CARIM ANNUAL REPORT 2018

SCHOOL FOR CARDIOVASCULAR DISEASES

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CONTENTS

PREFACE

THE FUTURE IS YOURS TO SHAPE...

The scientific world is slowly changing, and similar to climate change, this comes with great worries. Future science is more than about performing excellent, curiosity-driven, translational research. Future science is about reflection, responsibility, team efforts, and foremost dedication to your hard work.

A first notion should be that hard work is not as difficult as it might seem. It should come naturally. The desire to discovery and continuous amazement about life on earth should be the driving force behind research. Unravelling the most detailed molecular mechanisms of disease and creating an awareness to the seemingly most insignificant molecular pathway crucial to human biology draws a parallel with the insignificant status of an individual. Only as an indispensable member of your group you can fully exploit your potential as a scientist. The goal of our endeavour is to explain how our extraordinary life came about, and which minute pathological changes in molecular pathways give rise to life-threatening disease. We are small alone but strong together, we have to be dedicated to science.

Do the self-test: in your private time, doing the dishes, walking, running or biking, mowing the lawn, hanging clothes to dry, ask yourself if you think about science? The status of your RCTs, passaging cell cultures, the data that came out of your well-thought-through experiment of this late afternoon? Science is a way of life, and it should be intricately coupled to a person's state of mind. And although it is not written in stone that only hard work or firm commitment leads to scientific success, if you do science nine-to-five, as an academic, you will likely suffer the consequences further in your academic career.

Recently in Monterey, 2018 Nobel laureate for Chemistry Frances Arnold opened her keynote lecture with the statement: "...PhD students should be underpaid and work 70 hours a week...". Imagine this producing a buzz in the auditorium. After discussing the purpose of this seemingly loose remark we agreed on an important message here: science is not a nine-to-five job, it's a way of life, and perhaps selection at entry will increase the relative success of individual scientific careers. When it comes to separating the wheat from the chaff at the stage of maturation from MSc to PhD, a boost in a vibrant scientific community might lead to an upheaval in thinking, and less academic dropouts in subsequent career development.

Some of you will be familiar with the ten-thousand-hour rule, a much-debated concept originating from analysis of Berlin Akademie für Musik violinists and generalised by Malcom Gladwell in his book Outliers (2008): 10,000 hours of practice - albeit it at the mercy of unique opportunities - will bring you extreme proficiency in any field. If you consider a 4-year PhD trajectory with 200 working days per year, you are getting awfully close to 10.000 hours of practice when you have arrived as an independent, self-reflective, innovative research professional at the time of your PhD defence. The privilege of scientists is that mental activity is the key to success, creating hypotheses, troubleshooting alternate outcomes, explaining the unexpected. This can be done anywhere; your brain is your playground.

Start with asking your colleagues and peers who are established and internationally renowned researchers, we have plenty in CARIM. Ask them for their opinion on key success factors for their career achievement, you are surely

allowed to do that in any pub, as science is thicker than water. Thanks to these researchers CARIM has quietly, but successfully celebrated its 30th anniversary. It is with delight that we report and appreciate the research that CARIM has undertaken, and by which we continuously try to improve our knowledge of cardiovascular diseases.

This is CARIM 2018.
I hope you enjoy your reading.

Professor Tilman Hackeng
Scientific Director CARIM
School for Cardiovascular Diseases

PROFILE

01

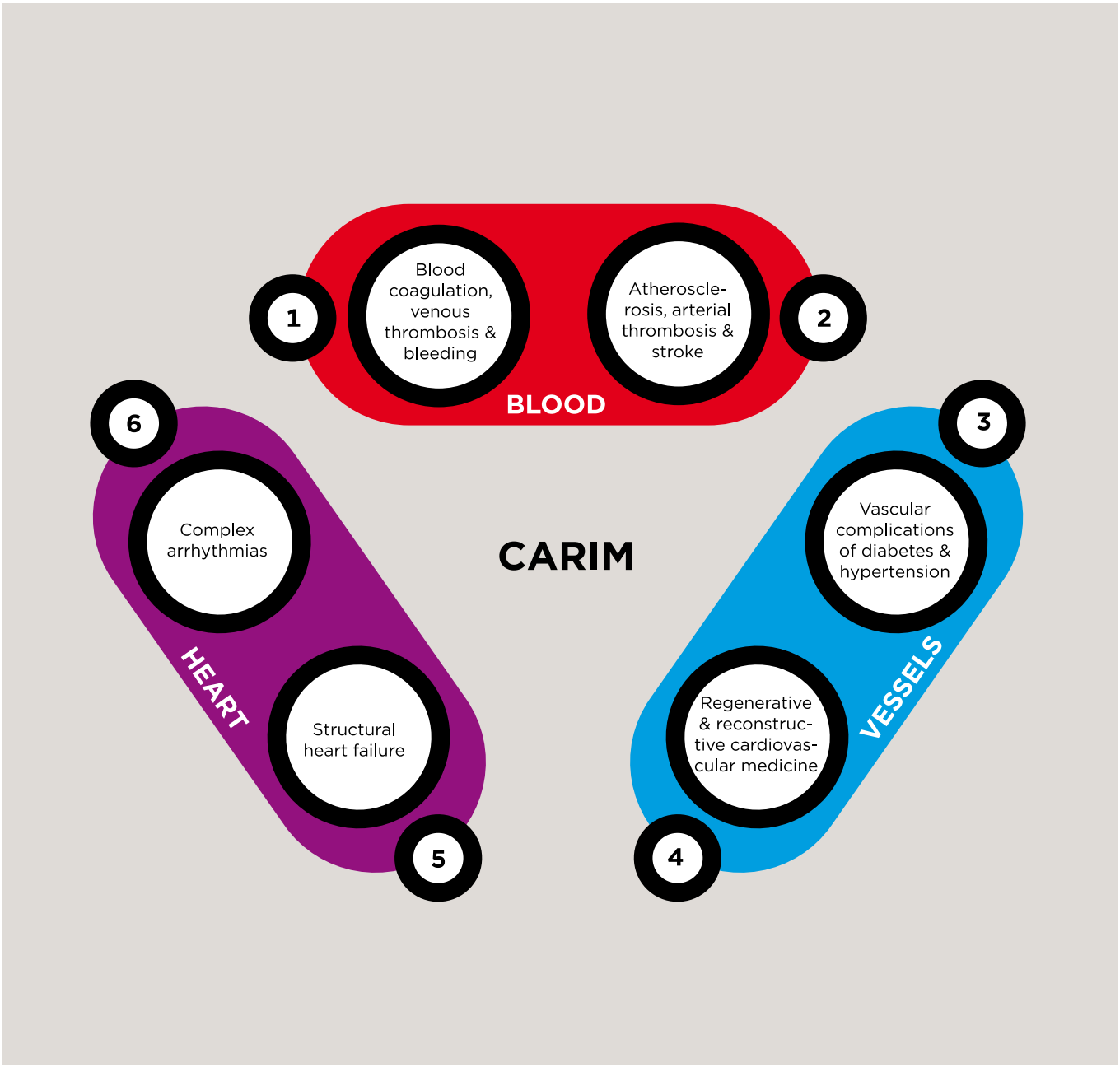
PROFILE

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. Masters students, PhD candidates 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 research Divisions, '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. These six programmes together host 22 Principal Investigator (PI) groups, which represent independent research, infrastructural and financial units within CARIM. CARIM addresses key scientific questions through optimal combinations of CARIM programmes, PIs, researchers, and infrastructure in an optimal team science setting combining track record, expertise, and innovative content and to disseminate results to scientific communities and to society as a whole.

All three Divisions involve basic as well as clinical programmes, and are led according to a shared governance principle, executed by the Division leader together with one or more basic and clinical scientists from the Division. This shared governance system enables shared responsibility for the scientific progress of programmes, for linking activities and seeking collaborations between PIs and Divisions and for mentoring of PhD candidates, postdocs and tenure tracks. The individual PIs are responsible for the financial management 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+ (Maastricht UMC+). 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.


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, Roche, Medtronic, and Abbott. Furthermore, CARIM researchers are involved in other Public Private collaborations in (inter)national networks such as NHF CVON, Horizon 2020, EUPlan, Interreg and Leducq Transatlantic Network.

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

KEY FIGURES 2018

ANNUAL BUDGET: **22.4** M€

NEW CONTRACTS AND GRANTS: **14.0** M€

RESEARCHERS: **170** FTE (103 PHD CANDIDATES)

TECHNICAL AND SUPPORTING STAFF: **48** FTE

DEPARTMENTS/DISCIPLINES: **17**

SCIENTIFIC ARTICLES: **698** (Wi-1: 581)

PHD THESES: **43**

FACTS AND FIGURES

02

FUNDING AND EXPENDITURE AT INSTITUTIONAL LEVEL 2013-2018

	2013	2014	2015	2016	2017	2018
	K€	K€	K€	K€	K€	K€
FUNDING						
Direct Funding structural	7,419	7,500	7,443	7,096	6,995	7,197
Direct Funding specific programmes	2,272	1,309	1,492	2,751	2,344	1,829
Total Direct Funding (1)	**9,691**	**8,809**	**8,935**	**9,847**	**9,339**	**9,026**
Research grants (2)	1,730	1,481	1,850	2,053	1,899	1,740
Contract research (3)	13,456	11,117	11,612	9,176	12,213	11,653
	15,186	**12,598**	**13,462**	**11,229**	**14,112**	**13,393**
Total funding	**24,877**	**21,407**	**22,397**	**21,076**	**23,451**	**22,419**
EXPENDITURE						
Personnel costs	17,501	16,343	15,039	14,098	14,651	14,137
Other costs	8,379	6,392	5,986	6,406	6,764	6,040
Total Expenditure	**25,880**	**22,736**	**21,025**	**20,504**	**21,415**	**20,177**
RESULT	**-1,003**	**-1,328**	**1,372**	**572**	**2,036**	**2,242**

Note 1: Direct funding originating from the University as provided by the Dutch government

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

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

RESEARCH OUTPUT IN 2013-2018

	2013	2014	2015	2016	2017	2018
SCHOOL LEVEL						
Refereed articles (SSI/SSCI) (1)	518	526	548	540	501	581
Other refereed articles (2)	117	87	120	107	123	115
Total refereed articles (3)	**635**	**613**	**668**	**647**	**624**	**698**
PhD theses	35	35	41	55	38	45
Total publications* (I)	**670**	**648**	**709**	**702**	**662**	**743**
Academic staff** (II)	32.4	33.4	32.6	28.7	28.8	28.5
Ratio I and II	20.7	19.4	21.7	24.5	23.0	26.1
DIVISION BLOOD						
Refereed articles (SSI/SSCI)	93	104	115	141	108	140
Other refereed articles	24	15	22	29	22	28
Total refereed articles	**117**	**119**	**137**	**170**	**130**	**168**
PhD theses	7	10	11	14	6	13
Total	**124**	**129**	**148**	**184**	**136**	**181**
DIVISION VESSELS						
Refereed articles (SSI/SSCI)	281	280	281	255	244	253
Other refereed articles	68	36	50	41	40	36
Total refereed articles	**349**	**316**	**331**	**296**	**284**	**289**
PhD theses	14	19	14	22	20	15
Total	**363**	**335**	**345**	**318**	**304**	**304**
DIVISION HEART						
Refereed articles (SSI/SSCI)	209	214	236	203	185	227
Other refereed articles	41	43	54	42	96	92
Total refereed articles	**250**	**257**	**290**	**245**	**254**	**289**
PhD theses	14	8	21	23	14	18
Total	**264**	**265**	**311**	**268**	**268**	**307**

* 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 division ** Academic staff: PhD candidates and postdocs not included

Note 1: Refereed articles published in an international journal, which is mentioned in the (Social) Science Citation Index (SCI or SSCI) of Journal Citation Reports (JCR) ('wi-1')

Note 2: Refereed articles published in an international journal, not included in the SSI/SSCI ('wi-2'), editorial materials, letters to the editor and refereed articles in a national (Dutch) journal ('wn').

Note 3: The sum of the refereed articles (SCI/SSCI) and the other refereed articles.

NEW CONTRACTS AND GRANTS CONCLUDED IN 2018

FUNDING	BLOOD	VESSELS	HEART	TOTAL SUPPORT
	K€	K€	K€	K€
Type 2	1,655	1,234	300	3,189
Type 3	1,772	3,960	2,582	8,314
Type 4	401	795	556	1,752
Type 5	250	250	250	750
Total	**4,077**	**6,239**	**3,689**	**14,005**

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 2018: 1,495 K€)

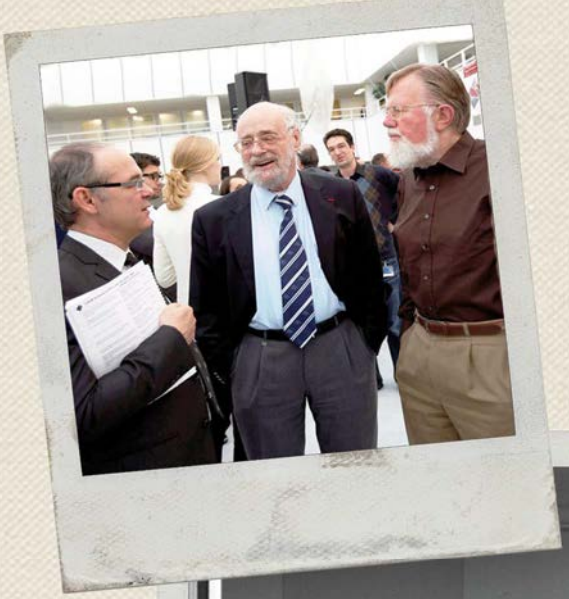
Type 5: Annual support Maastricht UMC+ (750 k€) Heart+Vascular Center-CARIM *'Pieken vanuit de Breedte'*

SUMMARY OF SCIENTIFIC AND TECHNICAL STAFF CARIM AT THE END OF 2018 (IN FTE)

	SCHOOL		BLOOD		VESSELS		HEART	
	#	fte	#	fte	#	fte	#	fte
Scientific staff FHML(1)	70	28.5	14	7.0	29	10.8	26	10.7
Scientific staff academic hospital	30	12.0	4	2.2	12	4.9	14	5.0
Post-docs (2)	37	28.0	7	7.0	20	12.7	10	8.3
Internal PhDs (3)	103	101.3	35	34.1	23	22.2	45	45.0
Total research staff	**240**	**169.7**	**60**	**50.3**	**84**	**50.6**	**95**	**69.0**
Support staff (research)(4)	54	42.4	10	7.8	26	17.8	13	12.6
Support staff (managerial)(5)	6	5.1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total staff incl academic hospital	**300**	**217.2**	**70**	**58.1**	**110**	**68.3**	**108**	**81.6**
Total staff excl academic hospital	**270**	**205.2**	**66**	**55.9**	**106**	**63.4**	**94**	**76.6**
External PhDs (6)	148		41		46		46	
Visiting fellows/professors (7)	26		10		4		12	

#	Number of persons active on the Research programme research activities
fte	Sum of actual fte-factors (in fulltime equivalents) labelled on the School/Research programme research activities
Note 1:	Comparable with WOPI-categories HGL, UHD and UD; tenured and non-tenured staff appointed at FHML.
Note 2:	Comparable with WOPI-category *'Onderzoeker'* (1, 2, 3, 4), with completed PhD, not belonging to scientific staff (with WOPI-categories HGL, UHD and UD)
Note 3:	Standard PhD (employed)
Note 4:	All support staff working on research (research assistants, lab technicians, and other support staff not working at the management office)
Note 5:	Support staff working at the School's management office including the Scientific Director
Note 6:	External PhD (externally or internally funded but not employed)
Note 7:	Visiting fellows are researchers/professors who visit the Research programme for a period of typically one week up to three months to work with Research programme staff members

30 JAAR CARIM



HIGHLIGHT
DIVISION BLOOD

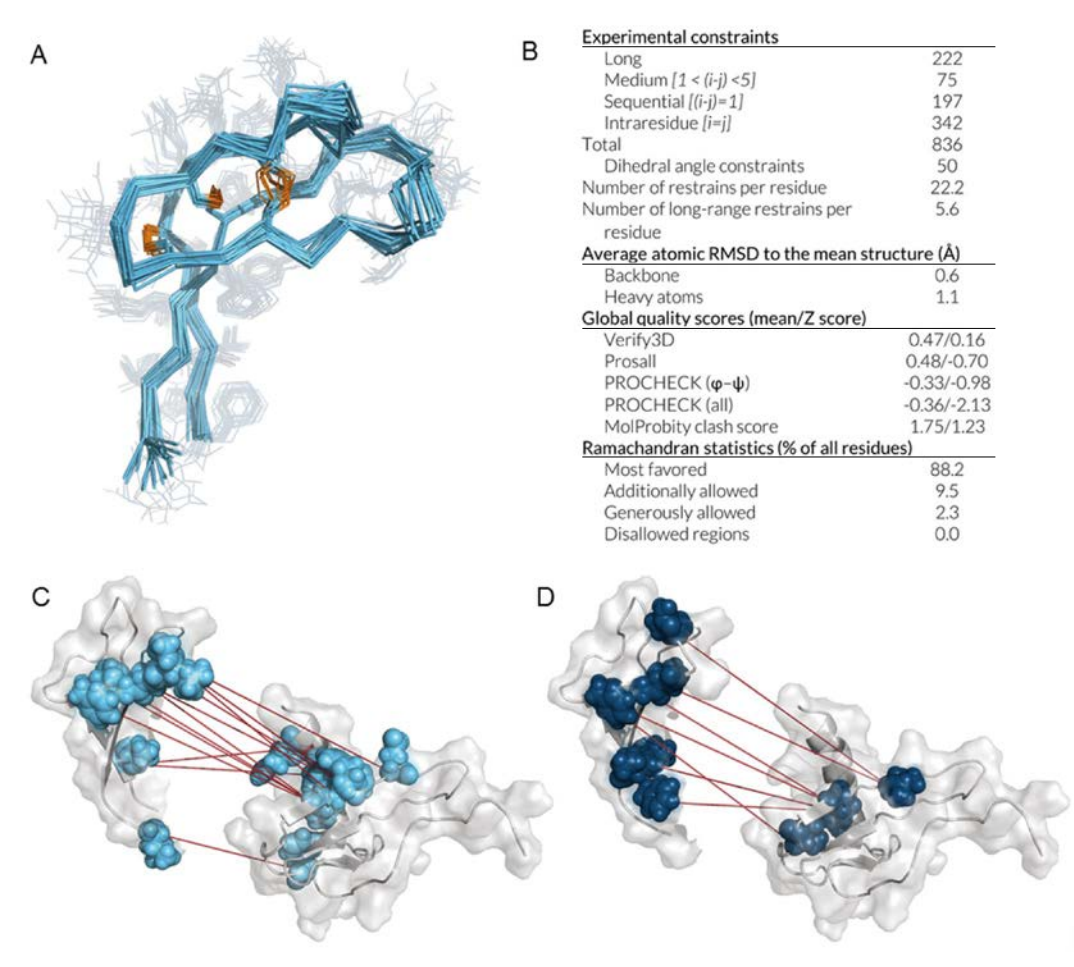
INGRID DIJKGRAAF

Department of Biochemistry

Last summer, the Netherlands was startled by the news that a giant tick, the so-called Hyalomma tick (*Hyalomma marginatum*), had been found in the country. The first news reports talked about a *giant tropical tick* that had been found near the village of Arcen in the province of Limburg, just across the German border. A few days later the same type of tick, now referred to as a *hunting horror tick*, was found in Odoorn, in the province of Drenthe. Ticks are indeed scary, since they can transmit several diseases such as Lyme disease and tick-borne encephalitis, which have unpleasant consequences for patients and society. But ticks are also very interesting for research into cardiovascular and other diseases.

As blood-feeding ectoparasites, ticks need to remain unnoticed by their host to enable them to ingest a complete meal, which can take from a few minutes for soft ticks (*Argasidae*), to as much as weeks for hard ticks (*Ixodidae*). To avoid host defences, ticks inject saliva containing numerous bioactive compounds, including anticoagulants, platelet aggregation inhibitors, anti-inflammatory factors and immunomodulatory proteins. Ticks are thus major sources of lead compounds for the development of new drugs to treat haemostatic disorders, cardiovascular disease, cancer and disorders of the immune system. Moreover, the proteins in tick saliva may serve as a starting point for the development of synthetic anti-tick vaccines. Tick salivary proteins are useful for drug discovery, as millions of years of evolution have acted as a lead optimization process, achieving stability and target specificity while reducing toxicity and immunogenicity. At the Department of Biochemistry, we are currently working on tick-derived proteins that are involved in one of three processes: immunomodulation, platelet aggregation and blood coagulation.

For the last few years, a protein family with immuno-modulatory properties has been the focus of our research. This group of chemokine-binding proteins was discovered in the saliva of the brown dog tick *Rhipicephalus sanguineus*, and was called evasins, since they are secreted by ticks to evade the host immune system [1]. It was already known that one family member, evasin-3, binds specifically to CXC chemokines CXCL1 and CXCL8. However, the structure of evasin-3 and its molecular interactions with its target proteins CXCL1 and -8 were still unknown. Lately, Stepan Denisov and Hans Ippel (Department of Biochemistry) have



Experimental constraints	
Long	222
Medium *[1 < (i-j) <5]*	75
Sequential *[(i-j)=1]*	197
Intraresidue *[i=j]*	342
Total	836
Dihedral angle constraints	50
Number of restrains per residue	22.2
Number of long-range restrains per residue	5.6
Average atomic RMSD to the mean structure (Å)	
Backbone	0.6
Heavy atoms	1.1
Global quality scores (mean/Z score)	
Verify3D	0.47/0.16
Prosall	0.48/-0.70
PROCHECK (φ–ψ)	-0.33/-0.98
PROCHECK (all)	-0.36/-2.13
MolProbity clash score	1.75/1.23
Ramachandran statistics (% of all residues)	
Most favored	88.2
Additionally allowed	9.5
Generously allowed	2.3
Disallowed regions	0.0

FIGURE 1 Ribbon representation of the ensemble of 10 lowest-energy structural models of the tEv3-1. (A) Disulfide bonds are indicated by yellow sticks. (B) NMR and refinement statistics for tEv3. (C) Contacts between evasin-3 (left) and CXCL8 (right) derived from ^{15}N and ^{13}C (D) filtered NOESY spectra of [^{15}N,^{13}C] CXCL8/evasin-3 complex. N- and C-termini of evasin-3 are hidden for the sake of visibility.

succeeded in elucidating the structure of evasin-3 (Figure 1) and the evasin-3/CXCL8 complex by means of solution-phase NMR spectroscopy [2].

However, some of evasin-3's cysteine residues are in close proximity to each other, making it difficult to differentiate which cysteine residues are forming disulfide bonds. The formation of the correct disulfide bonds within a protein is a pivotal post-translational modification and is crucial for it to acquire its biological function and to maintain its structural integrity. To elucidate the disulfide bond connectivity of evasin-3 and other cysteine-rich proteins (CRP), an NMR spectroscopy-based technique was developed, which was dubbed selenocysteine scanning

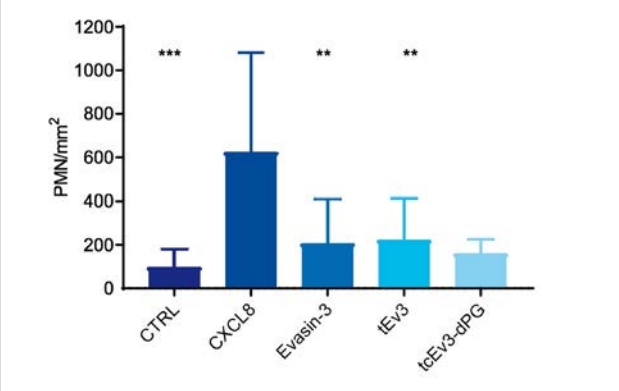


FIGURE 2 Influence of evasin-3 and its variants tEv3 and tcEv3-dPG on CXCL8-induced neutrophil (polymorphonuclear leukocytes; PMN) migration. CXCL8 caused significant migration of neutrophils (n = 10) compared to controls without chemoattractant (n = 10). The addition of evasin-3, or truncated derivatives tEv3 (n = 9) or tcEv3-dPG (n = 5), significantly reduced CXCL8-induced migration. Data are presented as means ± standard deviations: ** P<0.01, ***P<0.001.

or SecScan [3]. In the SecScan method, a single cysteine (Cys) residue in the protein is systematically replaced by a selenocysteine (Sec) residue. The Se-S bond thus formed (instead of an S-S bond between two cysteines) causes chemical shift effects which can be measured with NMR spectroscopy. By systemically substituting single Cys by Sec residues at defined sequence positions in proteins with multiple cysteines, the disulfide bond connectivity can be determined reliably and unambiguously. It appeared that evasin-3 has a unique fold and that the N- and C-termini of this protein are unstructured. This allowed chemical synthesis of two truncated evasin-3 derivatives (tEv3 and tcEv3-dPG) without the flexible N- and C-termini. These newly developed evasin-3 analogues were able to inhibit neutrophil migration towards a CXCL8 gradient as effectively as native evasin-3 (Figure 2). This indicated that evasin-3 affects the interactions between CXCL8 and its cognate G-protein-coupled receptors (GPCRs) CXCR1 and CXCR2 on neutrophils. Since chemokines control cell trafficking not only by interaction with GPCRs but also with glycosaminoglycans (GAGs) on endothelial and epithelial cells, NMR studies were performed with CXCL8, evasin-3 and Fondaparinux, a penta-saccharide that mimics GAGs. These NMR experiments showed that evasin-3 slowly substitutes GAGs from the CXCL8/GAGs complex, which means that in addition to neutralizing CXCL8, evasin-3 also diminishes the storage of CXCL8 in the GAG-bound form.

In contrast to the tick protein evasin-3, which binds CXC chemokines, evasin-4 binds CC chemokines CCL5 and CCL11. Since CCL5 is considered to play a key role in atherosclerosis severity by recruiting monocytes towards the atherosclerotic plaque, evasin-4 is of particular interest. Hence, evasin-4 was synthesized chemically and by recombinant techniques.

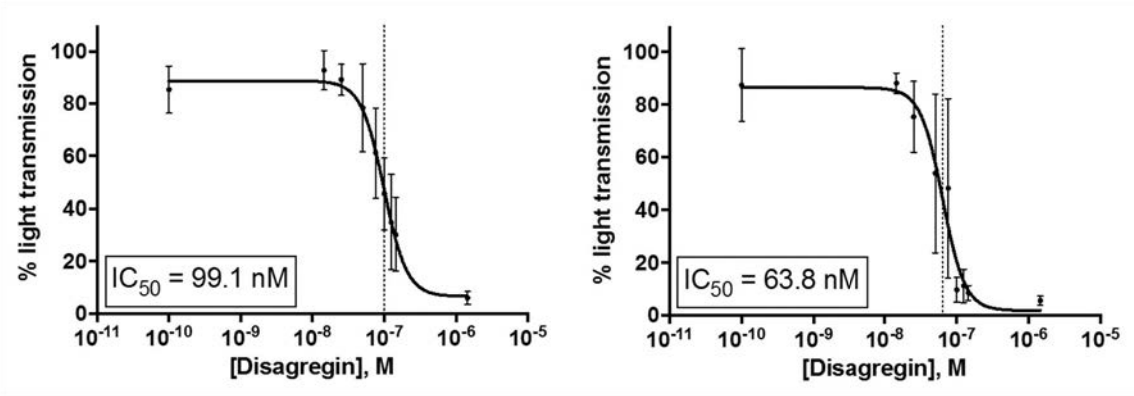


FIGURE 3 Disagregin demonstrated dose-dependent inhibition of adenosine diphosphate- (ADP, 5 μM, left) and collagen- (1 μg/mL, right) induced platelet aggregation in human platelet-rich plasma (PRP).

Subsequently, structural information about evasin-4 and structural determinants of evasin-4/CCL5 interactions were obtained. It appeared that the structure of evasin-4 is difficult to solve with NMR spectroscopy, but lately its structure was elucidated by X-ray crystallography, in collaboration with the Department of Crystal and Structural Chemistry of Utrecht University. Initial NMR results indicated that pro-atherogenic CCL5/CXCL4 heterodimer formation might be prevented. *In vitro* assays, such as monocyte migration assays to investigate the influence of evasin-4 on leukocyte adhesion, are planned to be performed in the near future.

In addition to the immunomodulatory evasin protein family, platelet aggregation inhibitors from tick saliva are also fascinating, and are being studied with regard to their structure and function. It is assumed that disagregin, a 60 amino acid protein derived from the salivary glands of the soft tick *Ornithodoros moubata* blocks signalling by the αIIbβ3 integrin receptor on platelets, resulting in less platelet aggregation and reduced fibrin levels. Indeed, it appeared that this protein inhibited platelet aggregation in adenosine diphosphate (ADP)- and collagen-activated platelet aggregation in plasma, with IC_{50} values of 99 nM and 64 nM, respectively (Figure 3, unpublished results). Furthermore, whole-blood thrombus formation measured at arterial shear conditions [4] demonstrated smaller platelet aggregates for disagregin than for eptifibatide (Integrilin), a clinically approved αIIbβ3 integrin inhibitor (Figure 4, unpublished results). Interestingly, eptifibatide has also been derived from nature, from the venom of the south-eastern pygmy rattlesnake (*Sistrurus miliarius barbouri*). Currently, the aim is to study the specificity of disagregin for the αIIbβ3 integrin, compared to other integrin receptors. In addition, NMR studies will be performed to elucidate the 3D structure of this interesting protein.

Recently, a challenging research project has been started in collaboration with the University of South Africa (Pretoria).

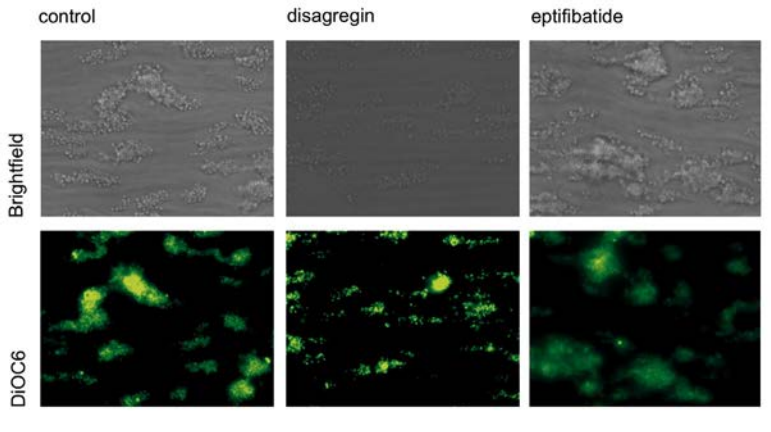


FIGURE 4 Brightfield images (top) show the effect of 100 nM disagregin or 100 nM eptifibatide on platelet aggregation under arterial shear conditions. Experiments were performed under coagulation conditions (addition of Tissue Factor). The lipophilic carbocyanine dye DiOC6 (which does not cause platelet activation) stained the polar membranes of platelets (bottom).

This project investigates a tick-derived protein that influences the blood coagulation cascade. It is assumed that this so-called BSAP1 (Barium Sulfate Adsorption Protein) binds to tissue factor (TF), the initiator of the extrinsic coagulation cascade and a risk factor for thrombotic disease [5]. So far, no structural information is available on BSAP1, and its structural determinants will be investigated by NMR and/or X-ray crystallography. To this end, we will synthesize BSAP1 chemically, allowing site-specific modifications of proteins, and by recombinant expression, which enables production of uniformly isotope-labelled proteins for NMR studies. Furthermore, its biological properties will be determined in *in vitro* assays such as thrombin generation assays. Our collaborator in Pretoria has also isolated the protein from the saliva of 50 ticks (*Ornithodoros savignyi*) for us, to be used for comparison studies.

There is still a lot to learn from ticks and the elegant molecular mechanisms they have evolved to obstruct haemostasis and avoid immune reactions in their hosts. Studying tick saliva proteins may provide insights into the immune-evasion mechanisms used by these organisms and the accompanying risk of pathogen transmission to humans and domestic animals susceptible to tick bites.

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INTERVIEW

ROB VAN DER ZANDER

Looking back on 30 years of CARIM, because it has to be done…

"You might wonder whether I've stayed with CARIM for 30 years just because I'm too lazy to look for something else, or simply because it's been too much fun to leave", says Rob van der Zander halfway through the interview. "I think it's a combination of the two." His mother has always been amazed that he managed to survive sitting behind a desk for so many years. As a child, he spent all of his time outdoors, so she would have thought that forester might have been a more suitable job for him. Now that he is approaching retirement, he is getting considerably more opportunity for outdoor living.
Rob van der Zander is looking back on thirty years of CARIM, even though he actually hates looking back.

He starts by announcing that this is going to be the most boring interview in the entire annual report. And he doesn't really see the need for it. He fails to see the value of looking back. As the conversation (which turns out to be anything but boring) goes along, it turns out that there is another reason why looking back is not like him. Rob van der Zander is already largely living a life of retirement. Since February 2019, he has been working at CARIM for one day a week only, in order to smooth the path for his successor, Wouter Hankel. "In practice," he smiles, "that day is mostly spent working on the tougher issues. But that's fine."

How did you get involved with the start of CARIM?

"I had worked for a couple of years at the Faculty office of the Medical Faculty. One of my colleagues there was Rob Reneman, with whom I collaborated in the research committee. When I left to join the Open University, Rob promised to get me involved when the cardiovascular diseases institute was going to be founded. And this happened in 1987. I became the managing director and started by writing the articles of association, what we would now call a business plan. We were one of the first institutes for cardiovascular diseases in the country, and were given a kind of protected status by the university. This implied, for instance, that we would be spared in case of cutbacks; that was quite something in those days."

Who came up with the name and logo?

Hein Wellens proposed CARIM, and soon after that, Chris Voskamp of the audio-visual services designed the logo, which has never been changed since. It's a very recognisable emblem of our institute, and I think if something works well, you shouldn't change it."

Rob Reneman once said that the first 25 years of CARIM were actually the best. What is your view on that?

"They were certainly peak years, in many ways, but I don't know if I'd draw the line so strictly. The first five years were a period of pioneering, while the next five years were spent consolidating the institute's basis. Rob Reneman was succeeded as Scientific Director by Harry Struijker-Boudier. That was the period in which external ties with the industry were expanded and strengthened, and when CARIM was for the first time asked to coordinate a SenterNovem BSIK programme worth over ten million guilders. That was quite a milestone. Mat Daemen particularly developed the quality assurance programme, and it was under his leadership that the prominent Maastricht Study was started. The arrival of Thomas Unger marked the start of our participation in European ITN networks for PhD students."

Did you get along equally well with all the Scientific Directors?

"I'm proud to say that I've managed to develop a good working relationship with all of them, even though they've all been strong characters. You do yourself a disservice by being obstructionist, but on the other hand you shouldn't go against your nature. You learn something new from everyone, and we've always respected each other's responsibilities. They never left me out in the cold, and I've always felt privileged by that.

You are not the only one to have worked here for a long time

"No, I've had a very pleasant collaboration for thirty years with Riet Daamen, who works at the CARIM Office. I hope she feels the same way about it... And other colleagues have also stayed a long time, which says something about the

I'VE ALWAYS WANTED TO BE ACCESSIBLE, FOR ALL 450 PEOPLE INVOLVED IN THE INSTITUTE

pleasant working environment. But then again, I've also been married to my wife for 43 years, so maybe I just like to leave things the way they are."

What have been the major developments in your work at CARIM?

I was responsible for everything that was not science-related. Finances, human resources, PR, legal. Of course the amounts of money have changed a lot. We started with an annual budget of three million guilders, while our current budget is over twenty million euros. In the old days, a researcher could work for a year on a 20,000 guilder grant, nowadays he couldn't last a month on that. As grants became larger, the duty of accountability towards grant providers also grew. We now have greater control over our own budget, whereas in the past it was more controlled by the Faculty. And while in the old days, external funding accounted for 25% of our budget, that's now over 50%."

And what about human resources?

"We were given control over the supporting and facilitating staff (what we call OBP in Dutch), even though they were still to be physically accommodated with the departments where they had always worked. That's actually still not the ideal situation we originally had in mind: a flexible pool of OBPs who could be deployed anywhere. Although I have to admit that in some cases that would be impossible, in view of the specialist nature of a person or function. At the same time, the number of technicians is dropping, as a result of automation."

If your tasks are so comprehensive, how do you determine what should be given priority on a specific working day?

"Anything that had to do with a PhD ceremony or a grant application was always a priority to me, as that primarily regards the quality and reputation of CARIM. For the rest I've always wanted to be accessible, for all 450 people involved in the institute. Whenever possible, my office door would be open."

Have there been any developments that worried you?

"We vigorously protested against the Dean's decision that researchers could allocate no more than half of their time to research paid for by CARIM. That's particularly devastating for those doing basic research. Those colleagues who were doing more clinical research usually couldn't spend more than 50% of their time on it anyway, as they have additional clinical labelling. But those doing basic research had until then been able to spend 70% of their time on research. And 70% is of course far more appealing to highly talented researchers than 50%. Why the Dean introduced this reduction of research capacity? I can't really think of a good argument. Research funding by the Dutch Ministry of

Education is already meagre compared to other countries. Actually, the fact that researchers can nowadays only survive thanks to external grants worries me."

When would you regard a working day as a success?

"When I'd solved more problems than came in. Or should you now call them challenges?"

To you, what were the highlights of your thirty years at CARIM?

"The first time we landed such a large project, over ten million guilders; that was a great milestone. I've always regarded and celebrated that as a success for the team. On a more personal level, a very special event was when my eldest daughter got her PhD, supervised by Peter de Leeuw at CARIM. Just as it was very special to receive the first CARIM medal a few years ago, and the honorary faculty award in appreciation of my work."

And of course we have to ask about the lows as well...

"That was undoubtedly the death of Martin Tossings in 2012... He was our controller, and a wonderful human being. He died in an accident six months before he was to retire. That was just awful... It still affects me very much. We both shared a love for sheep and had had so much fun together. Although he was always working on the things he felt were important, his death also taught me that you shouldn't wait until you're retired to enjoy the good things in life. It can be over before you know it."

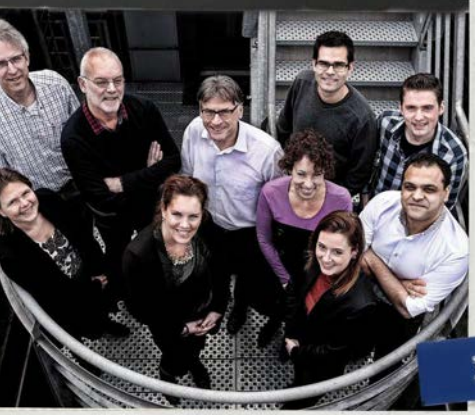
What are the good things in life for you?

"I love herding sheep, and I own a few sheep and a border collie. And I'm starting an allotment and a small vineyard. Together with a glass blower, I've already organised a few staff outings, for groups of colleagues, for instance from the Heart+Vascular Center. That proved a lot of fun. Plus I have seven grandchildren, and I'm on baby-sitting duty one day a week, which is of course also great."

Are there similarities between tending a flock of sheep and a flock of 450 CARIM staff?

Laughs: "I was just thinking: sheep are easier to control. It's the teamwork that you do together with the dog that just makes it such a very relaxing pastime. And if along the way you see roe-deer, hares, pheasants and buzzards, that's just great. My mother could never understand why I opted for a desk job, and managed to keep it up for so long. But I've never been bored."


30 JAAR CARIM



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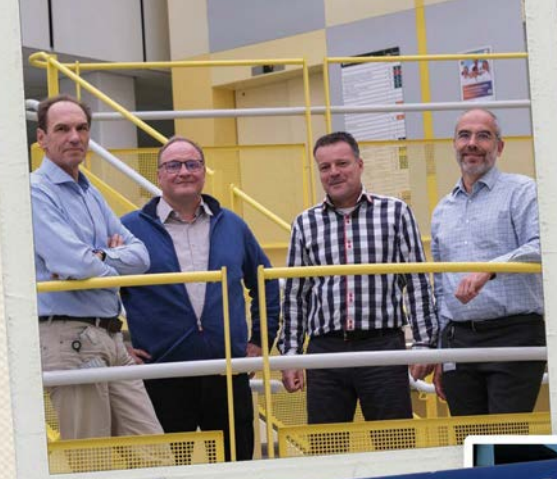
30 JAAR CARIM



INTERVIEW

MOHAMED KASSEM

From Syrian neurosurgeon to Maastricht researcher

"My dad fled from Syria to the Netherlands in 2014, and because he could no longer practise as a neurosurgeon here, he opted for a career as a researcher, starting at CARIM in Maastricht. I'm very proud of him." This is what Mohamed Kassem (41) hopes his now one-year-old son will once say, and what motivates him every day. Last year, Kassem made an excellent start, by winning an NWO grant, enabling him to work in Professor Eline Kooi's team for one year.

Quite soon after Mohamed Kassem arrived in the Netherlands, he learned that his Syrian degrees that allowed him to work as a neurosurgeon were not accepted here. He was told that six more years of study might gain him better prospects. That did not sound very appealing to a man who was among the very few top medical students in his home country to be accepted to specialise in neurosurgery. “I’ve always liked research as well, so that seemed the best possible alternative to me. I really like the fact that you’re able to potentially help many people as a researcher, as opposed to individuals as a physician.”

STUDYING AND BUILDING A NEW NETWORK

To enhance his chances on the Dutch labour market, he decided to do the Master’s programme on Biomedical Sciences at Maastricht University, which he expects to complete before the summer of 2019. Neurosurgeon Peter Kubben from Maastricht UMC+ encouraged him to do so. “He’s a very nice person and helps me in any way he can. I met him via a Belgian reporter who I got to know very well when I was working for the Red Cross at the Turkish-Syrian border. I helped him with his work in Syria and he lives in Lanaken. So after I arrived in Maastricht, we got back in touch and it turned out that his mother works at Maastricht UMC+ and she knew Peter Kubben. What a story,” he smiles.

Although his fellow students in the programme are some twenty years younger, that is not a problem at all. “They learn from my wider knowledge of medicine and physiology, and I learn things like statistics and faster thinking from them. The teaching method here is quite different from what I was used to, you know.”

TAKING THE FIRST STEPS AS A RESEARCHER

For the Master’s placement he was welcomed by Professor Eline Kooi’s research group. She pointed out the possibility of applying for an NWO grant for refugees with a residence status. They were invited to the interview together and a few days before Christmas 2018, the good news arrived in Maastricht. Kassem smiles from ear to ear when he

I REALLY LIKE THE FACT THAT YOU’RE ABLE TO POTENTIALLY HELP MANY PEOPLE AS A RESEARCHER, AS OPPOSED TO INDIVIDUALS AS A PHYSICIAN

remembers the moment. “Because I want to make my son proud.” Not his mum, no, who is still living in Syria, and for whom the biggest reward would be to have her fifth son close to her as well. But to make his son proud, who was born in Maastricht and who will have Dutch class mates in the future. His wife, who was a pharmacist in Syria, decided to stay at home with their child for another year.

THE RESEARCH PROJECT

After his graduation, Kassem will start the NWO grant research year at Professor Kooi’s lab. “Twenty to thirty percent of all strokes are caused by the carotid artery being narrowed because of atherosclerosis. There are two options for treatment: medication or surgery to remove the plaque. Surgery is costly and carries the risk of complications, and it is not essential for every patient, as not everyone is at high risk of another stroke. We want to distinguish between high- and low-risk patients by imaging the plaque with MRI. Only the high-risk patients would then be operated upon, the ones who will benefit most from it.” The study is nested in the second randomised European Carotid Surgery Trial, ECST2.

DREAMS TO REALISE IN THE FUTURE

Kassem hopes to pursue his research career from there, hopefully leading to a PhD and who knows what else. The second grant has already been applied for. “Professor Kooi is very well organised and she offers me ample opportunities to develop my skills and knowledge in this field. I really appreciate that.” His motivation, apart from his son, also comes from the feeling that there is no more time to waste, after all the time he has lost in the Dutch asylum centres. “I want to move forward.” And maybe, after having established a research career, he will one day be able to combine working as a neurosurgeon in the Arab region with doing research in Europe. “And also doing research in that region, bridging the gap between the Arab medical world and European research. That would be very interesting.”

EVENTS AND HIGHLIGHTS

03

SCIENTIFIC HIGHLIGHTS

In 2018, the successful work of our researchers was reflected in **698** scientific publications in peer refereed journals (**581** refereed articles with Impact Factor, excluding abstracts and **29** letters to the editor), **43** PhD theses, **10** patents and **3.2** million Euros funding received in competition from national and international science foundations and **10.1** million Euros funding from third money parties, charities, EU framework programmes, industry, etc. In 2018, the overall average Impact Factor is **5.6**.

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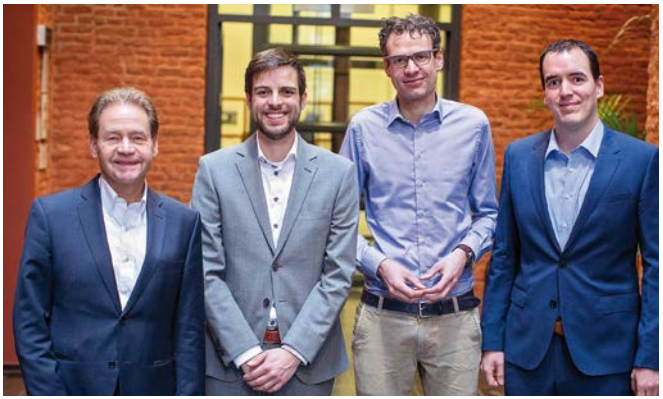
Neuroimaging and clinical outcomes of oral anticoagulant-associated intracerebral hemorrhage.
Ann Neurol 2018; 84(5): 694-704 IF 10.24

RESEARCHERS GRANTS AWARDED TO INDIVIDUALS

NWO TALENT SCHEME

Dr **Judith Sluimer** (Dept. of Pathology) received a Vidi grant for her project 'Barcoding the fibroblast: single cell sequencing to reveal heterogeneity and functional impact of atherosclerotic plaque fibroblasts'. This personal career grant with a success rate of ~17% amounts to 800 K€ for her research over the next five years to investigate the rupture of atherosclerotic plaques, which is the cause of myocardial infarct and/or stroke. It is already known that this is partly due to a disturbed connective tissue production and degradation. Judith will investigate the underlying cause of this, 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 recognise new subtypes. The aim of the project is to detect new subtypes of matrix-producing fibroblast-like cells in the vessel wall, and to investigate whether they can repair the disturbed matrix production and breakdown in plaques in order to prevent myocardial infarct and/or stroke in the future. See pages 66-69 for a full interview with Judith Sluimer and Andy Baker.

Three Veni grants were awarded to CARIM researchers. The grant provides the laureates with the opportunity to further elaborate their own ideas during a period of three years. Dr **Thomas van Sloten** (Dept. of Internal Medicine) received the grant for his project 'Small vessels, big impact: does microvascular dysfunction lead to late-life depression' and will investigate whether dysfunction of the smallest vessels in the brain leads to depression by causing subtle brain changes. He will use a unique combination of genetic, advanced brain imaging and pharmacoepidemiologic data from large studies, including The Maastricht Study.



In his project 'Personalized medicine in sudden cardiac death: Integrating advanced imaging with computer modelling', Dr **Matthijs Cluitmans** (Dept. of Cardiology) will study arrhythmia mechanisms in sudden cardiac death. Such life-threatening heart-rhythm disorders can develop suddenly in apparently healthy individuals, without evident substrate. In his study, Matthijs will use new imaging techniques to detect the substrate in patients. He will then study the exposed substrate with computer simulations to understand the mechanisms of these rhythm disorders in an individual patient. In the future, such personalised computer simulations might help to predict an individual's risk for sudden cardiac death and choose appropriate treatment.

Dr **Emiel van der Vorst** (Dept. of Pathology) will explore two entirely new ways of this so called immune-lipid crosstalk, where chemokine/chemokine-receptor activity is modulated by High-Density Lipoproteins, defining unprecedented targets for intervention in this crosstalk that underlie many cardio-metabolic disorders in his project 'Targeting immune-lipid crosstalk in cardio-metabolic diseases: focus on High-Density Lipoproteins dependent regulation of chemokine-receptor signalling'. Until now, therapies for cardiovascular diseases have primarily focussed on specific atherogenic drivers, e.g. dyslipidaemia or inflammation. However, recently it became evident that there is considerable crosstalk between these features.

ASPASIA ELINE KOOI

Prof. **Eline Kooi** was awarded an Aspasia grant by NWO based on her Vici application. The Aspasia grant is coupled to the Vidi and Vici programme and is a personal grant. It is intended to accomplish a proportional distribution of female associate and full professors. It can be awarded to female candidates that are invited for a Vidi or Vici interview and that have received an overall score by the committee of excellent or very good.

RUBICON KOSTA THEODOROU

Kosta Theodorou (Dept. of Pathology) received a Rubicon grant from NWO. This grant gives young, highly promising researchers the opportunity to gain international research experience. Using his Rubicon, Kosta has started his research at the Institute of Cardiovascular Regeneration at Goethe University Frankfurt, Germany.

NHS DR E DEKKER PROGRAMME

Within the framework of the Dr E. Dekker programme of the Dutch Heart Foundation, Dr **Thomas van Sloten** (Dept. of Internal Medicine) received a Physician in Specialty training grant for his project 'Late-life depression: a cerebral microvascular disorder? A cross disciplinary approach to understand the link between late-life depression and cardiovascular disease'.

NWO ECHO INGRID DIJKGRAAF

Dr **Ingrid Dijkgraaf** (Dept. of Biochemistry) received a NWO ECHO grant for her project 'Thrilled by ticks to study anticoagulant protein BSAP1'. The focus of Ingrid's project will be on tick-derived anticoagulant protein BSAP1. Ticks are very interesting bloodsucking parasites as they express a vast variety of anticoagulant, anti-inflammatory, immuno-modulatory, and vasodilating proteins in their saliva that evade or counteract host defence mechanisms, enabling them to feed for longer periods. Preliminary experiments indicated that BSAP1 inhibits blood coagulation. The aim of this project is to unravel the structure of BSAP1 and to investigate molecular interactions between BSAP1 and

certain blood coagulation proteins in order to provide novel insights in design of therapeutics for treatment of thrombotic disease in the future. See pages 18-23 for more information.

DIABETES I BREAKTHROUGH MARLEEN VAN GREEVENBROEK

Dr **Marleen van Greevenbroek** (Dept. of Internal Medicine) received one of the Diabetes II Breakthrough grants within the joint ZonMw/DFN programme 'Partnership Diabetes' for her project 'Control of insulin secretion: Methylglyoxal (MGO)-modification of intracellular CD59 impairs insulin secretion by ß-cells'. In this project, she will focus on a newly identified molecule in the ß-cell that has been classified as a novel player in the secretion of insulin from its secretory granules. The main goal of this project is to investigate how modifications of this protein, CD59, in prediabetes and (early) diabetes can impair the insulin secretion process.

NWO REFUGEES IN SCIENCE: MOHAMED KASSEM

Mohamed Kassem, MD (Syrian neurosurgeon, currently BMS Master Student, Imaging specialisation) and Prof. **Eline Kooi** (Dept. of Radiology and Nuclear Medicine) have been awarded a grant from NWO in the programme Refugees in Science. Mohamed fled his home country in 2014. Since 2016, he has been living in Maastricht. This grant will allow him to study whether advanced carotid MR imaging can be used to select patients that benefit from carotid endarterectomy to prevent a (recurrent) stroke. The project is nested in the second European Carotid Surgery Trial (ECST-2). See pages 32-35 for a full interview with Mohamed Kassem.

ESC FCI GRANT SINGAPORE EMMA ROBINSON

Dr **Emma Robinson** (Dept. of Cardiology) received a European Society of Cardiology First Contact Initiative grant to work as a visiting researcher in the laboratory of Prof. Roger SY Foo at the prestigious Genome Institute Singapore and University of Singapore. There, she will initially be trained in specialist molecular biology methods and bioinformatics tools to identify and measure the recently discovered circular RNAs. The grant will be used to kick-start a new long-term ambitious collaborative project to identify novel circulating biomarkers and molecular mechanisms inciting delayed onset chemotherapy-associated dilated cardiomyopathy.

KOOTSTRA TALENT FELLOWSHIPS

In the first round of the Kootstra Talent Fellowships 2018, two fellowships in the category talented PhD candidates/ talented future postdocs were granted to Dr **Mark Hazebroek** (Dept. of Cardiology) and Dr **Stijn Agten** (Dept. of Biochemistry). The Kootstra Talent Fellowships are granted to young scientific talents by the Board of Maastricht UMC+ with the aim to support developing their scientific careers.

OTHER AWARDS, PRIZES AND GRANTS

In 2018, many CARIM researchers were awarded with other grants, prizes and awards. Below, some of them are highlighted.

CLINICAL CHEMISTRY YOUNG INVESTIGATOR AWARD STEVEN MEEX

Dr **Steven Meex** (Dept. of Clinical Chemistry) won the Clinical Chemistry Young investigator award at the conference of the Dutch Federation for Clinical Chemistry (NVKC). This is a two-yearly award for a scientist <41 years with important scientific contributions in the field of Clinical Chemistry.
He received the award for his distinctive work in the field of cardiac biomarkers and innovative e-health contributions in clinical chemistry: ‘Labtracker’ (a CE certified medical smartphone app) and ‘Labchain’ (a block chain based Lab-to-Lab connection).

SCHOLARSHIP STEFAN REINHOLD

Stefan Reinhold (Dept. of Pharmacology and Toxicology) was awarded a scholarship for the International Summer School for Doctoral Students entitled 'Vascular cell functions in health and diseases'. He was one of the 25 PhD candidates that were selected within all applicants from European and Latin America universities.

EFSD GRANT CASPER SCHALKWIJK, ROBERT VAN OOSTENBRUGGE AND SÉBASTIEN FOULQUIER

Prof. **Robert van Oostenbrugge** (Dept. of Neurology), Prof. **Casper Schalkwijk** (Dept. of Internal Medicine) and Dr **Sébastien Foulquier** (Dept. of Pharmacology and Toxicology) were granted 100 K€ by the European Foundation for the Study of Diabetes (EFSD) and the Boehringer Ingelheim European Research Programme in Microvascular Complications of Diabetes. Their granted project, entitled 'AGE-ing of the brain microvessels: the road to the onset of Vascular Cognitive Impairment', aims to elucidate the role of methylglyoxal, a precursor of Advanced Glycation End-products, in the development of Vascular Cognitive Impairment.

INVESTMENT GRANT NWO MEDIUM CASPER SCHALKWIJK AND JEAN SCHEIJEN

Prof. **Casper Schalkwijk** and Dr **Jean Scheijen** (Dept. of Internal Medicine) received an Investment Grant NWO Medium of 450 K€. With their granted project, entitled 'Detection of AGEs with mass spectrometry at unprecedented levels; on the road to precision medicine', an UPLC I-class XevoTQ-XS system of Waters will be purchased. The unique specific features of this XevoTQ-XS system will enlarge the scope of analysis of specific AGEs at unprecedented levels of performance and will advance several groundbreaking projects within CARIM.

CARIM-BASED EMPATHY PROJECT GRANTED BY ERA-CVD

One of the projects funded by ERA-CVD is the 'Electro-mechanical Presages of Sudden Cardiac Death in the Young: integrating imaging, modelling and genetics for patient stratification (EMPATHY)' project. This multidisciplinary project is initiated and will be coordinated by Dr **Joost Lumens** (Dept. of Biomedical Engineering) and includes two other European partners: Dr Kristina Haugaa, Oslo and Dr Lia Crotti, Milan. Together, they will receive 800 K€ for three years of research.

The EMPATHY project aims to unravel the complex pro-arrhythmic electro-mechanical interactions in the apparently healthy yet vulnerable hosts of genetic cardiac diseases by combining three highly complementary scientific fields: clinical cardiac imaging (Oslo), genetics and cellular electrophysiology (Milan), and multi-scale computational modelling (Maastricht). It is expected that EMPATHY will reveal novel genetic and electro-mechanical signatures of arrhythmogenic diseases, enabling earlier disease recognition, personalised therapeutic intervention, and effective prevention of sudden cardiac death in the young.

UNILEVER RESEARCH PRIZE AND STUDENT AWARD MAURICE HALDER

Maurice Halder won a Unilever Research Prize 2017. The prize was awarded to outstanding postgraduate students, one from each of the 13 Dutch universities, with research theses contributing to the Global Goals. The prize was established in 1956 to strengthen the bond between industry and academic research, and to motivate students to excel. Maurice' thesis focussed on the effects of arterial remodelling, i.e. vascular calcification, on the development of cardiovascular diseases. The prize consisted of a sum of 2,500 € and a work of art in glass. Maurice Halder has also won one of the 2017 Student Awards of Maastricht University, presented to students who achieved the highest marks for their final theses in 2017. The title of his thesis is 'Arterial remodelling: a key player in cardiovascular diseases'.

OTHER HIGHLIGHTS

CARIM COMMITMENT AWARD

Dr **Koen Reesink** (Dept. of BME) received the CARIM Commitment Award, 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. Koen performs many duties within our CARIM community without any form of self-interest, this in addition to his own scientific and teaching work. The award consists of a bronze coin of the sculptor Marina van der Kooi.

CARIM IN TOPTALENT PROGRAMME Maastricht UMC+ Dr **Joost Lumens** (Dept. of Biomedical Engineering), Dr **Judith Sluimer** (Dept. of Pathology) and Dr **Julie Staals** (Dept. of Neurology) have been selected for the Toptalent Programme of Maastricht UMC+. At the highest level, Maastricht UMC+ offers this programme to potential professors and to offer them a track towards chair with a specialised remit (*profileringsleerstoel*) with the prospect of moving on to a full professor personal chair or a full professor with a key domain chair after assessment of their performance and professional growth potential. This

track includes course work on personal development and leadership skills.

SANDRO GELSOMINO APPOINTED AS PROFESSOR

Sandro Gelsomino (Dept. of Cardiothoracic Surgery) has been appointed as Professor of Cardiac Surgery. It is a full-time appointment. His research focusses on clinical and experimental cardiovascular medicine and surgery, in particular atrial fibrillation, coronary, mitral and aortic pathologies. He is committed in developing new tools for minimal invasive interventions and new cardiac surgery techniques aiming for a more patient-specific tailored approach.

CHRISTIAN WEBER HIGHLY CITED RESEARCHER 2018

Prof. **Christian Weber** (Dept. of Biochemistry) was named a Highly Cited Researcher for 2018, meaning he is among an elite group recognised for exceptional research performance demonstrated by production of multiple highly cited papers that rank in the top 1% by citations for field and year in Web of Science.

JOINT PHD PROJECTS BIRMINGHAM-MAASTRICHT

Three CARIM projects have been awarded in the framework of the joint PhD projects between the University of Birmingham and Maastricht University:

- Dr **Sébastien Foulquier** and Dr **Matthijs Blankesteijn** (Dept. of Pharmacology & Toxicology): 'White matter really matters in cSVD: Wnt signaling in the endothelial – oligodendroglial crosstalk'.
- Prof. **Erik Biessen** and Dr **Marjo Donners** (Dept. of Pathology): 'The Tspan14/ADAM10 dyad: a major regulator of Notch signaling in atherosclerosis?'
- Prof. **Uli Schotten** (Dept. of Physiology) and Prof. **Monika Stoll** (Dept. of Biochemistry): 'Systems Biology Approach for Assessment of the Electro-Molecular Phenotype of Atrial Fibrillation'.

CARIM'S 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 each step of their career, be it at Bachelor, Master, postgraduate, PhD or post-doc level. These grants will be enabled through our '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.

a. 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.

b. **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 program.

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

2018 Jasper Demandt

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.

2018 Mueez Aizaz, Jens Posma

3. HS-BAFTA TALENTED POSTDOCS

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 (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 specifically CARIM.

2016 Stijn Agten

2017 Robin Verjans

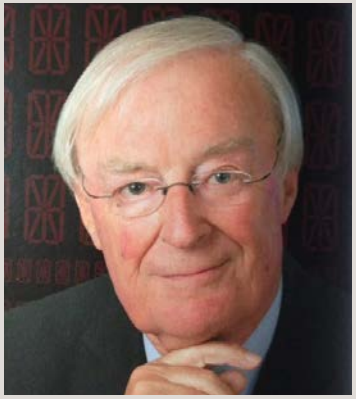
2018 Mitchel Bijnen

ROBERT RENEMAN LECTURE

The Robert Reneman Lecture takes place during the annual CARIM Scientific Symposium, and is named in honor 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
2018	M. Giacca	Trieste, Italy

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. Hein 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

SINT ANNADAL FOUNDATION

2014-2019	J. Hoorntje

HIGHLIGHT
DIVISION VESSELS

ILJA ARTS

Department of Epidemiology

"When I was in college, I was told that biology was too complicated to use mathematics for its analysis. Today, it rather seems that biology is too complicated *not* to use mathematics." Eberhard Voit, 2013

Technology is advancing fast. It gives us unprecedented insights into the human body on both a large and a microscopic scale. We can peek into the brain, without opening the skull. Our heartbeat can be measured using an app on our iPhone. The entire human genome is available as one large roadmap, and more and more knowledge about molecules in health and disease is becoming available every day. What if all available human data could be combined and deciphered by computers to create a "virtual physiological human"? The Maastricht Centre for Systems Biology strives to perform cutting edge research in the interdisciplinary field of systems biology, combining biology and state-of-the-art technology for the acquisition of biological data by advanced mathematical and computational methods. Research projects at MaCSBio focus on human, multiscale modelling, and within CARIM we collaborate in the research line of Systems Medicine of Cardiometabolic Diseases.

MODELLING HETEROGENEOUS HUMAN DISEASE

Non-communicable conditions account for almost two-thirds of deaths worldwide. With the increasing prevalence of obesity and the aging of populations in the Western world, chronic illnesses are emerging as the principal challenge to global health. In the Netherlands, chronic diseases are the main driver of increasing healthcare expenditures. Current treatment for such conditions is often inadequate, due to their complexity, but perhaps even more due to the large heterogeneity in disease phenotypes between individuals. Projects within the research line aim to increase our understanding of obesity, type 2 diabetes and cardiovascular disease, and to develop new, biology-based, personalised approaches to the prevention and treatment of these diseases, using a systems biology approach.

In order to address these challenges, we develop new systems biology models and approaches to modelling that cross several scales of investigation, both in terms of size and time (**Figure 1**). We focus on the use of human data, and use a wide range of modelling tools and approaches to integrate these data, such as (1) genome-scale metabolic and smaller scale dynamic models to simulate and predict changes in metabolism; (2) machine learning and statistical

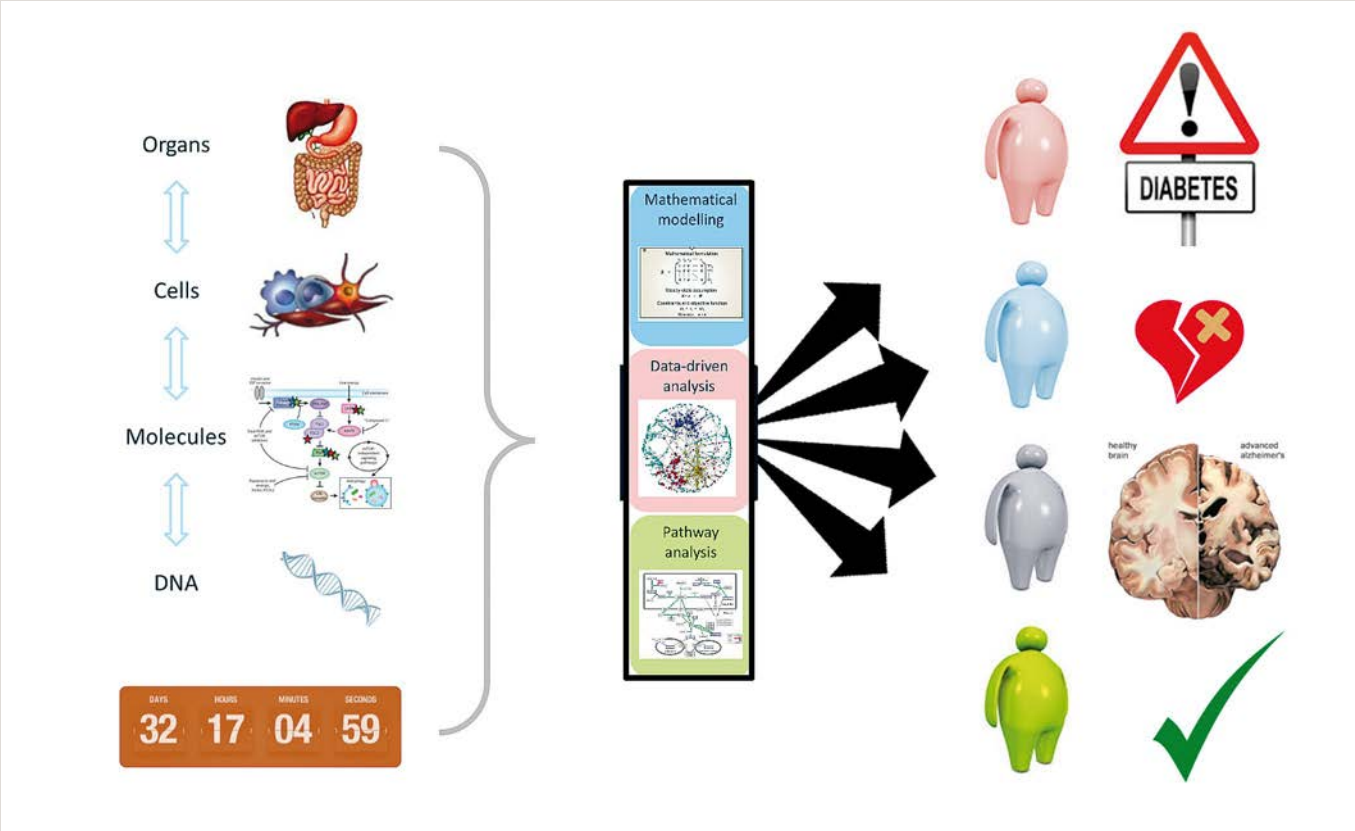
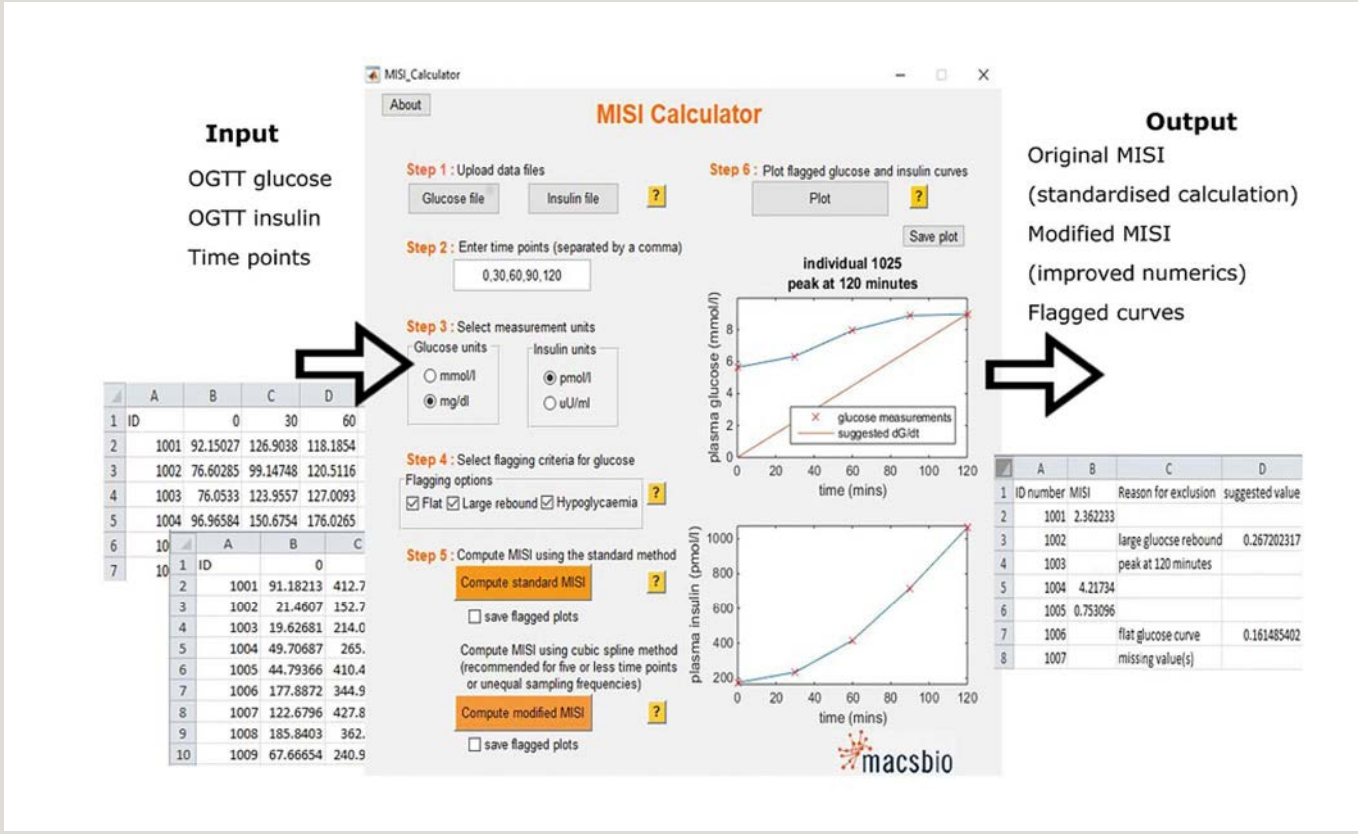


FIGURE 1 Crossing multiple scales of investigation in terms of size and time requires a wide range of modelling tools and approaches

inference to integrate heterogeneous multi-omics data starting from a hypothesis-free, data-driven perspective; (3) network and pathway biology to visualise and interpret genome-scale data in their biological context.

At MaCSBio we have developed mathematical tools that are freely available for use by other scientists, such as the Muscle Insulin Sensitivity Index (MISI) Calculator. We have used this calculator to examine biological mechanisms underlying tissue-specific insulin resistance in overweight but otherwise healthy individuals, using data generated in collaboration with The Maastricht Study and the BBMRI Biobanking Netherlands initiative. And we have applied novel network biology methods to analyse complex time-series data.



ID		0	30	60
1001	92.15027	126.9038	118.1854	
1002	76.60285	99.14748	120.5116	
1003	76.0533	123.9557	127.0093	
1004	96.96584	150.6754	176.0265	

ID		0	
1001	91.18213	412.7	
1002	21.4607	152.7	
1003	19.62681	214.0	
1004	49.70687	265.	
1005	44.79366	410.4	
1006	177.8872	344.9	
1007	122.6796	427.8	
1008	185.8403	362.	
1009	67.66654	240.9	

ID number	MISI	Reason for exclusion	suggested value
1001	2.362233		
1002		large gluocse rebound	0.267202317
1003		peak at 120 minutes	
1004	4.21734		
1005	0.753096		
1006		flat glucose curve	0.161485402
1007		missing value(s)	

MISI CALCULATOR

The Muscle Insulin Sensitivity Index (MISI) has been developed to estimate muscle-specific insulin sensitivity based on data from an oral glucose tolerance test (OGTT). To date, the index has been implemented with considerable variation in the findings reported in the literature, and initial positive evaluations were not reproduced in subsequent studies. We investigated the computation of MISI using oral OGTT data with differing sampling schedules, and aimed to standardise and improve its calculation. The performance of MISI was evaluated using seven-time-point OGTT data for 2631 individuals from the Maastricht Study and hyperinsulinaemic-euglycaemic clamp data for 71 individuals

FIGURE 2 MISI score calculator indicating input and output for its use. The calculator can be downloaded from: https://www.maastrichtuniversity.nl/macsbio-misi-calculator.

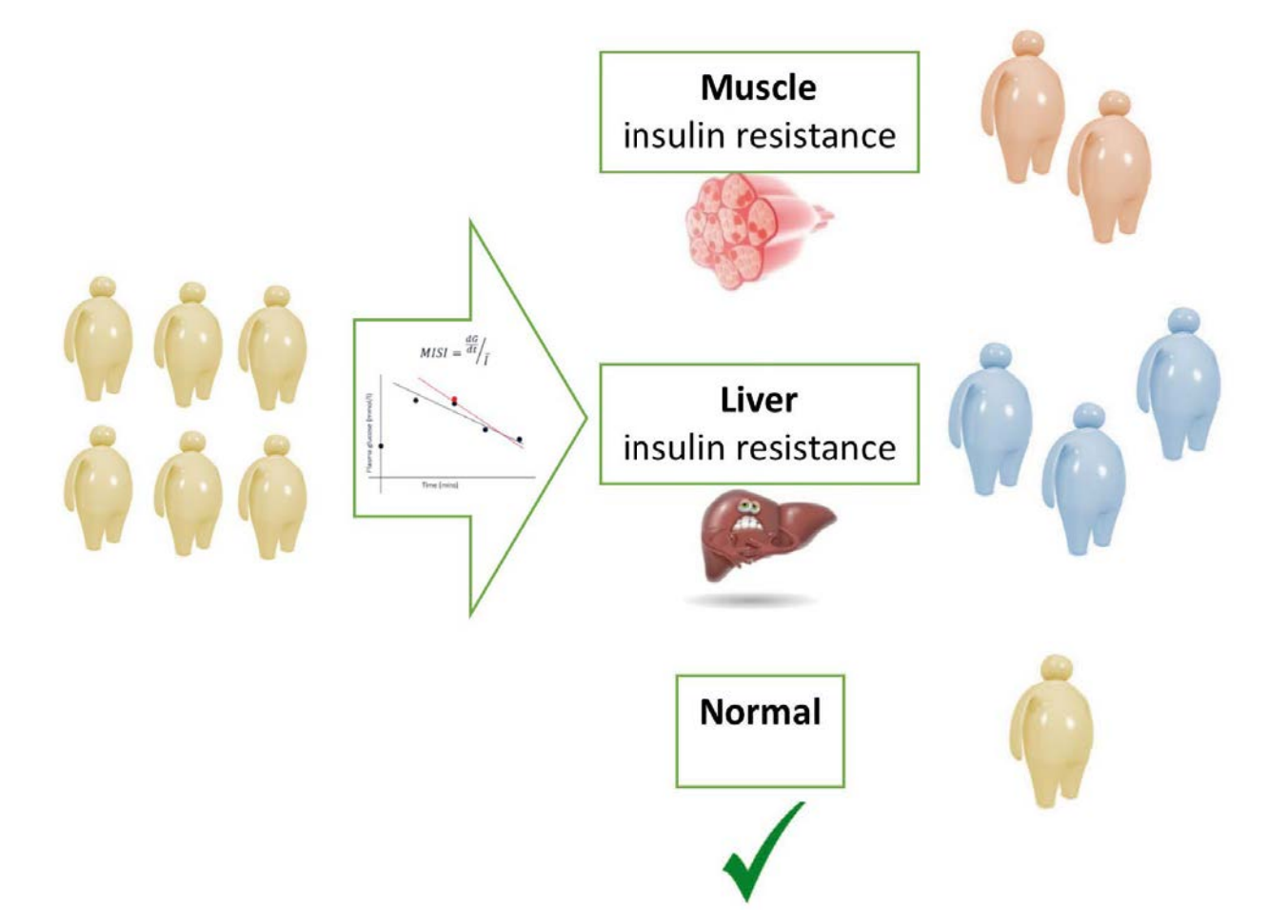


FIGURE 3 Hepatic insulin resistance index and muscle insulin sensitivity index were derived from a 5-point oral glucose tolerance test (OGTT) and participants were classified accordingly.

from the PRESERVE Study. MISI was computed on subsets of OGTT data representing four- and five-time-point sampling schedules, to determine minimal requirements for accurate computation of the score. A modified MISI computed on cubic splines of the measured data, resulting in improved identification of glucose peak and nadir, was compared with the original method, yielding an increased correlation ($\rho = 0.576$) with the clamp measurement of peripheral insulin sensitivity as compared to the original method ($\rho = 0.513$). Finally, a standalone MISI calculator (**Figure 2**) was developed, which offers a standardised method of calculation using both the original and improved methods. (O'Donovan et al. Scientific Reports 9, 9388, 2019.

INVESTIGATING TISSUE-SPECIFIC INSULIN RESISTANCE

Recent evidence indicates that insulin resistance (IR) in obesity may develop independently in different organs, representing different aetiologies towards type-2 diabetes and other cardiometabolic diseases. We investigated whether non-diabetic IR in the liver and in the skeletal muscle are associated with distinct metabolic profiles. Our study included 634 overweight/obese (BMI≥27 kg/m2) non-diabetic adults (≤65 years; 63% women) of the European multicentre Diogenes Study. Hepatic insulin resistance index and muscle insulin sensitivity index were derived from a 5-point oral glucose tolerance test (OGTT) (**Figure 3**). Seventeen plasma metabolites were quantified by nuclear-magnetic-resonance spectroscopy. In an independent sample of 540 overweight/obese non-diabetic participants (BMI≥27 kg/m2; 40-65 years; 46% women) of the Maastricht Study, 11 metabolites and a 7-point OGTT were available for validation. Replicated results indicated that both liver and muscle IR was associated with elevated levels of (branched-chain) amino acids (isoleucine, alanine), lactate and triglycerides and lower glycine levels, but only liver IR was associated with lower ketone body levels (acetoacetate, 3-OH-butyrate) and elevated levels of ketogenic amino acids (leucine, tyrosine), suggestive of decreased ketogenesis. These findings suggest that distinct metabolic profiles of liver IR and skeletal muscle IR can be observed in early stages of cardiometabolic disease development. This knowledge might enhance the development of more targeted tissue-specific interventions to prevent progression to more severe disease stages. (Vogelzangs et al. presented at the BBMRI Metabolomics Consortium meeting, Utrecht, Jan 2018).

OMICS TIME-SERIES

Obesity is a global epidemic identified as a major risk factor for multiple chronic diseases, and consequently, diet-induced weight loss is used to counter obesity. The adipose tissue is the primary tissue affected in diet-induced weight loss, yet the underlying molecular mechanisms and changes have not been completely unravelled. In this study, we developed a network biology analysis workflow which enables the profiling of the cellular processes affected by weight loss in the subcutaneous adipose tissue (**Figure 4**). We analysed time-series gene expression data from a dietary intervention dataset with two diets, the YoYo study. Differentially expressed genes were used to generate co-expression networks using a method that capitalises on the repeat measurements in the data and finds correlations between gene expression changes over time. Using the Cytoscape network analysis tool, we constructed an overlap network of conserved components in the co-expression networks,

clustered on topology to find densely correlated genes, and analysed it using Gene Ontology enrichment analysis. We found five clusters involved in key metabolic processes, but adipose tissue development and tissue remodelling processes were also enriched. In conclusion, we present a flexible network biology workflow for finding important processes and relevant genes associated with weight loss, using a time series co-expression network approach that is robust towards the high inter-individual variation in humans. (Tareen et al. 9, 525, 2018.

ACTIVITIES

Together with other research institutes, we regularly organise well-attended events, such as: the annual MaCSBio Science Day; the Maastricht Systems Biology Forum (MSBF), which brings together all UM/Maastricht UMC+ researchers interested in the application of modelling and computational approaches to cardiovascular physiology, metabolism, and neurosciences; and Peer Groups, i.e. groups of researchers using a similar methodology or working on a similar topic, who interact regularly to exchange information, critically follow new developments, and come up with innovative solutions.

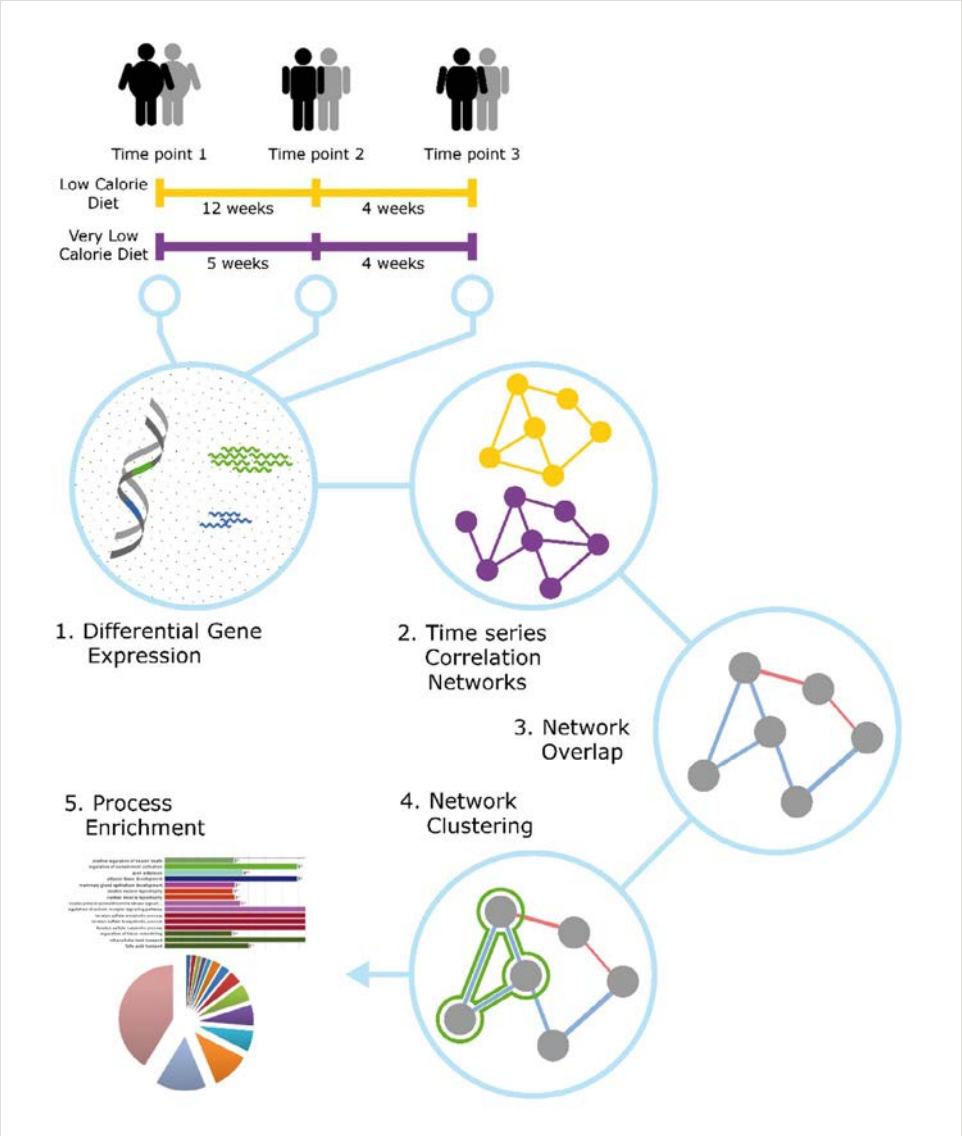


FIGURE 4 Network biology analysis workflow. (1) The time-series expression data from the time points is normalised and differential expression analysis is performed. (2) Correlation networks are constructed on the time series for each respective diet. (3) The overlap network is generated from the two networks, showing the correlations which are shared between the two diets. (4) Community clustering is performed to find clusters of genes which show the most similar expression patterns. (5) The overlap network and the gene clusters are then used for process enrichment to find the affected cellular processes.

INTERVIEW

JUDITH SLUIMER AND ANDY BAKER

A shared love for science and each other

He lives in Edinburgh and is a visiting professor in Maastricht, she lives in Maastricht and is a visiting scientist in Edinburgh. He received an ERC Advanced grant in 2014, she received a Vidi in 2018. He is an expert in vascular injury and advanced therapies, she in atherosclerosis. He has three children, one of whom still lives at home, she has two in elementary school. They share a love for vascular biology science... and each other. In February 2019, Andy Baker and Judith Sluimer got married, sealing a relationship that's also bearing scientific fruit.

First, to get the logistics question out of everyone's head, the practical details of this relationship. Judith Sluimer and Andy Baker have been sponsoring airlines and rail companies big time in the past 3.5 years. Since they got together as a couple at the end of 2015, they've tried every reasonable way of travelling, leading to the conclusion that flying between Amsterdam and Edinburgh, plus train rides before and after, is most efficient. Hence, when her kids are with their dad, she travels to Edinburgh on Friday and returns on Monday/Tuesday. The other weekend, he will do the same in the opposite direction. The Monday they spend in each other's lab (well, for Andy that's the office – the lab coat was last used some time ago!), since they are visiting scientists in each other's institutes. Sluimer: "When you talk a lot about science, you discover common ground and you start working together. After our first publications and grant applications together, our Universities agreed that there was enough common ground to formalise the arrangement, with unpaid visiting professorship for Andy and an honorary senior lectureship for Judith. It allows us to make the most out of our relationship, also scientifically." Baker adds: "We do work in a similar area but with individual strengths that are different, so there was an immediate impact and it wasn't in any way forced."

SHAPING A SCIENTIFIC COLLABORATION

The single cell technology available in Baker's University via a very rewarding collaboration with Neil Henderson was one of the strong pillars under Sluimer's Vidi-proposal that was awarded in 2018. Her research evolves around single cell sequencing of atherosclerotic plaque fibroblasts. "During the interview I could show the data I had already collected in the lab in Edinburgh. That gave me an enormous leverage and also confidence for the interview. I could say: No worries, I'm already doing this." Her team also benefits from Baker's expertise on the biology of smooth muscle

JUDITH SLUIMER AND ANDY BAKER HAVE BEEN SPONSORING AIRLINES AND RAIL COMPANIES BIG TIME IN THE PAST 3.5 YEARS

cells. The other way around, Baker's students gain a lot from Sluimer's expertise in atherosclerosis. All in all, the scientific collaboration includes student and staff exchanges, shared publications and grant applications.

LIFESAVING THIRTY MINUTES

Four years earlier, in 2014, Baker obtained the prestigious ERC Advanced grant for his work on modifying the vasculature in order to control injury. A particularly interesting study is about to enter the clinic at the time of the interview. "We have developed a way to modify the bypass graft that's is first taken out of a patient's leg then grafted into the heart. He does this in the thirty minutes outside the body (*ex vivo*) in the cardiac theatre. Until today, many of those grafts fail in the long term, because veins try to turn into arteries, so it can cope with the higher blood pressure environment. And sometimes that leads to adverse remodeling and occlusion of the vessel again." Baker's group has worked out a way to deliver a gene to the vessel in the thirty minutes in the operating theatre, which prevents the adverse remodeling of the vessel. They insert a virus that infects the vessel wall and expresses a "therapeutic gene" in the subsequent days and weeks, it expresses the therapeutic gene that prevents remodeling, TIMP-3.

THE FUN AND THE HARD PART OF SCIENCE

Apart from these major steps you get to take in scientific research every now and then, and celebrating a publication or an obtained grant, they both enjoy the daily practice of research a lot. Sluimer: "Discovering things that you didn't know before, or even no one knew before, that's what I love most about science. Plus guiding my five PhD students, who all need different things and approaches. I spend less time in the lab, but I like writing and thinking about new steps even better." Baker would even feel lost in a lab coat by now, he admits. "But generating new ideas and new data every week, turning around things that aren't working and pushing those that are, that's the fun part for me. You've got to make sure you're first, that's the incentive that keeps people going all the time." Sluimer expected, or hoped, that this pressure would lessen, the further you get in your career. "Five years ago, I gave myself another five years to prove I was a worthy part of academia. Now I'm doing good with funding and I'm in the faculty's top talent programme, hopefully leading to a professor's title someday. So now I want a big paper, or even two." Baker confirms: "That pressure never goes away in science." Sluimer: "And that's OK, but you need to learn how to deal with that and relax."

HAVING A MENTOR AT THE KITCHEN TABLE

Although scientifically they are in different stages of their career, on a daily basis they are equals. That makes acting as each other's mentor quite effective as well. Sluimer: "If you're senior, fewer people dare to tell you what you could do differently." Baker: "She does, which is a bit of an eye opener. But at the end of the day, whatever you can improve is a positive thing." Sluimer: "The way Andy governs his projects, cutting to the chase, is inspiring, but also when he pushes me to not unnecessarily postpone a publication." Also language wise, she learned a lot. "I thought that my English was pretty good, after having lived three years in the United States." Baker with a smile: "That's not English." Sluimer laughs: "Yeah, potato and tomato etcetera. Now I even dream in English sometimes."

MAKING A NEW FAMILY

Learning Dutch has not yet had the priority in Baker's busy schedule, but he knows the basics, like 'Boterham met pindakaas' (peanut butter sandwich) and 'Ga naar je kamer' (go to your room). Getting along with her kids is anyhow no problem at all, just like it isn't the other way around. The few times a year the recomposed family is complete, things naturally flow. Sluimer: "Andy's son is a born Scotsman, who my son Jasper truly admires. So they wore the same kilts at our wedding in Edinburgh for example. That was also what our wedding was about: making a new family."

Judith Sluimer, *PhD, is an Associate Professor in Experimental Vascular Pathology. Her research is focussed non-invasive imaging of vulnerable plaques and the pathogenesis of atherosclerosis. She defended her PhD thesis at Maastricht University in 2008. In 2010 she acquired the Veni grant from NOW, followed by the Vidi in 2018. In 2016 she received a Leducq grant and a Dr. E. Dekker senior postdoc fellowship from the Dutch Heart Foundation.*

Andy Baker *is a British Heart Foundation Professor of Translational Cardiovascular Sciences and holds the Gustav Born Chair of Vascular Biology. In 2015, he was recruited by the University of Edinburgh, where he became head of the Centre for Cardiovascular Science in 2017, one of the largest Centre's at the University with 250 staff and students. Until then he had been working at the University of Glasgow for sixteen years. In 2014, he obtained a prestigious ERC Advanced grant.*

INTERVIEW

A DISCUSSION WITH ITALIANER, HACKENG AND CRIJNS

Grab your chances and be proud

It was the first time a director of the Dutch Heart Foundation attended the annual CARIM symposium. In 2018, Floris Italianer travelled to Maastricht to meet the CARIM community face-to-face, and he returned to The Hague with something tangible. Together with biochemist and director of CARIM, Tilman Hackeng and cardiologist and chairman of the scientific advisory board of the Heart Foundation, Harry Crijns he looks back and ahead. A conversation about “integrators”, culture change and antennae.

Tilman Hackeng remembers vividly: in a room full of CARIM researchers young and old, Floris Italianer expressed his surprise that the young did not ask him more questions. Hackeng: “So you then ask yourself what’s the reason for that? I guess that at a similar meeting in Amsterdam he would be inundated with questions by self-assured researchers. That may be our weakness: we do a lot of great things here, but maybe we’re not so up front about it.” Harry Crijns; “The further south you go, the more reticent people tend to be, right?” Italianer immediately qualifies that: “I don’t believe in those large cultural differences between the Randstad region and Maastricht, although people in Maastricht may be a bit more polite. What I tried to say with that challenging remark was: grab your chances when you meet people in your network who might be of use to you. That’s just an aspect that’s becoming ever more important for scientists. During the ninety minutes that I was at CARIM, nobody tried to sell me anything. Not that that would have had an immediate effect, but what I most of all wanted to say was: merely doing excellent research isn’t enough.”

GRAB YOUR CHANCES WHEN YOU MEET PEOPLE IN YOUR NETWORK WHO MIGHT BE OF USE TO YOU

THE CHANGING CULTURE AT THE HEART FOUNDATION

Crijns suspects that the reservedness of CARIM researchers might also relate to the public image of the Dutch Heart Foundation. “There’s a kind of aura around it, although I have to say that’s changed a lot in recent years. But it’s always been an organisation that kept its distance through a formal attitude, and people were always slightly overawed by that. Fortunately, there’s now more interaction: we now know who to call when we have an idea or a question.” Italianer is glad to hear that. “I really do my best to open up the doors and windows as much as possible. Young people in our organisation are working in a much more transparent way now, through social media, and I also like to chat with researchers myself; it’s making my work so much more lively and fun. That’s why I was happy to accept CARIM’s invitation, quite apart from the fact that it’s of course a wonderful institution, and that we’ve had ties with them through Harry, who’s the chairman of our scientific advisory board.”

AN INSPIRING VISIT TO MAASTRICHT

As Italianer explains, the largest part of the Heart Foundation’s budget is spent on research. “That’s not just something on paper; we want to understand what it’s all about and what researchers need.” The fact that Italianer does not have a cardiovascular background himself is no hindrance at an event such as the CARIM symposium. “If I try hard enough to follow what’s being said, I will always pick up at least something. And in private conversations I’m not afraid to ask ‘stupid’ questions. Healthy inquisitiveness

on the part of an outsider can never hurt." What particularly struck him at the symposium was the visualisation of a "disease system" in one CARIM researcher's presentation. Afterwards, he asked the researcher whether he might have that picture, and it is now hanging in his office, right across from his desk. "It has these coloured spheres, which represent diseases, plus the beauty of the human body and the interrelations between the various systems. But for me, it's also about the importance of collaboration, between researchers, institutes, organisations like ours, and so on. Many people are working on highly specialised subjects, whereas in the end everything is connected."

COMMON GOAL: FURTHERING RESEARCH

This was precisely the reason for starting the Dutch Cardiovascular Alliance (DCVA) in 2018. Whereas CVON (Cardiovascular Research Netherlands) is where researchers collaborate, DCVA brings together researchers, universities of technology and businesses. Where CVON is mostly concerned with research, DCVA also addresses the other conditions that that are required to further the development of cardiovascular medicine in the Netherlands: from data processing to valorisation and talent development. Crijns: "The idea is to get politicians and the wider public debate involved in the cardiovascular field, and to raise another billion euros over the next ten years, which will be needed for this research."

It reflects the growing realisation in this field of research that collaboration is the only way forward. Italianer has also transformed the Heart Foundation towards an organisation that mostly tries to raise funding for projects, together with parties like the Dutch Cancer Society (KWF) and the Netherlands Organisation for Health Research and Development (ZonMW). An organisation that promotes grant applications and brings researchers together to make progress on topics in the context of the Dutch Research Agenda. Hackeng: "It used to be that if a young researcher submitted comparable grant proposals to two organisations, and was awarded both of them, one of the two had to be chosen. Now we've had a few situations where we consulted with the Heart Foundation to find a way for the researcher to accept both grants. That's a great boost for such a researcher. Our common goal is that the research needs to be done. And that's a very pleasant way to collaborate."

THE IMPORTANCE OF ANTENNAE

So how does the Heart Foundation set out its course, aside from the research agenda? Five years ago, it developed a research agenda, after having consulted benefactors and scientists about the key themes to focus on. Italianer: "On the occasion of our fiftieth anniversary, we decided to identify five topics for five years and to spend an extra 50 million euros on them." The topics were: finding and identifying cardiovascular diseases at an earlier stage, cardiovascular diseases in women, heart failure, atrial fibrillation and a healthy lifestyle. The agenda is currently being evaluated, and in the meantime, new avenues are being explored. Hackeng: "To our surprise, the Heart Foundation approved a chemical research project in 2018, as it offered good translational prospects. This means that we're now going to develop a programme on translational cardiovascular chemistry with the help of the Heart Foundation, which is a ground-breaking initiative." Crijns: "The fact that that was recognised by Floris' organisation has encouraged us greatly. Just as with the other research fields we are good at, like atrial fibrillation." Hackeng: "And thrombosis. The Heart Foundation used not to support that kind of research so much, as there is a separate foundation for that. But it does contribute greatly to the development

of cardiovascular diseases, and together with Leiden and Groningen we've secured a CVON grant for our research in this field, and have managed to put thrombosis on the map for the Heart Foundation." The fact that Italianer is not a peer working in the same field makes no difference to the two researchers. Hackeng: "He does have antennae for what's needed by those working in the field, and that's what matters."

"INTEGRATORS": THE BACKBONE OF RESEARCH

Now that Crijns and Hackeng have a chance to chat to director of the Heart Foundation, they would like to raise a topic that was also discussed at the symposium: the "integrators". Hackeng introduces the subject: "The Heart Foundation has excellent programmes for young talents and top academics, and is very effective in supporting crowd-funding. But what we feel is to some extent lacking in the programme grants is funding for technicians and research staff. They're the ones who form the structural backbone of a research department, its continuity, its sustainment." Crijns: "they may not be at the hub of international networks, but they are certainly their mainstay." Hackeng: "And we're in danger of losing them, as they are systematically overlooked in the programme grants." Crijns: "Our motto, at the symposium too, was 'Teams, not champions'. The high-flyers are also very well aware that they really need those integrators." Hackeng: "As it is, keeping those teams together is the responsibility of the research grant principal applicants, but you really have to pull out all the stops." They eagerly watch Italianer's reaction. But he regards the matter as something for the DCVA and the government. "At the end of the day, our resources are limited," he starts. "Of course we are prepared to discuss this with the scientists, and with the advisory board that Harry chairs. But ten percent of the large consortia grants that we offer is already set aside for talent development. If we were to earmark another percentage for assistants and analysts, that would mean dismantling research."

In Italianer's view, that kind of infrastructure is a task for the universities, and thus ultimately for the government, which needs to invest enough money. "The government is happy to leave these matters to be solved by societal organisations, as we also do with the network of citizen health workers and the AEDs throughout the land. But I think this is a task for the government, which has to ensure that we remain competitive as a country with a knowledge-based economy. It's the government which invests in employment. We're not just any small country: we're in the premier as regards the quality of research and care." Hackeng fully agrees: "More money needs to be allocated to research. If you see the amount of high-quality research output realised in the Netherlands for the money that's being invested, we're top of the range worldwide." Crijns: "And the same goes for CARIM's work in fields like biochemistry and atrial fibrillation." Italianer: "And there's every reason to be proud of that, and to share your successes with the outside world. That's what I wanted to impress upon the young researchers in Maastricht."

30 JAAR CARIM

TRAINING AND EDUCATION

04

INTRODUCTION

CARIM offers a flexible and integrated education and training programme that suits the individual ambitions of its 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, Masters 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 become 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 candidates 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 2018, 112 PhD candidates attended our PhD programme. In 2018, 42% 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 candidates with a background in medicine or in the basic sciences. The principal goal of the four-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 31-12-2018)

FUNDING SOURCE	2015	2016	2017	2018
UNIVERSITY	34	18	13	17
NWO	11	12	13	13
NON-PROFIT AND INDUSTRY	51	65	80	82
TOTAL	**96**	**95**	**106**	**112**

POSTGRADUATE PROGRAMME

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 Maastricht UMC+, European Heart Academy (EHA) and the European Heart Rhythm Association (EHRA); a longstanding 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 organise 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.

PHD DELIVERABLES

In 2018, 36 PhD candidates finished their theses within our institute, and seven theses were externally prepared. The table below illustrates the numbers of PhD candidates in the years 2009-2014, 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 2009 UNTIL 2014 (date set 31-12-2018)

YEAR INTAKE	2010	2011	2012	2013	2014
COHORT VOLUME (annual intake)	33	33	21	22	27
MALE	13	18	9	7	12
FEMALE	20	15	12	15	15
PHD FROM ABROAD	12	11	5	8	11
ONGOING	0	5	2	3	9
GRADUATED > 5 YEARS	14	16	10	12	15
DROP OUT	6	0	5	3	3
AVERAGE DURATION (in months)	62.5	61.1	53.6	53.2	53.7
THESIS COMPLETED	27	28	13	16	10

CARIM THESES 2018

Theodorou K - CUM LAUDE
Title: Disarray at the membrane; regulation of vascular inflammation by cholesterol and proteases
Supervisor: Prof. E.A.L. Biessen
Co-supervisor: Dr M. Donners
19 January

Van der Linden N - CUM LAUDE
Title: Cardiac troponins: state of the (he)art; towards optimization of interpretation
Supervisors: Prof. M.P. van Dieijen Visser, Prof. L.J.C. van Loon
Co-supervisor: Dr S.J.R. Meex
19 January

Sörensen B
Title: Determinants of microvascular function in individuals with and without type 2 diabetes: a population-based approach
Supervisor: Prof. C.D.A. Stehouwer
Co-supervisors: Dr A.J.H.M. Houben, Dr M. Schram
19 January

Verjans R
Title: MicroRNAs Orchestra the Cellular Processes Driving Failure of the Heart
Supervisor: Prof. S.R.B. Heymans
Co-supervisors: Dr B. Schroen, Dr M. van Bilsen
23 February

Vries M
Title: Assessment of Bleeding Risk. Preoperatively and in the context of antiplatelet therapy
Supervisor: Prof. H. ten Cate
Co-supervisors: Dr Y. Henskens; Dr M. Lancé
23 February

Gräni C
Title: Non-invasive cardiac imaging of coronary artery anomalies
Supervisor: Prof. H.P. Brunner-La Rocca
Co-supervisor: Dr S.C.A.M. Bekkers
23 February

Casas Guijarro A - CUM LAUDE
Title: Network pharmacology for a first-in class neuroprotective therapy in ischemic stroke
Supervisors: Prof. H.H.H.W. Schmitz, Prof. C. Kleinschnitz
Co-supervisor: Dr F. de Vries
1 March

Nielen Y
Title: Osteoarthritis: association with diabetes mellitus, and treatment-related outcomes
Supervisors: Prof. A. Boonen, Prof. P. Dagnelie
9 March

Baaten C
Title: Acquired alteration in platelets: Insight into impairment and recovery in platelet function
Supervisor: Prof. J.W.M. Heemskerk
Co-supervisor: Dr P.E.J. van der Meijden
15 March

Kietadisorn R
Title: Drainage versus defense: The management of vascular leakage in cardiovascular diseases
Supervisor: Prof. E. Biessen
Co-supervisor: Dr J. Sluimer
23 May

Rech M
Title: Unraveling metabolic mechanisms in heart failure: microRNAs as part of the puzzle
Supervisor: Prof. B. Schroen
Co-supervisors: Dr M. van Bilsen, Prof. S. Heymans
23 May

Kuiper G
Title: Haemostasis monitoring: pinpointing using point of care
Supervisors: Prof. H. ten Cate, Prof. W. Buhre
Co-supervisors: Dr Y. Henskens, Dr M. Lancé
31 May

CARIM THESES 2018

Posthuma J
Title: Haemostatic and Cellular Effects of Coagulation Proteases; exploring new areas of pleiotropy
Supervisor: Prof. H. ten Cate
Co-supervisor: Dr H. Spronk
13 June

Maeder M
Title: The trial of Intensified Medical Therapy in Elderly patients with Congestive Heart Failure (TIME-CHF): Novel Insights into Hot Topics in Heart Failure
Supervisor: Prof. H.P Brunner-La Rocca
Co-supervisor: Dr S. Sanders-van Wijk
14 June

Eurlings L
Title: Biomarkers for risk stratification and guidance in heart failure
Supervisors: Prof. H.P Brunner-La Rocca, Prof. Y. Pinto
14 June

Ter Bekke R
Title: Ventricular arrhythmogenesis in the genetically-susceptible Heart; time to change concepts of mechanisms and management
Supervisor: Prof. P. Volders
22 June

Solari F
Title: Characterization of platelet disorders using quantitative proteomics
Supervisors: Prof. J. Heemskerk, Prof. A. Sickmann
Co-supervisor: Dr R.P. Zahedi
26 June

Roolvink V
Title: Pre-hospitale Beta-blockers in ST-elevation acute myocardial infarction
Supervisor: Prof. A. van 't Hof
Co-supervisor: Dr J. Ottervanger
29 June

Davarzani N
Title: Biomarker Discovery in Heart Failure
Supervisors: Prof. R.L.M. Peeters, Prof. H.P. Brunner-La Rocca
Co-supervisors: Dr E.N. Smirnov, Dr J.M.H. Karel
2 July

Kemna M
Title: Predicting relapses in ANCA associated vasculitis
Supervisor: Prof. J.W. Cohen Tervaert
Co-supervisors: Dr J. Damoiseaux, Dr P. van Paassen
5 July

de Wolf M
Title: Outflow Reconstruction of the Lower Extremity in Chronic Venous Obstructive Disease
Supervisor: Prof. C.H.A. Wittens
Co-supervisor: Dr R. de Graaf
6 July

Out M
Title: Metformin; Pharmacogenetics and Metabolic Effects
Supervisor: Prof. C.D.A. Stehouwer
Co-supervisor: Dr A. Kooy, UMC Groningen
9 July

van Agtmaal M
Title: Diabetes, microvascular dysfunction, and depression: A population-based approach
Supervisor: Prof. C.D.A. Stehouwer
Co-supervisors: Dr M.T. Schram, Dr A.J.H.M. Houben
27 September

Loos C
Title: Evolution of MRI features of cerebral small vessel disease
Supervisor: Prof. R.J. van Oostenbrugge
Co-supervisor: Dr J.E.A. Staals
28 September

Kilic S
Title: Therapeutic Challenges in ST-Elevation Myocardial Infarction
Supervisor: Prof. A.W.J. van 't Hof
Co-supervisors: Dr R. Hermanides, Dr E. Kedhi
3 October

CARIM THESES 2018

van Geffen J
Title: Complex platelet phenotyping: integrative assessment of platelet activity in haemostasis and thrombosis
Supervisor: Prof. J.W.M. Heemskerk
Co-supervisors: Dr M.E.J. Kuipers, Dr B. de Laat
3 October

van Haare J
Title: Microvascular dysfunction as an early hallmark of cardiac disease
Supervisors: Prof. M. Post, Prof. M.E. Kooi
Co-supervisor: Dr M. van Bilsen
12 October

Brinkhues S
Title: Social networks in relation to infectious diseases and type 2 diabetes
Supervisors: Prof. C.J.P.A. Hoebe, Prof. P.H.M. Savelkoul
Co-supervisors: Dr N.H.T.M. Dukers-Muijrers, Dr M.T. Schram
31 October

Heinen S
Title: Towards a non-invasive patient-specific vascular model for iliac artery stenosis severity assessment
Supervisors: Prof. T. Delhaas, Prof. F.N. van de Vosse
Co-supervisors: Dr W. Huberts, Dr J.P.P.M. de Vries
31 October

van Overbeek E
Title: Markers of endothelial function and progression of cerebral small vessel disease; A longitudinal MR Imaging study
Supervisor: Prof. R. van Oostenbrugge
Co-supervisor: Dr J. Staals
2 November

Onete V
Title: Arterial Stiffness: Neuropsychiatric Consequences and Pathophysiologic Mechanisms; Late Life Depression, Cognitive Dysfuntion and Advanced Glycation End-Products
Supervisor: Prof. C. Stehouwer
Co-supervisors: Dr R. Henry, Dr M. Schram
8 November

Dupuis L
Title: Forced to Cooperate; Mechano-Chemical Interactions in Cardiac Sarcomeres
Supervisor: Prof. T. Delhaas
Co-supervisor: Dr J. Lumens
9 November

van Varik B
Title: Arterial remodeling and hypertensive damage; Clinical studies in patients with essential hypertension
Supervisors: Prof. P. de Leeuw, Prof. A. Kroon
Co-supervisor: Dr R. Rennenberg
14 November

Vignoli A
Title: Heparins in Thrombosis and Cancer: Effects on the Vascular Endothelium
Supervisors: Prof. H. ten Cate, Prof. A. Falanga
Co-supervisor: Dr M. Marchetti
16 November

Lemkens P
Title: Arterial Function and Structure in Experimental Hypertension. Effects of NEP/ECE Inhibition
Supervisor: Prof. J. De Mey
Co-supervisor: Dr P. Schiffers
28 November

Bidar E
Title: Assessment of the clinical and electrophysiological characteristics of atrial fibrillation during and after cardiac surgery
Supervisors: Prof. U. Schotten, Prof. J. Maessen
Co-supervisor: Dr S. Verheule
30 November

Alshaikh N
Title: Quantification and evaluation of the anticoagulant activities of protein S in plasma
Supervisors: Prof. T. Hackeng, Prof. J. Rosing
28 November

CARIM THESES 2018

Dudink E
Title: The link between vascular disease and atrial fibrillation
Supervisor: Prof. H. Crijns
Co-supervisors: Dr B. Weijs, Dr J. Luermans
7 December

Poels Th
Title: Left Bundle Branch Block in Transcatheter Aortic Valve Implantation – Determinants of Development and Persistence
Supervisors: Prof. J. Maessen, Prof. F. Prinzen
13 December

Poels E
Title: New insights into the failing right ventricle
Supervisors: Dr P. da Costa Martins, Prof. L. de Windt
Co-supervisor: Dr V. van Empel
18 December

Zhang H
Title: Dynamics of Oxygen saturation, fluid and blood pressure during hemodialysis and their associations with clinical outcomes
Supervisors: Prof. J. Kooman, Prof. P. Kotanko
Co-supervisors: Dr J. Raimann, Dr F. van der Sande
18 December

Maddux D
Title: Clinical factors impacting quality of life and outcomes through the transition from pre-dialysis chronic kidney disease to early dialysis treatment
Supervisors: Prof. J. Kooman, Prof. P. Kotanko
Co-supervisors: Dr L. Usvyat, Dr F. van der Sande
18 December

Van der Weg K
Title: Reperfusion cardiac arrhythmias and their relation to reperfusion induced cell death
Supervisors: Prof. T. Gorgels, Prof. M. Krucoff, Prof. R. de Winter
21 December

PATENTS 2018

Heemskerk J, Cosemans J
Method for determining haemostasis under shear
European Patent Office. 2018;16804763.7.
Date 18-07-2018

Reutelingsperger C
Annexin-1 BBB
Date 12-06-2018

Sardari Nia P
Echo imaging
Date 22-11-2018

Lorusso, R
Venous canula
Date 20-11-2018

Gelsomino S
Ablation Catheter
Date 19-11-2018

Prinzen F, Vernooy K
Integrated assessment of electrical activation and myocardial strain
04-06-2018

Schotten U
Circulating ESM-1 (Endocan) in the assessment of atrial fibrillation
04-08-2018

Schotten U
Circulating Spon-1 in the assessment of atrial fibrillation
22-08-2018

Schotten U
Circulating FGFBP-1 in the assessment of atrial fibrillation and the prediction of stroke
24-08-2018

Schotten U
Circulating TFPI-2 in the assessment of atrial fibrillation and anticoagulant therapy
16-08-2018

DISSERTATION PRIZE 2017

Dr **Mark Hazebroek** (Dept. of Cardiology) received the CARIM Dissertation Award 2017 for his thesis 'Unraveling the origins of dilated cardiomyopathy: How genes, viruses, toxic, metabolic, electric and autoimmune disorders interact to cause dilated cardiomyopathy'.

KNOWLEDGE TRANSFER

CARIM COURSE WEEK

From 4 until 8 June, 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 PhD candidates. In 2017, three courses were organised by CARIM researchers: 'Non-invasive Cardiovascular Imaging', 'Heart Failure Research: Getting to Excellence' and 'Advanced Microscopy and Vital Imaging'. Almost 50 PhD and Master's students participated.

CARDIOVASCULAR GRAND ROUNDS, CARIM SYMPOSIUM 2018 AND CARIM LECTURES

The Cardiovascular Grand Rounds Maastricht, the yearly CARIM Symposium and the CARIM lectures, 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 2018 by Prof. **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 programme please visit www.carimmaastricht.nl, 'CARIM lectures' in the 'Education' section.

CARIM's annual scientific symposium was held in Maastricht on 21 November. During the morning programme, this year's

NWO and Dutch Heart Foundation laureates presented their research, followed by a session on the importance of big data. In the afternoon, a session focussed on the future of cardiovascular research took place followed by presentations of our first two awardees of the CARIM Postdoctoral Fellowship. 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 traditional Robert Reneman lecture was presented by Prof. Mauro Giacca, Director-General of the International Centre for Genetic Engineering and Biotechnology (ICGEB), an international research organisation with seats in Trieste, Italy, New Delhi, India and Cape Town, South Africa, and full professor of molecular biology at the University of Trieste. His current research focusses on the development of novel biotherapeutics for cardiovascular disorders, in particular on the identification of growth factors and microRNAs able to stimulate new blood vessel formation and cardiac regeneration in patients with myocardial infarction and heart failure. He is an expert in the use of viral vectors for cardiovascular applications and maintains a strong interest in the molecular biology of HIV-1 infection.

Finally, the CARIM Award (see page 50), Dissertation prize (see page 84) and the poster prizes were awarded. The following posters were awarded with a prize:

- 'Barcoding in obese: who's at increased risk for the development of cardiovascular disease?' by Fontaine M, Aliyev T, Sikkens R, Jin H, van Greevenbroek M, van der Kallen C, Schalkwijk C, Stehouwer C, Sluimer J
- 'Hyperglycemia-induced vascular dysfunction' by Chimhanda T & LI W, Foreman Y, Hanssen N, Sörensen B, Scheijen J, van der Kallen C, van Greevenbroek M, Brouwers M
- 'Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias' by Verdonschot J, Hazebroek M, Derks K, Barandiarán Aizpurua A, Merken J, Wang P, Bierau J, van den Wijngaard A, Schalla S

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.

On 14 March, the first CARIM lecture session was organised and included the following lectures: Prof. Maarten Honing (M4I); 'Analytical Sciences in Multi-Disciplinary Research; closing the gap between private inspired/Science driven & Private demanded/Technology enabled Research', Dr Koen Reesink (Dept. of Biomedical Engineering); 'The value of arterial stiffness assessment: working behind the scenes' and Dr Joost Lumens (Dept. of Biomedical Engineering); The virtual heart patient: from education to in silico clinical trials'.

The second series of CARIM lectures took place on 24 October with a lecture from Prof. **Eva van Rooij** (Hubrecht Institute & Dept. Of Cardiology UMC, Utrecht); 'Using novel sequencing methods to identify factors involved in cardiac disease'. The scope of the CARIM lectures is to stimulate interaction between the divisions and by focussing on cellular processes and techniques that may benefit science across CARIM's divisions.

OTHER CARIM LECTURES, SEMINARS AND SYMPOSIA 2018

Complementary to the regular lecture series and CARIM symposium, several lectures, seminars and conferences were organised by our research staff in 2018. 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 **Cardiorenal 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 2018, seven keynote lectures were given by Dr **Reinier Boon** (VUMC Amsterdam, 22 March), Prof. **Gerd Walz** (Universitätsklinikum Freiburg, 19 April), Prof. **Christian Schulze** (University of Bonn, 17 May), Prof. **Charles Alpers** (University of Washington School of Medicine, 21 June), Dr **Sibylle von Vietinghoff** (Hannover Medical School, 20 September), Dr **Caroline Cheng** (UMC Utrecht, 25 October) and Prof. **Andrew Baker** (University of Edinburgh, 15 November).

The **Maastricht Systems Biology Forum** 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 held three meetings in 2018. 'Imaging Methods' were discussed on 29 January and 'Network Science and its Application in Biomedical Research' on 7 June. In addition, a special highlights session was organised on 11 December in which six PhD candidates from various departments showcased the wide range of Systems Biology topics that are being researched in Maastricht. The Forum is organised by Dr **Michiel Adriaens** (MaCSBio), Dr **Pietro Bonizzi** (DKE), Dr **Mike Gerards** (MaCSBio), Dr **Jordi Heijman** (CARDIO), Dr **Martina Kutmon** (BiGCaT & MaCSBio), Dr **Joost Lumens** (BME), and Dr **Stef Zeemering** (FYS).

On 30 January, the kick-off meeting of the atherothrombosis platform took place. After a life-cooking lunch, CARIM staff members presented their current research and future plans on atherothrombosis. Dr **Marjo Donners**, Prof. **Uli Schotten** and Prof. **Hugo ten Cate** provided an overview on atherosclerosis, thrombosis, and the interaction between atrial fibrillation, thrombosis and atherosclerosis. The fifteen presenters of the pitches did a great job in showing the highlights of their research in only six minutes, so that a broad overview of atherotrombosis research within CARIM could be obtained in one afternoon.

On 20 March, **the 6th annual scientific meeting of The Maastricht Study**, entitled 'From Dee-Phenotyping To Big Data', took place at Maastricht UMC+. The aim of the scientific meeting is to present recent results from the Maastricht Study, in order to facilitate discussions between scientists from a broad range of disciplines and

to strengthen collaborations within Maastricht UMC+ and Maastricht University. This year, duos of senior and junior researchers presented. The senior researcher introduced the topic, followed by the junior researcher, who presented a selection of their results within The Maastricht Study. Prof. David Linden, Scientific Director of the School for Mental Health and Neuroscience, opened the meeting where after an update of the study was given by Prof. **Coen Stehouwer**. Dr **Kristiaan Wouters**, presented his work on immune cells in The Maastricht Study. Furthermore, results of The Maastricht Study showed that; microvascular dysfunction precedes the clinical diagnosis of type-2 diabetes; a greater blood pressure variability was found to be an important risk factor, and may be a potential target for prevention and treatment of cardiovascular and neurodegenerative disease. Preliminary results indicated that fracture incidence differs per fracture location in patients with T2DM as compared to controls; while markers of microvascular dysfunction in the retina and plasma were associated with the incidence of depressive symptoms over a four-year follow-up period. Keynote speaker Dr Jeroen Lakerveld, threw out a challenge to us to consider how to investigate 'upstream' determinants of chronic disease, and highlighted the importance of investigating these overlooked factors. In addition, he spoke about the Geoscience and Health Cohort Consortium (GECCO) collaboration in which large-scale Dutch cohort studies including The Maastricht Study, share their data.

On 6 April, the farewell symposium 'Shuntchirurgie: een verbinding voor het leven' of Dr **Jan Tordoir** took place. At his farewell, Jan was awarded the royal honour of Officer in the Order of Orange-Nassau because of his great personal merit in the field of vascular access and received a Maastricht UMC+ medal of honour for his many years' worth for the hospital.

On 1 June, the **MaCSBio Science Day** took place. The theme of the meeting was 'the Bigger Picture' and focussed on the importance of interdisciplinary collaboration in systems biology for education, research and knowledge transfer.

On 19 June, the symposium entitled **'Pathology of Obesity'** with world-renowned speakers took place in Maastricht. This symposium was part of the Maastricht Pathology 2018 meeting of the British PathSoc and the NVvP.

On 5 September, the first **'Maastricht Immunology Seminar Series'** meeting was held. These three-monthly research meetings aim to bring together researchers from Maastricht that are interested in immunology and inflammation. These informal meetings are ideal to expand local networks, and to share research techniques and experience. Each seminar, an external invited speaker is invited and two PhD candidates or postdocs from Maastricht present their research. Afterwards, there are drinks to stimulate networking and exchange between researchers of the different research schools. For this inaugural meeting, Prof. Jo Van Ginderachter (VIB-VUB, Brussels) was the invited speaker, presenting cutting edge data on tumor-associated macrophage biology. The meetings were initiated by Dr **Kristiaan Wouters** (Dept. of Internal Medicine) and Dr **Lotte Wieten** (Dept. of Transplantation Immunology). The Organisation Committee also contains PhD candidates from different research schools: Xiaodi Zhang (Dept. of Internal Medicine), Femke Ehlers (Dept. of Transplantation Immunology), Ines Reis (Dept. of Molecular Genetics), and Marina Damas (Dept. of Psychiatry and Neuropsychology).

The following inaugural lectures took place in 2018:

- Prof. **Arnoud van 't Hof** (21 September): 'Less is More'
- Prof. **Eline Kooi** (28 September): *'Hart en vaten beter in beeld'*
- Prof. **Marc van Zandvoort** (28 September): *'Le luci sono accesse: oplichten in de duisternis'*
- Prof. **Leon Schurgers** (12 October): *'Vasculaire verkalking: een hard-nekkig probleem'*
- Prof. **Blanche Schroen** (9 November): 'What fills the heart'

Prior to the inaugural lecture of Prof. **Leon Schurgers** on 12 October, the symposium 'Vascular calcification: hard disease in the heart. A rocky road towards diagnosis and intervention' was organised with lectures from Prof. **Cathy Shanahan** (London), Prof. **Willi Jahnen-Dechent** (Aachen), Prof. **Mark Vervloet** (Amsterdam) and Prof. **Bram Kroon** (Maastricht).

On 13 November, **an introduction course to flow cytometry** was organised. Flow cytometry is a very important technique for immunological research which generates a lot of interest at Maastricht UMC+. The course started with lectures in the morning session and in the afternoon hands-on workshops on the machine as well as data analysis for unexperienced users were organised.

From 2 until 4 December, the **4th Scientific Conference on Cultured Meat** took place in Maastricht. The conference is a unique opportunity to showcase research in cell biology, large scale cell culture, tissue engineering, food technology, meat science and social science in order to bring the development of cultured meat to maturity. We invited scientists from all over the world and all disciplines related to culturing meat to explore and discuss the best ways to move science on cultured meat forward towards a solution for global food insecurity, livestock related environmental impact and animal welfare concerns. We particularly want to give young scientists the opportunity to share their ideas and experience and encourage them to execute their ideas. Cultured meat is a more sustainable option, it will change the way we eat and think about food forever.

Furthermore, several (internationally) high profile scientists were invited to present a lecture at CARIM, a.o. Dr Danilo Norata, Prof. Zoltan Ungvari, Dr Remi Peyronnet, Dr Michael Tomlinson.

WORLD THROMBOSIS DAY 2018

On 13 October, the 5th World Thrombosis Day (WTD) was celebrated worldwide. Five years ago the International Society on Thrombosis and Haemostasis decided to dedicate the birthday of the German physician Rudolf Virchow (1821-1902) to increase awareness on thrombosis among the general population. The Department of Biochemistry together with Maastricht UMC+ uses this day to bring their research results to the general public. On 12 October, the local radio programme *'Het beleg'* from RTV Maastricht gave Dr **Kristien Winckers** and Dr **Tom van de Berg** the opportunity to explain the importance of the WTD.

Different from other years we took our campaign one step closer to the general public by establishing an information stand on the Vrijthof. Flyers and info charts were distributed, people could talk to employees from the *Trombosedienst* and medical doctors were available for advice. In the afternoon, the programme continued in the Groote Societeit where people could visit an information market of the Netherlands Thrombosis Foundation and *Harteraad*. After a clear introduction by Prof. **Tilman Hackeng**, people could enjoy clear lectures by Dr **Kristien Winckers** on DVT, Dr **Rachel Ter Bekke** on atrial fibrillation and Dr J**ulie Staals** on stroke. There was a vivid discussion afterwards, from which we concluded that our setup and cast for the 5th WTD was a complete success.

HIGHLIGHT
DIVISION HEART

RACHEL TER BEKKE

Department of Cardiology

INTRODUCTION

Long-QT syndrome (LQTS) is an inherited cardiac disease caused by mutations in genes that encode cardiac ion-channel (related) subunits. It is characterized by prolonged ventricular repolarization (QT interval) on the ECG and predisposes to tachyarrhythmias and sudden cardiac death (SCD). The arrhythmogenic consequences of LQTS have traditionally been considered to be due to prolonged and spatiotemporally dispersed repolarization, i.e., purely electrical substrates, often during sympathetic hyperactivity. Recent publications, however, claim that concomitant aberrant cardiac mechanical dispersion contributes to the arrhythmogenic substrate and triggers. These insights induced a paradigm shift in the field of cardiac electrophysiology: LQTS is now proposed as an electro*mechanical* disease with *mechano*-electrical influences on the substrate and triggers of arrhythmia.

The main focus of our current work is to elucidate the role of regional (compared to global) electromechanical inhomogeneities with regard to lethal ventricular arrhythmogenesis in the LQTS. We specifically investigate electromechanical interrelations at baseline and, more importantly, during pharmacological and electrical provocation. We thus aim to investigate the ventricular electromechanical plasticity and unravel novel triggers of arrhythmias. To optimally translate insights into such proarrhythmic mechano-electrical feedback to the human heart, we will investigate intact hemodynamic responses, excitation-contraction coupling and autonomic nervous system reflexes.

INCREASED ELECTROMECHANICAL HETEROGENEITY IN LQTS

Intrinsic electromechanical heterogeneity is normally present in the beating mammalian heart. This is due to differences in action-potential morphology and duration that exist between various regions of the ventricular myocardium under physiological conditions. Likewise, there are spatial gradients of contraction and relaxation, e.g., between the endo- and epicardium, apex and base, left (LV) and right ventricle, and at the circumferential diameter. Differential expressions of transmembrane ion currents, and Ca^{2+} transport and storage mechanisms underlie these non-uniformities.

Cardiac electromechanical heterogeneity is more pronounced in patients with LQTS-related gene mutations. On the one hand, LQTS results in prolonged and spatiotemporally dispersed repolarization and predisposes to the generation of afterdepolarizations, unidirectional functional block and

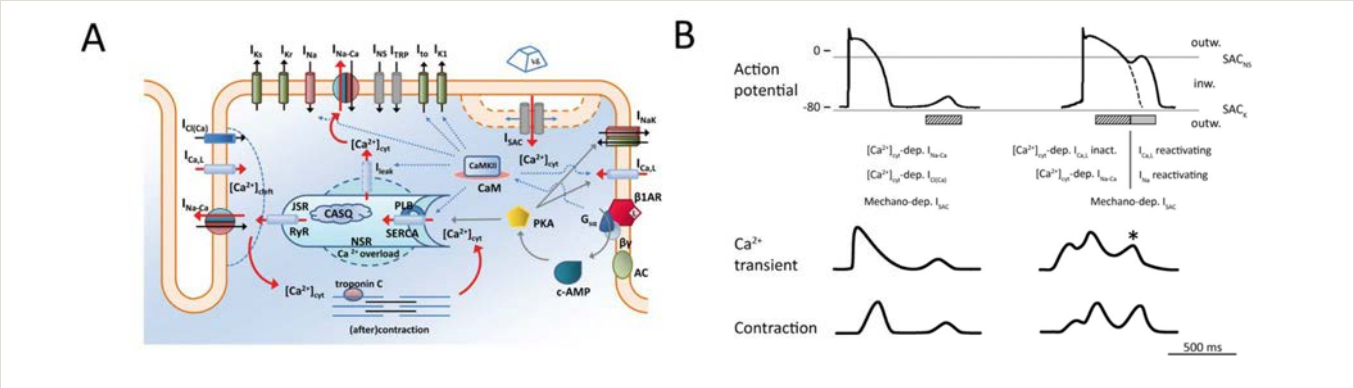
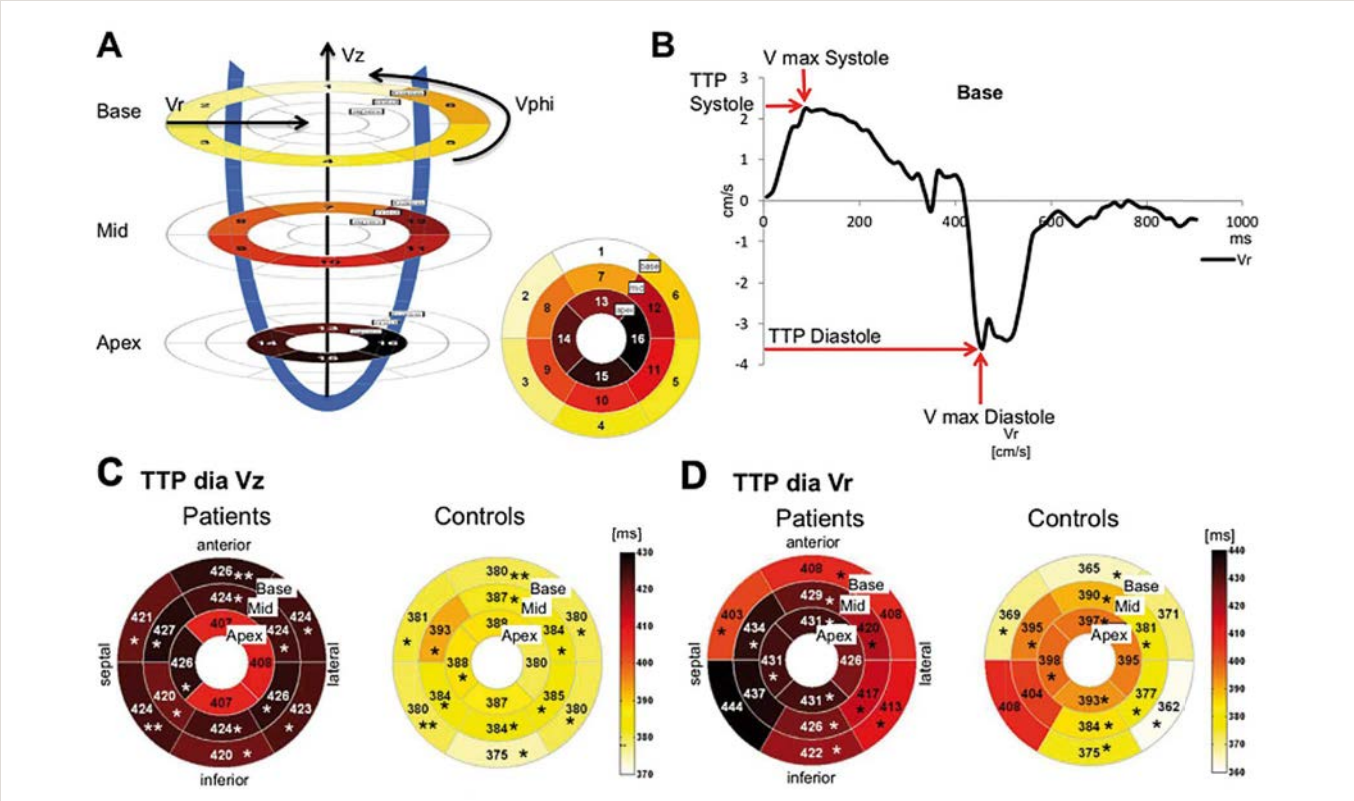


FIGURE 1 Overview of $[Ca^{2+}]_{cyt}$-dependent and mechano-dependent pathways underlying membrane depolarizations during myocyte Ca^{2+} overload and spontaneous SR Ca^{2+} release. (A) Transmembrane ion currents, and Ca^{2+} transport and storage mechanisms. β-Adrenergic-receptor stimulation initiates two intracellular signaling cascades: (1) cAMP- and PKA-dependent phosphorylation of target proteins (e.g., L-type Ca^{2+} current (I_{CaL}) and phospholamban (PLB)); (2) Ca^{2+}/Calmodulin-dependent protein kinase (CaMKII)- mediated signaling (e.g., I_{CaL}, PLB and ryanodine receptors (RyR)). Elevated $[Ca^{2+}]_{cyt}$ can evoke Ca^{2+}-dependent transient inward currents (I_{NaCa}, $I_{Cl(Ca)}$ and I_{NS}) and Ca^{2+}-sensitive transient receptor potential current (I_{TRP}). In addition, (after)contractions resulting from (spontaneous) SR Ca^{2+} release can activate mechano-dependent inward currents via non- selective stretch-activated cation channels (I_{SAC}), carrying Na^+, Ca^{2+} or K^+ For clarity, not all PKA- and CaMKII-dependent pathways are depicted. (B) Left, diastolic Ca^{2+} aftertransient causing aftercontraction and DAD carried by $[Ca^{2+}]_{cyt}$-dependent I_{NaCa} and $I_{Cl(Ca)}$. Based on known reversal potentials for SAC_{NS} and SAC_K, mechano-dependent inward I_{SAC} could contribute to DAD during aftercontraction. Right, systolic Ca^{2+} aftertransient (*) underlying aftercontraction and initial repolarization delay (EAD-conditioning phase by $[Ca^{2+}]_{cyt}$-dependent I_{NaCa} and inactivating I_{CaL}) versus the EAD upstroke (reactivating I_{CaL} and/or I_{Na}). Based on known reversal potentials for SAC_{NS} and SAC_K, mechano-dependent inward I_{SAC} can be present throughout both EAD-conditioning and upstroke phases when aftercontraction occurs. Reference: ter Bekke et al. Prog Biophys Mol Biol 2012:110;347-358.

reentrant excitation-dependent tachyarrhythmias. On the other hand, we know that action-potential amplitude and/or duration per se are important regulators of cardiomyocyte contraction, mainly by changing the amount of Ca^{2+} released from the sarcoplasmic reticulum.

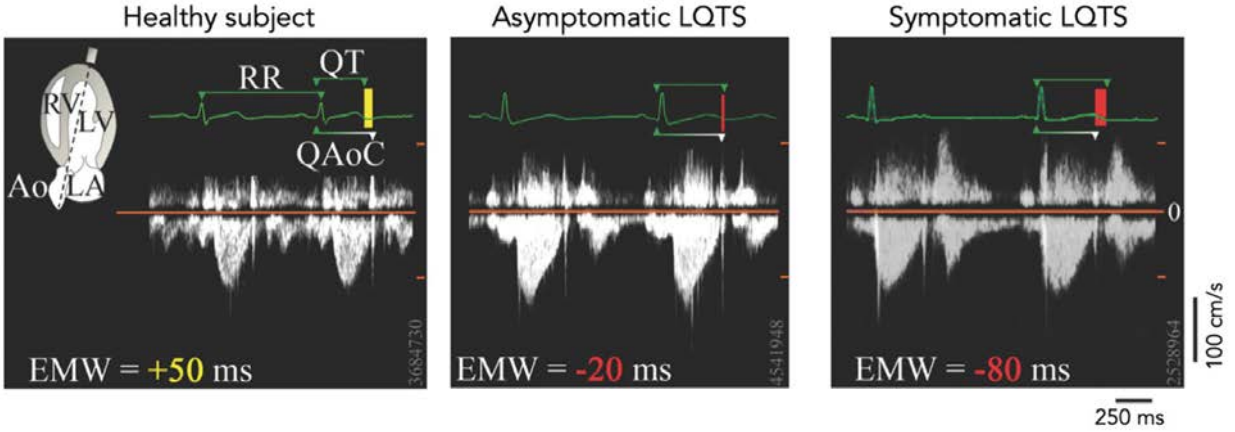
Superimposed intense ß-adrenergic receptor stimulation, a well-recognised proarrhythmic trigger, promotes cellular Ca^{2+} accumulation and regenerative release of sarcoplasmic reticulum Ca^{2+} through the phosphorylation of cAMP- and PKA-dependent downstream targets (Figure 1A). These spontaneous Ca^{2+} aftertransients can activate (1) the contractile apparatus to generate aftercontractions and mechano-dependent inward ion currents, and/or (2) Ca^{2+}-sensitive transient inward current, which promote delayed afterdepolarizations and/or the "conditioning phase" of early afterdepolarizations (EADs), depending on the phase in the cardiac cycle at which they occur (Figure 1B). ß-adrenergic EADs often coincide with early aftercontractions based on Ca^{2+} aftertransients. Taking these marked repolarization inhomogeneities, non-uniform regional Ca^{2+} transients and aftercontractions into consideration, one can expect that myocardial mechanical performance is altered in LQTS, particularly during the



dynamic beat-to-beat changes that precede torsades-de-pointes ventricular arrhythmias.

Indeed, it is increasingly recognized that LQTS patients harbour discrete ventricular wall motion abnormalities that are more pronounced in symptomatic cases. Faster early contraction kinetics and a protracted contraction plateau phase prior to rapid relaxation are primarily located in, but not restricted to, the left-ventricular posterior wall. A protracted contraction plateau phase or prolonged contraction duration

FIGURE 2 Phase contrast cardiac MRI. (A) Schematic representation of LV and bulls-eye plots in myocardial velocity in longitudional (Vz), radial (Vr) and circumferential directions (Vphi). (B) Velocity-time plot of basal radial motion. Systolic and diastolic peak velocities (Vmax) and the corresponding time-to-peak velocities are indicated (TTP). Prolonged time-to-diastolic longitudinal (C) and radial (D) peak velocities in LQTS patients compared to controls. Reference: Brado et al. Heart Rhythm 2017:14;1388-1397.



can be assessed globally using ultrasound or MRI techniques (time to diastolic peak (Figure 2) or to aortic-valve closure) and by measuring invasive pressures (time to end LV pressure); regional assessment can be achieved using speckle-tracking echocardiography. Symptomatic patients demonstrate significantly longer global myocardial contraction durations compared to healthy controls and asymptomatic LQTS mutation carriers, even after correction for QTc. The global myocardial contraction duration often exceeds the time to aortic-valve closure. Moreover, a significantly pronounced post-ejection velocity can be observed, defined as a post-ejection peak after closure of the aortic valve. This phenomenon is predominantly present in the LV posteroseptal region, but can also be observed in the anteroseptal, anterior and lateral walls. Increased regional and transmural mechanical inhomogeneities (or mechanical dispersion) are present in the interventricular septum and anterior LV wall, especially in symptomatic single-mutation carriers.

FIGURE 3 Representative EMW calculations in the same beat during continuous-wave Doppler echocardiography of the LV-outflow tract. (Left) EMW positivity in a healthy individual. (Middle) EMW negativity in an asymptomatic LQTS-mutation carrier. (Right) pronounced EMW negativity in a symptomatic LQTS patient. Reference: ter Bekke et al. Eur Heart J 2015:36;179-186.

In the intact LQTS heart, these altered electrical and mechanical parameters contribute to a reversed LV electromechanical sequence, a phenomenon in which the aortic-valve closure occurs after T-wave completion. The ensuing negative 'electromechanical window' (EMW = time to aortic-valve closure (QAoC) minus QT) occurs primarily due to a prolonged QT interval in the absence of a correspondingly increased global myocardial contraction duration (Figure 3). Interestingly, in LQTS the EMW is more negative for any QTc, suggesting repolarization-independent influences. Moreover, the EMW is an easy-to-obtain, heart-rate-independent parameter that can be dynamic and very negative prior to the onset of torsades de pointes. The

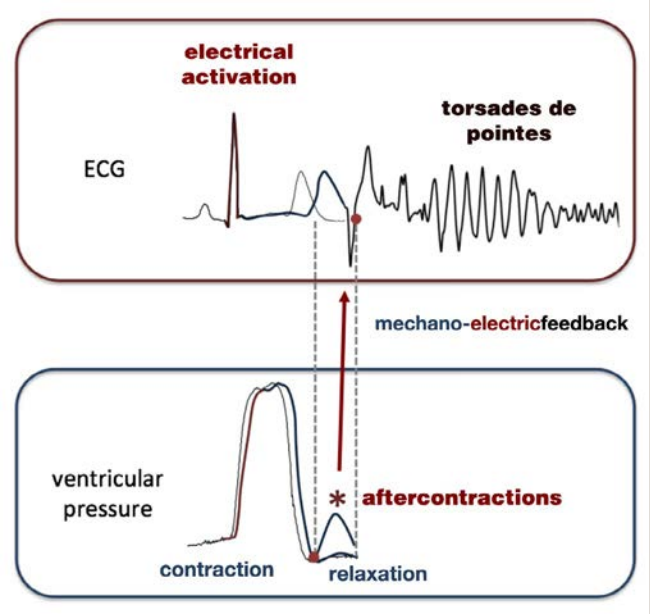


FIGURE 4 Schematic representation of global mechano-electric influences prior to torsades-de-pointes arrhythmias in LQTS. Sizeable aftercontractions (*) occur within a negative EMW (dashed grey lines), preceding the first premature ventricular electrical activation and ventricular tachyarrhythmias.

altered electromechanical sequence appears similar for I_{Ks} and I_{Kr}-related LQTS genotypes, whereas a shorter LV contraction duration is found to underlie the EMW in LQTS3 (the late Na+ current may contribute to electromechanical divergence via altered myocardial Na+ and Ca^{2+} handling), and is even shorter in symptomatic individuals. In 55% of LQTS patients, the late systolic phase is accompanied by a secondary inward motion, or contraction of the LV endocardium (in the absence of abnormal impulse formation). These contractile events and corresponding postsystolic increases in LV pressure can mount substantially in the final seconds prior to the occurrence of torsades de pointes (Figure 4). As a possible electrical footprint, notched T waves or U waves are observed. The above-described mechanical abnormalities are more strongly correlated with cardiac arrhythmic events than the traditionally used QTc, thus offering prognostic value and suggesting that altered mechanical dynamics influence cardiac repolarization via mechano-electric coupling.

PROSPECTS

Our current research focuses on the regional aspects of dispersed repolarization and strain patterns in the beating heart with LQTS, with the aim of increasing our understanding of mechano-electric feedback and its relation to ventricular arrhythmogenesis. We will focus on the relation between regionally augmented electromechanical inhomogeneities, the origin of ventricular aftercontractions and the site of first abnormal electrical impulse formation. To this end, we rely on state-of-the-art high-resolution electromechanical imaging techniques for studies in the intact human and animal hearts. Ultimately, this will improve the prediction of sudden cardiac death risk in LQTS patients and, as we anticipate, in other those with mechano-sensitive arrhythmia syndromes. This research project has been recently rewarded with a Veni grant (ZonMw 091 501 61 8101 32 to Rachel ter Bekke).

INTERVIEW
MATTHIJS CLUITMANS

Interview with Matthijs Cluitmans

The human bridge between science and industry

That Matthijs Cluitmans combines his scientific research at CARIM with two workdays a week at Philips Research is not surprising when you look at his CV. While studying medicine he also obtained a Bachelor's degree in Knowledge Engineering and a Master's degree in Operations Research. And while doing his clinical rotations he was also working towards a PhD, all at Maastricht University. But the fact that a "hybrid researcher" like him is still a rarity these days shows that this is not yet normal practice. In 2018 he was the recipient of both a Veni grant and a Philips Outstanding Achievement Award.

One of the things that Matthijs Cluitmans learned when he started working for Philips Research in 2016 was that not every interesting idea is necessarily of interest to the industry. “If as a researcher you have a bright idea that might save society some money, that doesn’t mean that companies or hospitals will adopt it. It has to be financially attractive as well. Originally I thought that Philips would definitely be interested in the ECGI technology we had developed at Maastricht, but it turned out that another company had already developed it further, so that put a stop to that. And also, manually analysing an ECGI scan, which would take a whole day for one patient, is not a practical approach for a cardiologist.” And that is where the Veni grant comes in.

A CORNERSTONE OF THE VENI GRANT

But let us return to the beginning: Cluitmans’ thesis, entitled “Noninvasive reconstruction of cardiac electrical activity: Mathematical innovation, in vivo validation and human application”, for which he received his PhD in 2016. It dealt with electrocardiographic imaging (ECGI), which can be regarded as a greatly extended variant of the well-known ECG. When combined with a CT-scan, it allows subtle abnormalities in the electrical impulses in the heart to be localised. The hypothesis is that these abnormalities might play a role in sudden cardiac death, which has been known to afflict football players and other apparently healthy people, without any prior warning. The current Vigilance study, led by Prof Paul Volders, and involving the universities of Maastricht, Amsterdam and Utrecht, is researching this hypothesis. It is a major cornerstone of Cluitmans’ Veni grant.

PERSONALISED COMPUTER MODEL OF THE HEART

“I’m trying to develop a computer model that can be personalised using all kinds of patient data. That will offer opportunities for further investigations. For instance, could we subject the model to a virtual stress test to see when a virtual cardiac arrest will occur? Or at a later stage even test medicines or therapies before prescribing them to a patient? And in the long term it could even become a screening instrument to select people at increased risk of cardiac arrest.” The population that Cluitmans will investigate in his Veni is too small to be of interest to a company like Philips, but since such personalised computer models can be applied to multiple disease entities, the company is nevertheless very much interested.

IF AS A RESEARCHER YOU HAVE A BRIGHT IDEA THAT MIGHT SAVE SOCIETY SOME MONEY, THAT DOESN’T MEAN THAT COMPANIES OR HOSPITALS WILL ADOPT IT

BRIDGING TWO WORLDS

And that is why he gets to spend one of his two weekly workdays at Philips Research on his Veni project, together with the team he is leading there. In fact, his colleagues at Philips and CARIM are currently working on a joint application for a grant for a clinical study using computer models. “There’s a growing overlap, and that only makes things more exciting.” It also perfectly matches his personal motivation, which is to actually improve patient care. This requires, on the one hand, accumulating thorough scientific knowledge about the heart, and on the other hand keeping an eye out for commercially attractive applications. Cluitmans acts as a kind of bridge between these two worlds.

AND WHAT ABOUT THE GUIDING HAND OF INDUSTRY?

Of course he does occasionally ask himself the question whether he is not being guided by the industry (“As nobody else has actually asked me that question so far.”). “In fact, I have the idea that I’m able to guide Philips with my insights into clinical and scientific developments, rather than the other way round. They give me complete freedom to do my academic work, and I have no financial interest in whether a product comes to the market or not. I always say: I want to understand the problem, but I also want to make the solution available to the clinic.” He therefore regards it as his personal mission to encourage this cross-fertilisation as much as possible. “In both places I feel I’m being appreciated for my work, and I also feel that I’m contributing something in both places. As long as there’s this added value, I can only see advantages of having these two work sites.”

DID THE IDEA ARISE ON A MONDAY OR A THURSDAY?

Hybrid researchers also face organisational challenges, which might be a good topic for a discussion, if there were such a thing as a network of “fellow hybrids”. To start with, there is the double “overhead”, ranging from mailboxes to courses. And then there is the legal aspect. “If I come up with an idea, then who owns the idea? The law says it’s your employer, but I have two of those. The overlap makes it impossible to decide whether an idea arose during CARIM time or during Philips time. That’s been the subject of extensive talks and negotiations among the colleagues of the IP departments.” And then of course there is the difference in work pace between a commercial company and a university. Plus the different perspectives. “For a company, the mere presence of a start-up with patent rights in a particular field might be sufficient reason to terminate a development; as a scientist you’re more likely to give your grant proposal just that little twist so that it will still appeal to grant providers.”

THE COMBINATION IS THE IDEAL

On the other hand, having two employers does provide a degree of job security for the future. “Theoretically, a company like Philips might lose interest in what I’m doing, and working at a university always means looking for money and temporary appointments. I do now have permission to start a tenure track at Maastricht University, so that could mean the perfect continuation of my academic career. And at Philips, they do keep your personal development in mind, so there are other opportunities waiting there as well. But if I have the choice, I still prefer the challenge of the combination, as that’s where I think the greatest benefits for patients are to be found.”

INTERVIEW

CENGIZ AKBULUT AND ROGIER VELTROP

The champion and the dancing scientist

This is neither a story about Cengiz Akbulut's love of dancing as if it were 1930 all over again, nor is it about the gold medal Rogier Veltrop won with team Netherlands at the world transplant games. Or is it? In any case it is the story of two people meeting in a "magic" CARIM office, who share the dream of doing a PhD. The rest is a fascinating history, and future.

Turning back the hands of time in a cell: that is what Cengiz Akbulut and Rogier Veltrop have managed to do in the first year (or two) of their PhD projects. Akbulut vividly remembers the day that he found this new guy sitting in his Maastricht office. He turned out to be Veltrop, who had a background in cell and pathway signalling in cardiovascular disease. Akbulut knew from his previous education about regenerative medicine and had learned a lot about stem cell technology in the previous year. "Actually, that was because a postdoc from Bonn happened to share the office then, and my supervisor Leon Schurgers encouraged me to learn about stem cell technology from her and her colleagues. That's how I built a fruitful cooperation with several Bonn PhD students as well. It's a magic office."

BUILDING A DATABASE WITH ALL SORTS OF CELLS

For their own respective research projects, they both needed different types of cells. Veltrop is studying the effect of renal failure on cardiac pathology. Obtaining diseased heart tissue from surgery is quite easy, but it is the healthy control tissues that are the problem. So what if you could turn a human cell into a cardiomyocyte? Akbulut, on the other hand, wants to investigate smooth muscle cells, in particular what happens when they start behaving like bone cells in the blood vessel, leading to arterial stiffening. Samples from patients may sometimes differ in their characteristics or behaviour, so what if you could turn infinitive pluripotent stem cells into smooth muscle cells, cardiomyocytes or into endothelial cells, which are important in cardiovascular disease and regulating blood function? Hey, they thought, why not build a big database with all sorts of cells, to help CARIM study every aspect of cardiovascular biology and medicine with stem cells…

A REVOLUTION IN MEDICAL AND BASIC BIOLOGY RESEARCH

It sounds simple, but it also sounds like magic at the same time. You take cells from blood or a skin biopsy and programme them to become stem cells again. And then you stimulate them to become a particular type of cell that you need for research, such as smooth muscle cell or cardiomyocyte. They will have the same genetic information as the actual heart cells of the person who donated the blood, and you can make infinite numbers of cells this way. "It's amazing", confirms Akbulut. "A very new technology for humanity. This idea to turn back the hands of time was first published in 2007. The guy from Japan who did it shared the Nobel Prize in medicine for it in 2012. It has revolutionised medical research and basic biology research."

FINDING A FUTURE-PROOF PROCEDURE

But everybody knows: in science, things are rarely simple. Many departments across the world have tried to create these cells, but without success. Despite a range of publications, there is no gold standard procedure. How exactly do you modify the cells? What tool do you use to reprogramme them? Akbulut: "The Japanese study used a virus to genetically modify the cells, but we want to create cells that may be used for stem cell therapies in the future. You can't give that to the patient using a virus." Veltrop: "For each step, there are different ways to approach it. Instead of a virus, we give the cell a little electric shock to scare it, and then we insert in there what we want, and the cell will repair itself." The two absolutely acknowledge the brilliance of the founding fathers of this technology, "but they mainly showed that you can turn back time", Veltrop says. "It's not the best viable option for the future treatment of patients. We try to make a start for CARIM to be able to move on in the next decades."

BUT EVERYBODY KNOWS: IN SCIENCE, THINGS ARE RARELY SIMPLE

GOING AFTER A DREAM AGAIN

For both of them, pursuing an academic career is a dream come true. Veltrop was already living that dream, almost ten years ago, while doing PhD research in Philadelphia on molecular virology. Then he had to stop, because of a genetic condition that started to destroy his heart's function. Eight years of illness later, and virtually on the brink of death, with only a few days left, a donor heart became available, and it fit. He recovered, and had to learn to walk again, since he had been in bed for a year. And the dream of earning a PhD was still alive too. "Because it gives you the opportunity to really delve into a subject and publish the data you obtained yourself. A Master's project, for example, is too short for that." Plus, a PhD offers the opportunity to explore branches you were not planning to in the beginning, as both of them have experienced. Veltrop: "My first goal, when doing my secondment within the Schurgers' group at CARIM, was to get training in calcification methods. A few months later we end up with great stem cell results. It feels like creating a full circle again to obtain a PhD."

CELLS DO NOT DO WEEKENDS

Akbulut was pleasantly surprised at the amount of freedom he encountered at CARIM, more specifically from his supervisor Leon Schurgers. "There's support and guidance along the way, but the way you're encouraged to develop your own ideas is great." It has led them to where they are now: in a brilliant position to start experiments on the cells they have created. Akbulut remembers vividly how he came into the lab every single day for three months in a row, at the beginning of the project. "Cells don't do weekends", he laughs. "But on a Sunday morning I would jump out of my bed smiling: let's go see my cells! Because I simply love what I do." Combining that with a private life was sometimes a bit of a challenge, he admits. Especially since he also was teaching swing dancing in Amsterdam at the time. "It's a group of dances from the 1920s to 1940s, like the Charleston or the Lindy Hop. I actually only started dancing in 2011, with zero experience. A year later, I visited Amsterdam for a Swing festival and that's where I fell in love with it. When I returned the year after, I started thinking of the Netherlands as a great place to live someday." In the meantime he is teaching it in Maastricht, which helps logistically.

SOMETHING IN ADDITION TO THE RESEARCH

Veltrop fully recognises the need to "have something else besides your research." "You need to refresh your mind every now and then. Next year, I will be an assistant coach for a Dutch premier league volleyball team. And I play volleyball in the Dutch team for transplants. Two years ago we became

world champions at the World Transplant Games in Malaga. In August we'll defend the title in Newcastle." "He's a world champion," the dancing scientist nods, with a proud smile.

Cengiz Akbulut, *born in Great Britain, obtained a Bachelor's in Biochemistry at the University of Aberdeen and a Master's degree in Regenerative Medicine at Queen Mary University in London. Following this he spent one year as a research assistant at the William Harvey Heart Centre, London. He started his PhD project at CARIM in March 2017, under the umbrella of the EU-funded Marie Skłodowska-Curie programme INTRICARE (International Network for Training on Risks of Vascular Intimal Calcification and roads to Regression of Cardiovascular Disease). It revolves around vulnerable plaque formation, with a particular focus on microcalcification and early prevention, diagnosis and treatment of atherosclerosis. Akbulut was awarded the CARIM HS BAFTA fellowship, enabling him to work at Cambridge University for half a year, starting in September 2019.*

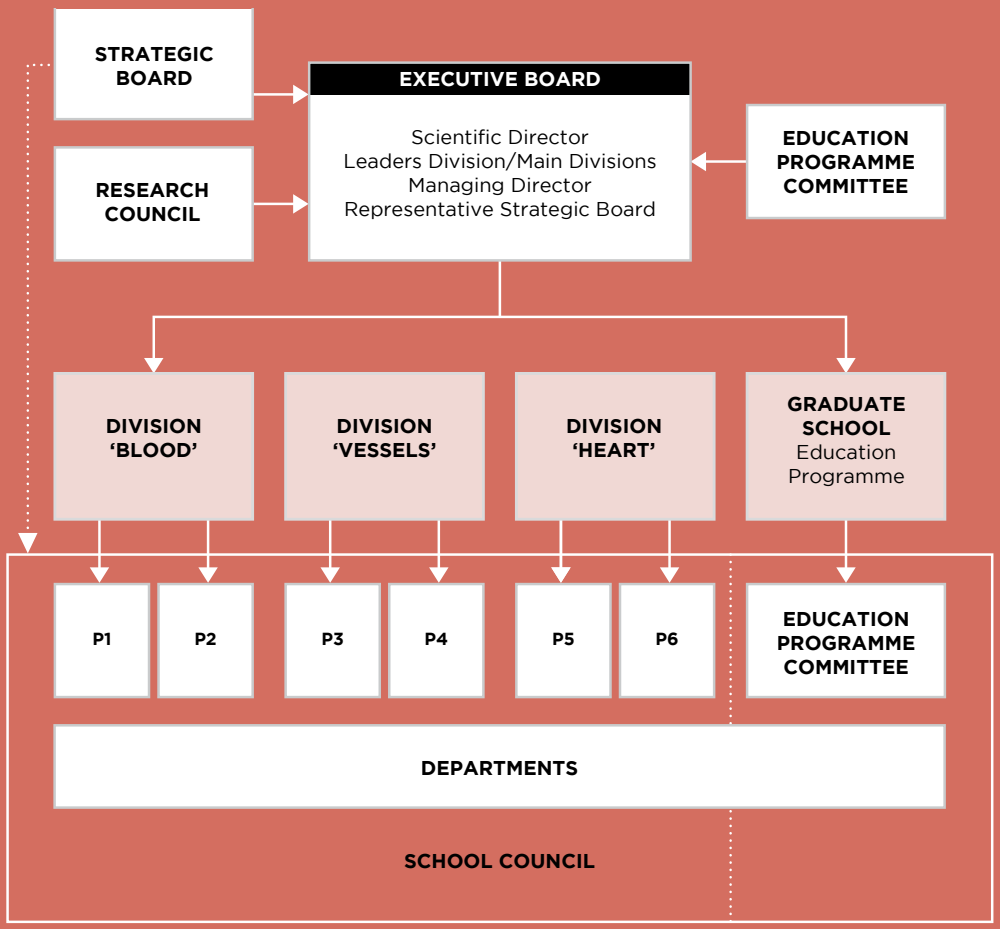
Rogier Veltrop, *born in the Netherlands, studied clinical chemistry in Eindhoven and molecular biology in Utrecht, followed by a PhD position at Drexel University College of Medicine in Philadelphia (US) on molecular virology, focusing on Coronavirus. Because of a genetic heart condition, he had to stop this PhD project after one year and two months. In 2016, he restarted his academic career with several internships, followed by the Research Master programme on Biomedical Sciences, specialising in cardiovascular biology and medicine at Maastricht University. In the summer of 2018, he enrolled in the EU-funded programme CaReSyAn (CArdioREnal SYndrome Analysis) at Uniklinik RWTH Aachen, which aims at reducing the cardiovascular burden in chronic kidney disease. He will defend his thesis in both Aachen and Maastricht.*

30 JAAR CARIM

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, the financial management and the public relations of the institute. The Scientific Director is assisted by the Managing Director, who takes care of the financial, legal and human resource issues. Together with the three leaders of the 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 (EPC) and CARIM Research Council.

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 international 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 EPC coordinates both the PhD and Master's training programmes. The EPC advises the Executive Board and PIs on the quality of 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. 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 Crijns, Leader Division Heart
- Prof. Coen Stehouwer, Leader Division Vessels
- Wouter Hankel, Managing Director
- Prof. Uli Schotten, Representative Strategic Board

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- Prof. Joachim Wildberger, Dept. of Radiology & Nuclear Medicine
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- Dr Boy Houben
- Margaux Fontaine
- Kim van Kuijk
- Federica de Majo
- Tate Chimhanda
- Kim Maasen

CARIM OFFICE

The CARIM Office consists of specialists that support the organisation and it's researchers with administrative, financial and legal issues, including HRM and funding. Tara de Koster, Riet Daamen and Esther Willigers are responsible for administrative issues, including supporting the executive management. The controller of CARIM is Lynn Lemeer. The Finance Department of Maastricht University provides support on accounting the CARIM research projects with Henny Kerckhoffs, Esther van Heel and Mark van Gisteren. Mechteld Ostendorf of the Human Resources Department of Maastricht University is dedicated to CARIM. In legal affairs, Suzanne ten Hoeve supports CARIM, and Willem Wolters is responsible for funding acquisition. Managing Director Wouter Hankel is the head of the CARIM office. Former Managing Director Rob van der Zander is a special advisor to the management of CARIM.

The research in CARIM's divisions involved the research activities of employees working in 17 (seven basic and eleven clinical) departments of Maastricht UMC+. Basic departments: Biochemistry; Physiology; Biomedical Engineering; Epidemiology; Genetics & Cell Biology; Pharmacology/Toxicology; Immunology. Clinical departments: Clinical Chemistry; Internal Medicine; Neurology; Pathology; Cardio-Thoracic Surgery; Radiology and Nuclear Medicine; Intensive Care; Anaesthesiology; Pharmacy; Cardiology; and Vascular Surgery.

FACES

BLOOD

P1 ▶


AARON ISAACS


ARINA TEN CATE-HOEK


ELISABETTA CASTOLDI


ERIK BECKERS


FRAUKE SWIERINGA


GERRY NICOLAES


HANS IPPEL


HENRI SPRONK


HUGO TEN CATE


INGRID DIJKGRAAF


JOHAN HEEMSKERK


JUDITH COSEMANS


KANIN WICHAPONG


MARIJKE KUIJPERS


MONIKA STOLL


OTTO BEKERS


PAOLA VAN DER MEIJDEN


RENSKE OLIE


RORY KOENEN


STIJN AGTEN


TILMAN HACKENG


YVONNE HENSKENS

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BAS BEKKERS


CARINE PEUTZ


CHRIS REUTELINGSPERGER


CHRISTIAN WEBER


DIETBERT NEUMANN


ELINE KOOI


ERIK BIESSEN


FELIX MOTTAGHY


GOSIA FURMANIK


JACK CLEUTJENS


JOACHIM JANKOWSKI


JOACHIM WILDBERGER


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REMCO MEGENS

ROBERT VAN OOSTENBRUGGE

SIMON SCHALLA

SUZAN WETZELS

SYLVIA HEENEMAN

WERNER MESS

WIM VAN ZWAM

P1 Blood coagulation, venous thrombosis & bleeding

P2 Atherosclerosis, arterial thrombosis & stroke

VESSELS

P3 ▶


AARON ISAACS


BOY HOUBEN


BRAM KROON


CARLA VAN DER KALLEN


CASPER SCHALKWIJK


COEN STEHOUWER


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MIRANDA SCHRAM


NICOLAAS SCHAPER


NORDIN HANSSEN


RONALD HENRY


SEBASTIEN FOULQUIER


SIMONE EUSSEN


THOMAS VAN SLOTEN


WALTER BACKES

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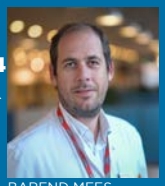
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PEYMAN SARDARI NIA


ROBERTO LORUSSO


SANDRO GELSOMINO

P3 Vascular complications of diabetes & hypertension

P4 Regenerative & reconstructive cardiovascular medicine

HEART

P5 ▶


ALMA MINGELS


BEN JANSSEN


BLANCHE SCHROEN


CHRISTIAN KNACKSTEDT


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STEF ZEEMERING

TAMMO DELHAAS

ULI SCHOTTEN

WOUTER HUBERTS

P5 Structural heart failure
P6 Complex arrhythmias

COLOPHON

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