche Schroen** and Dr **Jordi Heijman** (Dept. of Cardiology), with cardiovascular lectures given by national and international experts, on a weekly basis. These lectures take place early in the morning, with breakfast provided, and are of very high scientific level, worthy of an early rise. For the current programmes please visit www.carimmaastricht.nl, 'CARIM lectures' in the 'Education' section.

CARIM's annual scientific symposium was held in Maastricht on November 29. As in previous years a substantial part of the programme was the poster session, in which scientists of the institute presented their recent research findings.

The focus of the symposium was 'networks'; from electrical networks in the heart, data networks, public-private and international networks with lectures from Dr **Joost Lumens,** Prof. **Leon Schurgers,** Dr **Paola van der Meijden,** Prof. **Hugo ten Cate,** Dr **Wim van Zwam,** Prof. **Ton van Raan** and Dr **Aaron Isaacs.**

The traditional Robert Reneman lecture was presented by Prof. **John Griffin,** Professor at the Department of Molecular & Experimental Medicine at The Scripps Research Institute. His research has ranged from basic biochemical studies of clotting factors, lipids and lipoproteins to clinical investigations of risk factors for venous thrombosis. His studies have often emphasised translational research which most recently involved the engineering and development of a signaling-selective activated protein C mutant that progressed to a phase 2 clinical trial for ischemic stroke. At the CARIM Symposium, he discussed recent advances in understanding previously unknown procoagulant and anticoagulant factors which were discovered in the last few years.

Finally, the CARIM Award (see page 44), Dissertation prize (see page 75) and the poster prizes were awarded. The following posters were awarded with a prize:

- **'Vernakalant inhibits wave front turning during atrial fibrillation'** by Hunnik A van, Zeemering S, Podziemski P, Kuiper M, Winters J, Zink M, Sobota V, Gatta G, Schönleitner P, Gilber M, Antoons G, Scaf B, D'Allesandro E, Chmelevsky M, Verheule S, Schotten U
- 'Hypertension-induces vascular cognitive impairment: the microglial culprit' by Kerkhofs D, van Hagen B, Milanova I, Wijnands E, Goossens P, Rutten B, Blankesteijn M, Prickaerts J, Unger Th, Biessen E, van Oostenbrugge R, Foulquier S
- **'Oral anticoagulants as modulators of the pathogenesis of atherothrombosis'** by Gorp R van, Jaminon A, Bauwens M, Bucerius J, Brandenburg V, Jahnen-Dechent W, Spronk H, Reutelingsperger C, Schurgers L

On March 22, the CARIM lecture session 'Tissue engineering and regenerative medicine' was organised, including the following lectures: Prof. **Jan de Boer** (cBITE-MERLN); 'Digitizing the interface between cells and implants', Prof. **Mark Post** (Physiology); 'Microvascular (re)generation' and Prof. **Leon de Windt** (Cardiology); 'Cardiac regeneration without stem cells'. The scope of the CARIM lectures is to stimulate interaction between the themes and by focusing on cellular processes and techniques that may benefit science across CARIM's themes. Future meetings will centre around e.g. tissue regeneration, CRISPR/cas, single cell sequencing, energy metabolism, autophagy, etc.

OTHER CARIM LECTURES, SEMINARS AND SYMPOSIA 2017

Complementary to the regular lecture series and CARIM symposium, several lectures, seminars and conferences were organised by our research staff in 2017. Some of them are presented below.

Since 2015, CARIM and the Institute of Cardiovascular Research (IMCAR) of the University Hospital RWTH Aachen (headed by Prof. **Joachim Jankowski**) organise joint Cardiovascular Seminars. This lecture series, which is alternately held in Aachen and Maastricht, offers a platform for international top scientists in the field of vascular biology and nephrology to present their recent work.
In 2017, seven keynote lectures were given by Dr **Timo Speer** (Saarland University Medical Centre, March 16), Prof. **Pieter Evenepoel** (University of Leuven, May 18), Prof. **Joachim H. Ix**

(University of Carolina, San Diego, July 6), Dr **Ilze Bot** (UMC Leiden, September 14), Prof. **Norbert Stefan** (University Tübingen, October 12), Prof. **Mihai G. Netea** (Radboud UMC Nijmegen, November 9) and Prof. **Dominique de Kleijn** (UMC Utrecht, December 7).

The **Maastricht Systems Biology Forum** held three meetings in 2017, covering 'Systems Biology of Neural and Genetic Networks (NeuGenNet)' on February 23, 'Biomedical Applications of Classification Methods' on July 11, and 'Risk Prediction of Thrombosis and Bleeding' on October 24. This working group brings together researchers in the Maastricht area who are interested in the development and application of systems biology approaches. The main aim is to share research, experience and, through this exchange, inspire and initiate new research directions and collaborations. The Forum is organised by Dr **Michiel Adriaens** (MaCSBio), Dr **Pietro Bonizzi** (DKE), Dr **Mike Gerards** (NeuGenNet), Dr **Jordi Heijman** (CARDIO), Dr **Martina Kutmon** (BiGCaT & MaCSBio), Dr **Joost Lumens** (BME), Dr **John Walmsley** (BME) and Dr **Stef Zeemering** (FYS).

On January 13, the inaugural lecture '*Niet alleen met medicatie*' of Prof. **Bram Kroon** (Dept. of Internal Medicine) took place.

From February 8 until 10, the **7th edition of Maastricht AF - Crossing Borders**, organised by the Department of Cardiology, was held at the Crown Plaza Maastricht. This course was dedicated the latest insights into hybrid surgical and EP treatment of complex persistent AF, including arrhythmia ablation and stroke prevention. Today, hybrid ablation has been advocated for complex AF for more than a decade.

The Maastricht Consensus Conference on Thrombosis (MCCT), organised by researchers from the Dept. of Biochemistry and the Dept. of Cardiology took place from February 22 until 24 in the Maastricht Exhibition & Congress Centre (MECC). The MCCT was a hybrid meeting containing both active as well as more 'passive' elements (intensive workshops, and plenary lectures), seeking consensus on future directions for thrombosis research. The MCCT, involving plenary lectures by prominent scientists and experts in the field on a chosen theme, followed by highly interactive, intensive workshops in which the interaction between the experienced scientists, PhD students and postdocs, is used to explore gaps in research or knowledge on specific topics.

CARIM-BAYER collaboration in action: achieving a first milestone!
The kick-off meeting for the CARIM-Bayer collaboration took place in January. Through mutual interest in atherothrombosis both parties worked consistently towards a first research programme aiming at identifying targets for atherothrombosis research (and therapeutic intervention).

The **21st European Vascular Course (EVC)** was organised from March 5 until 7 in the MECC. The main topics in the theoretical part of EVC concentrated on arterial and venous pathologies and vascular access. The practical curriculum consisted of 50 workshops and master classes. The course hosted 2300 participants from 60 different countries. More information is available at www.vascular-course.com.

On March 6, the **Symposium on Doppler ultrasound phenotyping** took place. A lecture, lunch-discussion and workshop 'The Role of Blood Flow Velocity Measurements in Rodent Models for Translational Research' by Dr Reddy, Assistant Professor, Baylor College of Medicine was hosted by the CARIM Muroidean Facility.

In the framework of the valedictory celebrations of Prof. **Thomas Unger,** the symposium **'Focus on hypertension, the number one killer worldwide'** was organised on March 24, in collaboration with the Royal Netherlands Academy of Arts and Sciences (KNAW). Awareness and control of hypertension are among the greatest medical challenges of our time, with an enormous therapeutic potential. The symposium brought together European experts to address various aspects of hypertension research. It aims to further our understanding of the epidemiological importance of high blood pressure as the global number one cause of death, its underlying pathologies, hypertension-induced end-organ damage (with sudden events like stroke and chronic diseases such as heart and kidney failure), and modern

therapeutic approaches based on antihypertensive drugs and non-pharmaceutical procedures such as baroreceptor stimulation or renal nerve ablation.

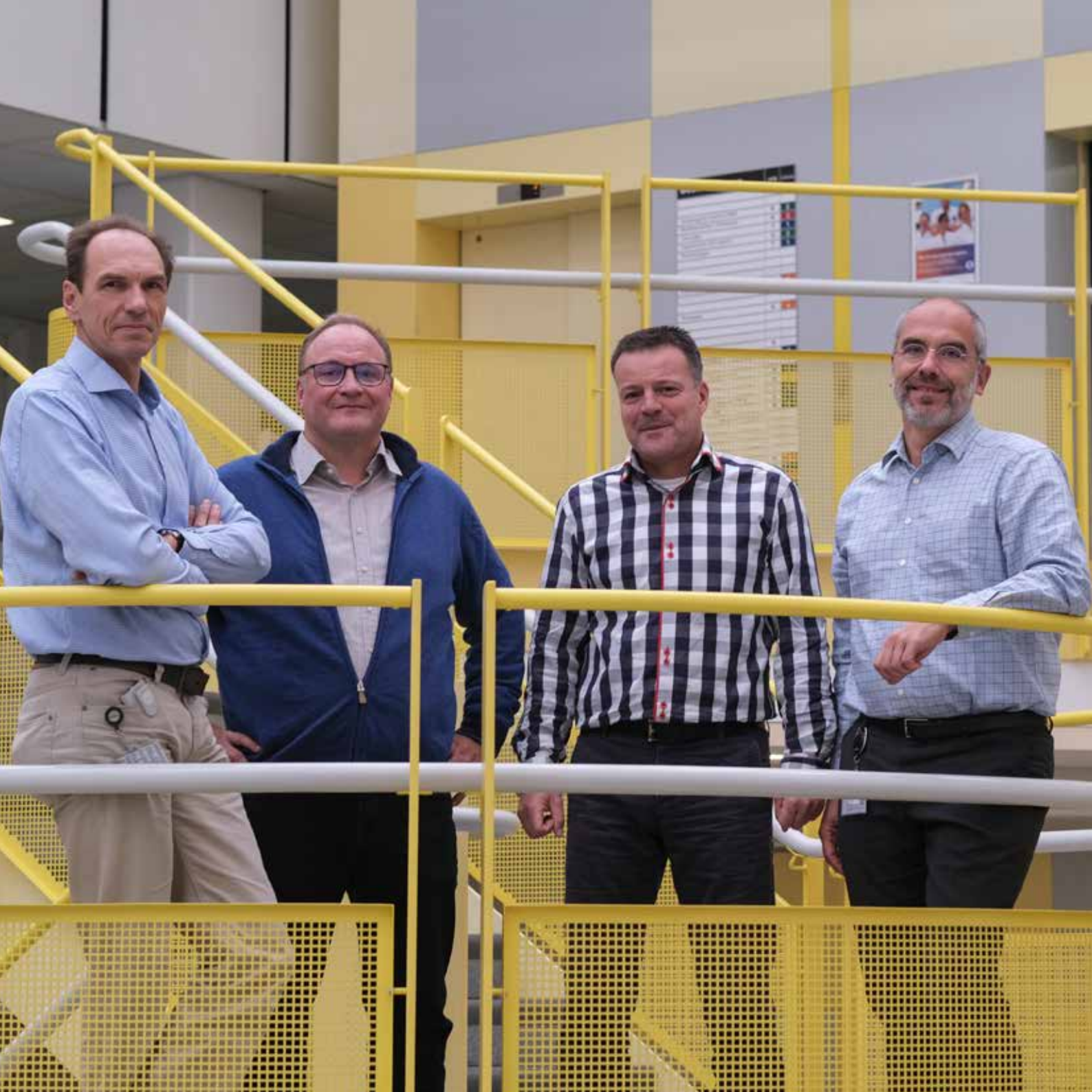
The **4th Scientific Meeting of the Maastricht Study** took place on March 30. The aim of the scientific meetings is to present recent results from the Maastricht Study, in order to facilitate discussions between scientists from Maastricht University from a broad range of disciplines and to strengthen collaborations. The key note lecture from Dr Annemarie Koster educated us on the causes and consequences of too much sitting. Several PhD students presented their studies. Results from the Maastricht Study indicated that biomarkers of left ventricular dysfunction and ischaemia are independently associated with abnormalities on brain magnetic resonance imaging (MRI) in both older and younger individuals, but with cognitive performance only in older individuals. Furthermore, results showed that prediabetes and type 2 diabetes are associated with generalized microvascular dysfunction and white matter abnormalities in the brain.

On June 9, the **MaCSBio Science Day** took place. The theme of the meeting was 'Extending Networks' and focused on fostering and expanding collaborations at Maastricht University and beyond.

On June 16, the **Maastricht Microscopy Meeting (M3) on Advanced Microscopy and Vital Imaging** took place at the MUMC+. Several international speakers presented the latest info on different microscopy and imaging techniques.

From September 3 until 5, the **3rd International Conference on Cultured Meat** took place in Maastricht. The conference is a unique, multidisciplinary event focusing on a specific application, Cultured Meat. The previous two editions were very successful and highly appreciated exactly because of the range of disciplines present, creating a lively atmosphere and debate.

On November 3, Prof. **Harry Struijker-Boudier,** former CARIM scientific director gave his farewell lecture on the occasion of his retirement from Maastricht University. In this lecture – entitled 'The pharmacologist: precision doctor or scapegoat' he reflected on the contemporary significance of the interpretation of Plato's classical Greek word pharmakos (scapegoat) as someone with both the power to heal and to threaten existing societal stability. In simpler, contemporary phrasing: how to balance therapeutic and toxic effects of drugs. In addition, he looked back on his 42 years career at Maastricht University, where he was appointed on January 1, 1976 with the assignment to establish a laboratory and department of Pharmacology in the new Maastricht Medical School together with the clinical pharmacologist Karl-Heinz Rahn. They set up the teaching of pharmacology and pharmacotherapeutics. Furthermore, they initiated a research programme on the pathophysiology and treatment of hypertension. This programme became the nucleus of one of the divisions in CARIM.



HIGHLIGHT

VASCULAR NEUROLOGY

RESEARCH THAT CROSSES BOUNDARIES

Wim van Zwam | Robert van Oostenbrugge | Walter Backes | Joachim Wildberger

Vascular neurology: research that crosses boundaries
A standing ovation at the World Stroke Conference in Istanbul in 2014, followed by worldwide adjustment of treatment guidelines for patients with an acute cerebral infarction. That was the scientific climax of the collaboration between interventional radiologist Wim van Zwam and neurologist Robert van Oostenbrugge. Van Oostenbrugge is also researching Cerebral Small Vessel Disease, a disorder of the smaller blood vessels in the brain, for which he collaborates closely with medical physicist Walter Backes. Backes was the author of the best article in the Radiology journal in 2017, for which he won the Alexander Margulis award for his group: they had managed to visualise the subtle leakage through the damaged blood-brain barrier in people with Alzheimer disease. An interview with a group that does not care about boundaries between disciplines or Schools.

Research into vascular neurology in Maastricht is working along two main lines: the smaller perforating vessels in the brain, and the larger blood vessels that feed them.

Since 1995, the standard method to dissolve clots in the (larger) cerebral vessels consists of intravenously administering clot-dissolving agents. However, this treatment is not effective if one of the larger, more proximal blood vessels in the brain (with a diameter of 3 to 5 millimetres) gets occluded. The idea arose to remove the clot from the vessel using a catheter. The study entitled MR CLEAN (the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) focused on people with a proven large vessel occlusion in the cerebrum. It was set up jointly with the Academic Medical Centre Amsterdam and Erasmus Medical Centre in Rotterdam.

PRAGMATIC APPROACH

The six coordinating researchers (one interventional radiologist and one neurologist from each of the three participating centres) decided upon a pragmatic approach: in order to be able to include five hundred patients in a short period of time, and to ensure that the results, if favourable, could be implemented across all hospitals, they were not

very selective in including patients. Also, all intervention centres, large or small, whether university-related or not, were asked to take part in the recruitment further increasing the generalisability of the results. Patients were included if a scan showed occlusion of a major afferent blood vessel in the brain, even if they were elderly or had a poor initial clinical status for other reasons. This approach, however, did involve a certain risk. As interventional radiologist Van Zwam explains: "We encountered quite a lot of criticism, as we were taking the risk that we would not be able to prove an effect in this heterogeneous sample. But it turned out otherwise: our assumptions proved to be correct and the trial found a clearly favourable effect on the clinical outcome."

CLOSELY KEPT SECRET

Whereas usually only one in five patients show full recovery after a cerebral infarction, the new endovascular treatment resulted in one in three recovering completely. The first occasion to present their results was in Istanbul, and they managed to guard the secret until then. Since the outcome of the trial could mean either a death blow to the intervention or a breakthrough in the treatment of acute cerebral infarctions, there was quite a lot of nervous excitement. When the audience came to realise the full impact of the results, a standing ovation followed, and immediately afterwards all ongoing trials in the world were halted for interim analysis. These trials also found overwhelmingly favourable outcomes, after which it was deemed unethical to continue randomising patients. Within three years, the treatment guidelines for acute cerebral infarction had been adjusted. Van Oostenbrugge: "Not bad for six guys from the Dutch polders, as that's how we were initially more or less regarded by the establishment, due to our pragmatic approach."

MR CLEAN KEEPS GOING

The MR CLEAN study did not stop after this. For example, of course, the clots you remove are excellent research material. They will be studied, for instance, by the Maastricht research group led by Prof. Ten Cate, which is renowned for its coagulation research. In addition, researchers will study biomarkers in the blood to establish more information on the aetiology of their stroke. All endovascular stroke treatments in the Netherlands are performed in sixteen centres, which has also resulted in a unique database with treatment results of over five thousand patients: the MR CLEAN Registry. Several PhD students, at Maastricht, Rotterdam and Amsterdam, are doing research using this data set. And follow-up research has been secured by founding CONTRAST (Consortium for New Treatments in Acute Stroke).

BRILLIANT RESEARCH

Researchers not involved in MR CLEAN can also get access to the data from the trials and the Registry. It has not been made fully open-source, as you need to understand the data well to be able to work with them, but anybody can apply for a specific data set. The group is receiving many requests for such data sets from other countries. Both, a Dutch and a European innovation award have already found its place on the wall in Maastricht. Joachim Wildberger, head of the Department of Medical Imaging at MUMC+, and a CARIM PI on imaging, is very proud of his colleagues: "This is crucial research, which has resulted in major changes to the care for acute stroke patients. That's not something that happens often. In my opinion, the important factors were the pragmatic approach and the close collaboration between Radiology and Neurology, as well as between centres. Maastricht couldn't have done it without Rotterdam and Amsterdam, and vice versa. And I think it's very impressive

that they've already defined four further trials. You can only do that if you have the right experts in all fields."

RESEARCH INTO SMALL VESSELS

He is also referring to clinical physicist Walter Backes, who is leading research into the smaller vessels in the brain, together with neurologist Van Oostenbrugge. This research represents a bridge between CARIM and the MHeNs research school, in which research into Alzheimer disease is concentrated. One of the main interests in this collaboration is the chronic effect of the minor perforating vessels in the brain on structural brain abnormalities and cognition. Cerebral Small Vessel Disease (cSVD) contributes to the development of dementia in at least forty percent of all cases. Early diagnostics might reduce this vascular contribution to neurodegeneration. Backes: "One of the problems is that the vessels becomes leaky due to damage to the blood-brain barrier, and with that the brain loses its protection. This explains why a disorder of the small vessels affects brain functions." Since eighty percent of the people with Alzheimer have some pathologic vascular burden in the brain, researchers assume that vascular factors are almost certainly contribute to Alzheimer disease. They also think it is still early days as far as research into this is concerned. This study's success is also due to the right collaboration, in this case between researchers at the Alzheimer centres and the Departments of Radiology of the Leiden and Maastricht UMCs.

MINOR HAMMER BLOWS TO THE BRAIN

A few years ago, Van Oostenbrugge and his colleagues were wondering how the small vessels in the brain could contribute to brain tissue damage when they become stiffer as a result of disease or ageing. Each quantity of blood that is pumped into the brain at high pressure causes a pressure pulse wave, which is not fully cushioned by elastic vessel walls. They were asking themselves what this minor hammer blow delivered to the brain at each heartbeat does to the cerebral tissue. Van Oostenbrugge: "So I turned to Walter with what seemed to me a simple question: whether he could measure the pulsating activity of the small vessels. There was no method for this available at that moment." And it was not just a matter of administering a contrast agent and make high-resolution images; to begin with it requires huge computing power and encoded video recording instead of photos. By now, it has become possible to measure this reliably using the 7T MRI machine located across the road at Scannexus. When examining healthy volunteers, Backes and his colleagues saw that the vessels in the older subjects were less flexible: they become hardened and so are less able to dampen the pressure pulse wave. The researchers are about to start recruiting patients for a large "proof of principle" study. By joining up a technician with a clinician, and collaborating with colleagues at Scannexus, this makes it possible to develop technological innovation that's really close to the clinic.

NEUROVASCULAR UNITOPATHY

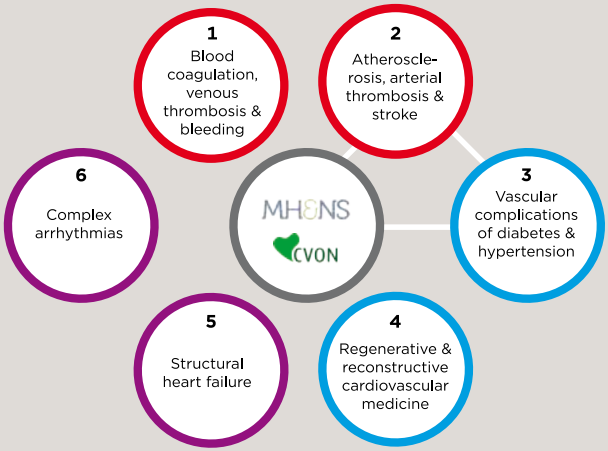
According to the four interviewees, Maastricht has a very strong position in research into vessel walls, especially their functional characteristics. Together, they recently figured out that the hardening of blood vessels in the brain also results in larger distances to the brain tissue (as Backes was able to record signals of water at these sites with his scanner), and that this is one of the first signs of cSVD. Van Oostenbrugge: "The research at Maastricht is often in the vanguard in this respect. Walter always says: 'I can scan and come up with technological innovations, but if there's no clinically relevant question to be answered, then what am I doing?' We always have very specific questions to help

us understand this disease better." And so their idea that this is not merely a vascular disease, but a disorder of the complex regulating mechanism between the brain and the vessels (a neurovascular unitopathy) which is important for the development of cognitive disease entities, is gaining solid footing.

PEOPLE MAKE THE DIFFERENCE

Each of them clearly understands that the others can offer the expertise they need to answer their scientific and clinical questions. As Backes puts it soberly: "So as long as there are no ego clashes, it should work..." Joachim Wildberger fully agrees: "These people are not flaunting their own ego, and that's what makes them so successful. Of course, together with the members of their group, who shape the collaboration on a daily basis. It's people who make the difference. It doesn't matter on whose territory you are: the emphasis is on collaboration, not on staking out territories in whatever structure. It's not where you're coming from, but where you're going to that's important."

***Wim van Zwam** is Interventional Radiologist at the MUMC+*
***Robert van Oostenbrugge** is Professor of Clinical Neurology, specialising in Vascular Neurology*
***Walter Backes** is Professor of Clinical Physics, specialising in Neuroimaging*
Joachim Wildberger is Professor of Radiology



HIGHLIGHT

INTERVIEW

HARRY CRIJNS AND PIM DASSEN

Shaping the leaders for the cardiac arrhythmia management of the future

Harry Crijns would definitely have wanted to attend the programme himself, had it already existed twenty years ago. The Diploma of Advanced Studies in Cardiac Arrhythmia Management (DAS-CAM) would have been the perfect preparation for his current position as head of the Department of Cardiology at MUMC+. “I did take some courses and had some coaching over the years.” Pim Dassen adds drily: “And we’ve been very patient with you.” Both men have been active members of the programme committee ever since DAS-CAM was set up, with Crijns acting as chair.

The first batch of 'students' have just completed the programme. The quotation marks are there to indicate that the name 'students' is actually a misnomer for the target population of DAS-CAM. They are experienced cardiac electrophysiologists, certified by the European Heart Rhythm Association (EHRA), who have the ambition to become leaders in their field and are highly interested in science and very eager and motivated to learn new things. Over a two-year period, they attend eight modules, two in Brussels and six in Maastricht. Each module focuses on a specific theme, whose content is designed by two 'anchor persons'. These experts in their specific fields attend the course in person to be with the participants for five consecutive days, while the students also attend lectures and seminars in a problem-based learning setting.

ALWAYS A JOY

"The face-to-face meetings are always a joy," says Crijns. "For instance, we have a whole morning to practise aspects of leadership in real-world situations, aspects that are never addressed in regular courses." Dassen adds: "It's one of the most highly valued components of the programme. It's where they learn things like negotiating, as they're given the assignment of setting up a new department of electrophysiology at a hospital. They then have to go and talk to the management about things like the numbers of operating rooms and beds that they would like. And then after the coffee break we switch roles: they're no longer the enthusiastic cardiologists, but they're now the hospital management. What they all take away from that exercise is that you can win most by not just asking yourself what you definitely want to get out of it, but asking yourself especially what the other party would value most. There might be some things that you'd really like to achieve but which are not that relevant to the other party, and vice versa. So your angle is that the other party definitely has an important point, and you use it to trade it off for something that isn't all that important to them. That was an eye opener to most participants." In addition to these leadership aspects, there is the 'hard-core science' of treatment and diagnosis, while they also learn about things like health economics or cardiovascular biostatistics.

INTERESTED IN THE YOUNGER GENERATIONS

The idea for this training programme was hatched by the ageing but highly experienced brain of Professor Panos Vardas, President of the European Heart Agency. Crijns chuckles about the paradoxical situation that a 'dinosaur' like

DAS-CAM WOULD HAVE BEEN THE PERFECT PREPARATION FOR HIS CURRENT POSITION AS HEAD OF THE DEPARTMENT OF CARDIOLOGY AT MUMC+

Vardas can still take an interest in the younger generation of leaders. “He was right on the ball there. There are so many topics that are relevant for this generation but which are insufficiently addressed in their training programmes.” Since Maastricht is internationally renowned for its expertise in cardiac rhythm, it was no surprise that they won the tender for developing the programme, beating centres in Barcelona, London and Zurich. “By a landslide, in fact,” says Crijns, justly proud. Together with colleagues from Maastricht like Schotten, Volders and Prinzen, he is also the 'anchor person' for one of the modules. “You do need to be on your toes all the time, as the participants are highly intelligent and eager people. And they’re great fun to work with.”

THIRTY-TWO PARTICIPANTS WITH A VARIETY OF BACKGROUNDS

The 32 participating doctors come from 22 different countries. This geographic spread was one of the preconditions set by EHRA. Another was to include enough women in the selection. In the end, twelve women attended. Crijns: “That’s less than half, but for a group of electrophysiologists, that’s still really a lot. Just like surgery, this is a discipline that is so far still dominated by men.” All participants but one have successfully completed the modules, and so will receive their diploma from Maastricht University at the end of the year. Dassen: “The one participant who didn’t complete the programme was offered a leadership position during the course, which meant he was a bit short of time.” Other participants also saw their dream jobs come true, probably helped to some extent by the DAS-CAM course, or so the two men assume.

SECOND BATCH TO START IN 2019

The second batch of participants will start the programme in February of 2019; there is already a waiting list of people who would like to attend. By the way, there is no direct involvement from the industry in the content of the programme, as often was the case with such programmes in the past. All they do is provide financial support. Crijns: “The relationships between cardiologists and the industry are becoming more and more transparent. And so the industry was very happy to take this opportunity to invest in the training of specialists who in the end are crucial for the infrastructure that is important to market their products.” Dassen, who is the intermediary between the training programme and the university, emphasises: “ Shaping future leaders includes making participants aware of their personal leader style, recognising that most of them do work in a team and are already exposed to leading that team. We encourage their awareness of the type of leadership that suits them.”

www.dascam.org

INTERVIEW

JOHAN HEEMSKERK AND STEVE WATSON

Working together in a friendly field

After they had grown up together scientifically in the platelet field for thirty years, Johan Heemskerk and Steve Watson have developed a deep sense of mutual trust and respect. Exchanging techniques, PhD students and even scientific secrets comes naturally to them. “In science, there’s a lot more cooperation than ever before, but I wouldn’t say there’s more trust as well,” says Watson. “It’s not a universal thing,” agrees Heemskerk. In November 2017, Steve Watson was appointed to the H.C. Hemker Chair as visiting professor for two years.

"Don't mention the 'thirty years' too often," laughs Watson halfway through the interview. It probably emphasises a bit too much that both men have left their younger years behind them, while the fact that they both have well-established positions is of course a huge advantage when it comes to opening up to colleagues. Watson: "We don't have to make sure so much anymore that we're seen as independent scientists. I think this is how science should be done, but it's only because we're relaxed enough with each other that we can." After meeting more and more often at conferences and meetings in the early years of their careers, they started exchanging PhD students for short periods, and one thing led to another.

FIFTEEN PHD STUDENTS, SEVEN INSTITUTES

So when Watson asked Heemskerk if it would be possible to visit his Maastricht laboratory to learn to perform in-depth flow experiments (a strength of the laboratory) on the GPVI-receptor he is working on, Heemskerk immediately saw an opportunity. Together with Watson's group and five other European laboratories, they had applied for a major European grant. This multidisciplinary programme of work entails both doing research and training fifteen PhD students to find new ways to develop drugs that block thrombosis. (See the TAPAS text box). The pursue of a joint PhD-programme made it necessary to intensify their cooperation, and Heemskerk saw a great opportunity in the Hemker Chair, which supports collaborations that are profitable to CARIM as well as the visiting professor. They also have a further shared PhD student, Gina Perrella, through the Birmingham-Maastricht joint PhD studentship scheme.

NATURALLY NOSY

Watson was "delighted" with the offer and did not need any time to think it over. In the first year he has been over

Johan Heemskerk

for a week on five occasions. He interacts with many of the members of the Department of Biochemistry, in the stimulating way he himself describes as "naturally nosy". Heemskerk: "That makes Steve a very stimulating scientist. The whole group profits from being able to speak in person with a leading scientist in the field." Watson: "Johan has been particularly supportive, by arranging for one of his PhD students, Magdi Nagy, to support me during the visits." Nagy and Perrella have since accompanied Watson to Santiago in Chile to replicate Maastricht experiments there, working with three of the only seven families in the world that lack the GPVI-receptor. "That's an absolutely unique experience. Johan's relaxed attitude is quite an unusual characteristic for a group leader." Heemskerk agrees: "It's not a universal thing indeed. I collaborate with many colleagues, but with a limited amount of openness. There's always the competition part

as well, but in this case, the collaboration is more important than the competition."
Apart from knowledge, they also exchange technology. The flow chamber to investigate thrombus formation in the lab, which was designed and perfected by Heemskerk's group in Maastricht, has made it to Watson's lab and to the partner in Chile. Watson: "We're now replicating the Maastricht experimental conditions, which allows us to make more direct comparisons of results between laboratories, and that's very important to delve deeper into the mechanisms of thrombus formation."

PRACTICAL HURDLES

By the end of 2018, all fifteen PhD students in the TAPAS programme will have started in seven different labs. They all stay at two different project partners, which makes it a challenging organisational puzzle. Between Maastricht and Birmingham for instance, two students will be jointly supervised. But the thesis trajectory in the two countries differs. Whereas in the Netherlands several scientific publications are necessary to obtain a PhD, that's not a requirement in the UK at all. And while a thesis in the UK is assessed in a closed room with two examiners, after which changes are nearly always made to the thesis, in the Netherlands it takes the form of a public defence in the presence of the candidate's family, and the degree is awarded on the same day. So these practical hurdles need to be overcome for each joint degree combination. Watson: "And then there's of course the fact that research doesn't always progress at the speed you hoped for. If a student has to move to another laboratory after twelve months, that can be a challenge as well." Heemskerk: "The best we can do is to attract the best possible students for these positions and to be clear in our plans and how the students can help each other. That helps, I think."

ONE MAJOR DIFFERENCE

They emphasise that the differences between their respective institutes look bigger on paper than they are in reality. Both of their departments provide a warm and supportive environment, and the research questions are the same on both sides of the Channel. Watson: "We've both trained several of the leading PIs in our institutions, so there's a critical mass around platelet biology and thrombus formation. The only major difference I see is that most of Johan's students are Dutch, except for Magdi. In my lab we have people from all over the world, which is probably the advantage of having English as your first language and being in a big city, rich in ethnic diversity." Heemskerk: "Maastricht aims to be a very international university indeed, but it's mostly true for the undergraduate programme so far. I think that we and CARIM can do better, and I hope that these joint PhDs will also help with that. Having Steve as a visiting professor is also inspiring in that respect."

A FRIENDLY FIELD

"The platelet field as a whole is a very friendly field", says Watson. "I don't know exactly why. Maybe because we pulled together when science became more interdisciplinary after the molecular biology methodology became a dominant force in other disciplines. Platelets don't have a nucleus, so we naturally came together with a common approach and set of experimental tools." Heemskerk: "I see another factor. We know by now that platelets are involved in so many processes that there is enough to look into scientifically for everyone. One group looks at inflammation, another at cancer, or diabetes. The platelet physiology and cell biology is their common denominator, but the applications are so widespread that there's no need for fierce competition."

TAPAS *(TArgeting Platelet Adhesion receptors in thrombosiS) will position Europe at the forefront of innovative research to prevent thrombosis and thrombo-inflammation, and will train a uniquely qualified cohort of early stage researchers (PhD students) in a highly intersectorial and multi-disciplinary programme, which will equip them with the knowledge and transferable skills required in the broad biomedical sector. The project, funded by the European Union, intends to find new ways to target thrombosis through co-operation of academic experts in distinct disciplines with key skills from the private sector.*

THE BENEFICIARIES ARE:

The University of Birmingham, UK (lead)
Maastricht University, The Netherlands
The University of Reading, UK
Leibniz-Institut für Analytische Wissenschaften ISAS-EV
Dortmund, Germany
Universitätsklinikum Würzburg – Klinikum der Bayerischen Julius-Maximilians-Universität, Germany
Alacris Theranostics GmbH Berlin, Germany
Universidad de Santiago de Compostela, Spain

INTERVIEW

VANESSA VAN EMPEL AND BLANCHE SCHROEN

The unique patient and the uniform model

Cardiologist Vanessa van Empel and Professor Blanche Schroen are a successful example of the collaboration between the clinic and scientific research. Together with other CARIM colleagues and researchers from Groningen (see text box) they are looking for new avenues to detect heart failure due to a thickened, hardened cardiac muscle at an early stage, and slow down its development. In May 2017, the group was awarded a 1 million euro CVON grant from the Netherlands Heart Foundation for this work. “Collaboration between preclinical and clinical experts requires investments from both parties, also at a personal level,” says Schroen. Van Empel adds: “It’s the science of the future”.

A thickened, hardened cardiac muscle as a cause of heart failure is more common among women than among men. And according to Van Empel: “we don’t really know why. These people are severely dyspnoeic, can no longer climb up stairs, and find it ever harder to manage at home. They are often elderly, can no longer ride a bike, and so their worlds become smaller and smaller. As long as they’re at rest everything is fine, but any exertion is too much for them.” There is as yet no effective treatment for this condition. The diagnosis is based on a combination of ultrasound examinations and the symptoms. “But dyspnoea is a feature of many other diseases as well, so we want to be able to recognise it more accurately and at an earlier stage.”

THE ROLE OF SMALL BLOOD VESSELS…

One of the hypotheses is that the process in women involves the very smallest branches of the heart’s blood vessels. Such small vessels can be more easily measured at other sites of the body than the heart, such as the arm or the eye. This is why, in addition to ultrasound examinations of the heart, special cameras are used to evaluate the condition of the small blood vessels in the skin and the eye. The mechanisms are investigated further with the help of animal studies. Schroen: “The question is whether it is the blood vessels which get damaged first and then cause the cardiac muscle to become thickened and hardened, or whether the blood vessel damage is a result. That can be simulated in test animals.”

… AND ABNORMAL INFLAMMATION

These patient also often have abnormal inflammations. Hence, human body materials and test animals are used to examine the gene expression patterns in certain inflammatory cells. “We’re finding differences between people with heart failure and people who only have high blood pressure, for instance,” explains Schroen. One aspect she is researching is whether suppressing the inflammation, or saving the small blood vessels, could slow down the disease process. “My expertise concerns linking up all these systems and finding out how we might use this as a basis for therapies in the distant future.”

AN EXCEPTIONAL PATIENT COHORT

The process of including patients in the studies, which at the time of this interview was still in full swing, is mostly done at Maastricht. Van Empel: “That’s because we have the expertise on microcirculation, partly through the Maastricht Study. We’re really very good at vascular measurements.” Schroen: “What Vanessa has achieved at the clinic in a short time is really exceptional.” She is referring to the large, extensively phenotyped cohort of patients with this disease, which is used to perform standardised research, including follow-up. Van Empel: “That’s the most important activity of a university medical centre. I think this cohort makes us unique in the Netherlands, even in Europe.” Schroen: “This is the result of Vanessa’s efforts, but also of the available infrastructure that makes this possible.” Van Empel: “The department gives me plenty of leeway, as it’s a focal point of the heart failure group.” Schroen also praises CARIM’s efforts to hire more young people, which means that the younger generation gets more opportunities and feel more committed to the institute.

A BULL IN A CHINA SHOP

Another major factor in the success story is the links that are continually being forged between the clinic and basic research. For these two researchers, it is the most intensive collaboration between clinic and basic research in their career so far. They were more or less paired up by Prof. Harry Crijns, head of the Department of Clinical Cardiology. “You two should get together someday,” he said, as he recognised the overlap in their research interests. It proved a good match, which both perceive as very fruitful. Schroen: “Vanessa’s

advantage is that she did her PhD at the lab, so we speak each other's language. And she has the patience to teach me about work at the clinic, as I can sometimes be a bit of a bull in a china shop there." Van Empel: "We sometimes tend to isolate one aspect of a disorder and then to suggest some 'simple' solution for that, which might not fit a particular patient's context, or which might prove too expensive in practice." Schroen: "At the clinic, each patient is unique, whereas as a researcher you have to work with groups, which means you sometimes lose sight of a patient's specific characteristics." Van Empel: "We use animal studies to construct a uniform model, but patients of course are never uniform."

NOT GETTING IN EACH OTHER'S WAY

Van Empel and Schroen are increasingly seeing the added value provided by collaboration between the clinic and basic research. Van Empel: "A lot of synergy goes into designing the studies, as a result of our combined expertise. For instance, if we find pathophysiological differences in inflammations in mice, we need to know whether we can also measure these in humans. And then Boy Houben might come up with an idea which I could never have thought of on my own." Schroen: "When I postulate something, I like to have it checked by Vanessa first." Van Empel: "That's where our strength lies: we don't get in each other's way. As a cardiologist, I don't do preclinical research, as that's Blanche's area; she has spent years studying that. We actually reinforce each other's work. My strength is that I know a lot about the clinical side, and I also understand a bit about the preclinical side."

PHYSICAL PROXIMITY IS USEFUL

Both emphasise that after a shared research interest has been identified, it is then important to make some real investment of time and effort. Schroen: "From a top-down point of view, it always seems like a good idea to team up clinicians with preclinicians. It can indeed work out very well, but only if both sides are willing to invest, also at a personal level." Van Empel: "There must be equality as well as commitment from both parties. Otherwise such a joint project will soon flounder." What does help is being located in close proximity. You get to know each other well, and it is practical in building up a long-term working relationship. "I think we're more efficient than many large EU projects," contends Van Empel.

THE FUTURE OF SCIENCE

Both have been struck by the level of transparency that researchers are nowadays displaying. Van Empel: "That's the future of science. I can't understand how the old guard have made the achievements they have with such a different attitude. Where is the scope for collaboration if you want to keep everything to yourself?" Schroen adds: "It's crucial, though, that people get to explore 'the other side' at an early stage of their career. Everyone's saying that multidisciplinary research is so important, but it still doesn't happen enough. Why aren't new university staff introduced to the hospital and vice versa?" Van Empel: "We might well develop a plan for that in cardiology." And so perhaps another new joint project is born.

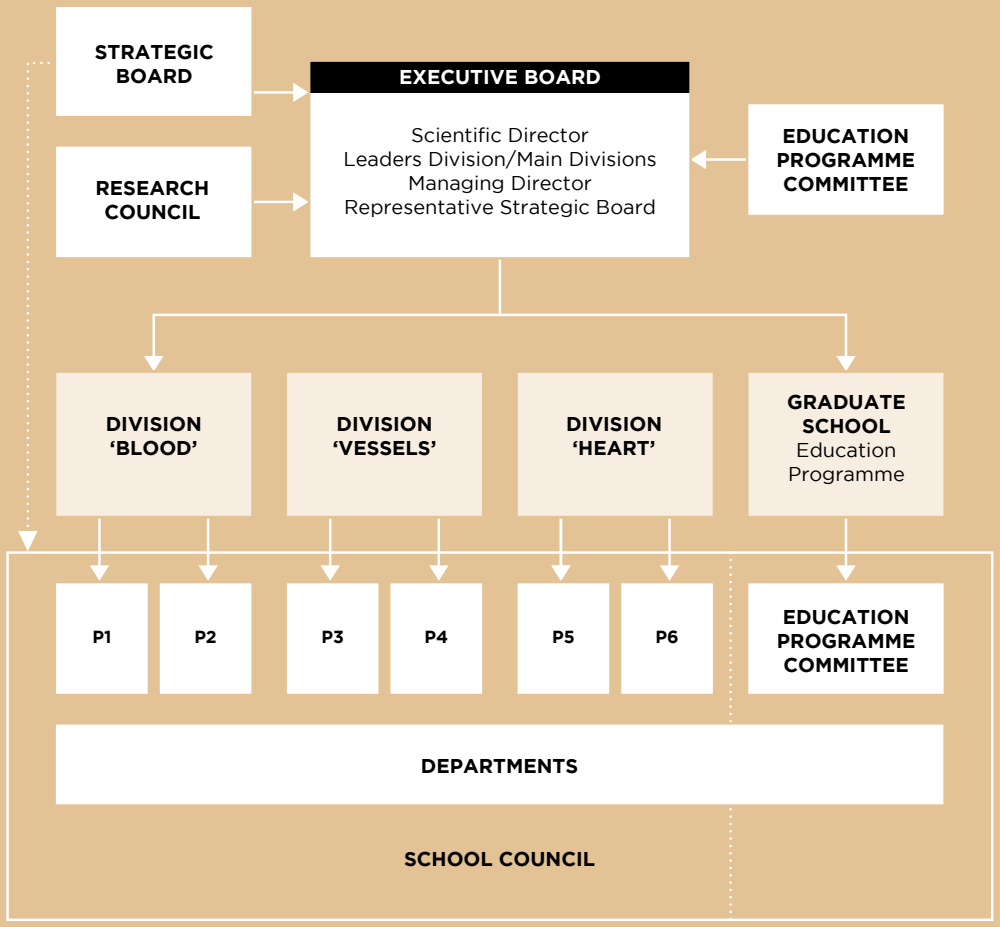
Who are involved in SHE-Predicts-HF?

The project, called SHE-Predicts-HF, is coordinated by Vanessa van Empel in Maastricht and Rudolf de Boer in Groningen. In addition to Blanche Schroen, Stephane Heymans, Boy Houben and Marc van Bilsen are also on the team

ORGANISATION

05

ORGANISATION



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

The Scientific Director is assisted by the Managing Director, who takes care of the financial and human resource management. Together with the three leaders of the main divisions and a representative from the Strategic Board, the Scientific and Managing directors constitute the Executive Board of the institute. The Executive Board meets monthly to discuss and decide upon issues at strategic and operational level. The Executive Board is advised by the Strategic Board, Education Programme Committee and CARIM Research Council. The Education Programme Committee coordinates both the PhD- and Master's training programmes. The Research Council advises the Executive Board and PIs on the quality of all research proposals and meets regularly to discuss and guide grant applications.

The School Council consists of all PIs and Department Chairs and meets four times a year. Junior staff members are also invited to the School Council meetings, but are excluded from voting rights. The School Council is informed by the Executive Board on ongoing matters and advises the Scientific Director on research within the School and the related education programmes.

EXECUTIVE BOARD

- Prof. Tilman Hackeng, Scientific Director
- Prof. Hugo ten Cate, Leader Division 'Blood'
- Prof. Harry Struijker Boudier, Leader Division 'Vessels' (until June 2018)
- Prof. Coen Stehouwer, Leader Division 'Vessels' (from June 2018)
- Prof. Harry Crijns, Leader Division 'Heart'
- Prof. Uli Schotten, representative Strategic Board
- Rob van der Zander, Managing Director

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- Dr Matthijs Blankesteijn, Dept. of Pharmacology & Toxicology
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- Prof. Paul Volders, Dept. of Cardiology
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- Dr Matthijs Blankesteijn, coordinator Biomedical Sciences Master (since October 2017)
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- Dr Hans Vink, staff member (until October 2017)
- Lauren Dupuis, PhD student (until May 2018)
- Armand Jaminon, PhD student
- Margaux Fontaine, PhD student
- Magdolna Nagy, PhD student (until June 2018)
- Kim van Kuijk, PhD student (since October 2017)
- Federica De Majo, PhD student (since May 2018)
- Alicia Veninga, PhD student (since June 2018)

CARIM OFFICE

The CARIM office consists of Riet Daamen, Tara de Koster and Esther Willigers. The financial controller is Lynn Lemeer.

HR-SUPPORT

Patrick Janssen (until 2018), **Dennis Aarts** (until 2018) and Machteld Ostendorf (from 2018) of the Human Resources Department of Maastricht University are dedicated to CARIM.

ADMINISTRATIVE SUPPORT

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

PARTICIPATING DEPARTMENTS AND DISCIPLINES

The research in the CARIM's three main divisions involves the research activities of employees working in fifteen basic and clinical departments/disciplines of MUMC+.

BASIC RESEARCH DEPARTMENTS

- BIOCHEMISTRY
- BIOMEDICAL ENGINEERING
- EPIDEMIOLOGY
- GENETICS & CELL BIOLOGY (UNTIL 2018)
- PHARMACOLOGY & TOXICOLOGY
- PHYSIOLOGY

CLINICAL RESEARCH DEPARTMENTS

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

P1


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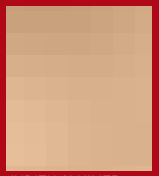
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P4


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P2 Atherosclerosis, arterial thrombosis & stroke

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MARIJKE KUIJPERS


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CHRIS REUTELINGSPERGER


CHRISTIAN WEBER


DIETBERT NEUMANN


ELINE KOOI


ERIK BIESSEN


FELIX MOTTAGHY

P3 Vascular complications of diabetes & hypertension

P4 Regenerative & reconstructive cardiovascular medicine

VESSELS


PIETER VAN PAASSEN


REMCO MEGENS


ROBERT VAN OOSTENBRUGGE


SIMON SCHALLA


WIM VAN ZWAM

P3


AARON ISAACS


BOY HOUBEN


KRISTIAAN WOUTERS


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MIRANDA SCHRAM


NICOLAAS SCHAPER


RONALD HENRY


SEBASTIEN FOULQUIER

P5 Structural heart failure

P6 Complex arrhythmias

HEART


PEYMAN SARDARI NIA


ROBERTO LORUSSO


SANDRO GELSOMINO

P5


BEN JANSSEN


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