CARIM ANNUAL REPORT 2023

CARDIOVASCULAR RESEARCH INSTITUTE MAASTRICHT

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CONTENTS

PREFACE

STICK TO WHAT YOU KNOW...

As cold war kids, we were instructed to crouch beneath our desks in class during monthly air raid drills, our arms shielding our heads and our mouths slightly open. In those years I had recurring nightmares in which I was caught up in war actions in our small street in Rotterdam, where my father would invariably come to my rescue. His tie would flap over his shoulder as he ran towards me, yet he would always trip over a loose paving stone just before reaching my side ...

At present, countless children around the world do not have the luxury of waking up safely in their beds after a nightmare of war; instead, they are living amidst it. Senseless aggression is escalating in various parts of the globe, while violent protests against this aggression are also erupting worldwide, with even our universities and their infrastructure not being spared. We all share concerns about our world, and people are eager to respond and support those in need. However, should universities be providing space for political activism?

Already in the early 19th century Wilhelm von Humboldt proposed his vision on external influences in our universities. He advocated for academic freedom as a fundamental principle for universities, and that researchers and lecturers should be free to conduct research and teach without interference from the state or other external forces. His concept of academic freedom thereby implies a separation between politics and academic activities, as politics could potentially hinder free intellectual exchange. This is exactly what we are witnessing today: violent demonstrations in our universities are aimed at preventing scientific interaction with other universities. In addition, Humboldt emphasised autonomy of universities, believing that they should be self-governing, free from political pressure or control. This would ensure that universities could focus on their primary goals: the advancement of knowledge and the development of free, critical individuals.

Despite this, our free-thinking and critical academic individuals will naturally have strong opinions on the current geopolitical turmoil, and perhaps it is their responsibility to actively engage in political discussions. However, it is important that they take these discussions and actions outside our universities.

"Auf diese Weise muss die Idee einer Akademie als die höchste und letzte Zufluchtsort der Wissenschaft und die vom Staat am meisten unabhängige Corporation festgehal–ten werden, und man muss es einmal auf die Gefahr ankommen lassen, ob eine solche Corporation durch zu geringe oder einseitige Thätigkeit beweisen wird, dass das Rechte nicht immer am leichtesten unter den günstigsten äusseren Bedingungen zu Stande kommt oder nicht".[1]

Interestingly, in this part of one of his concluding paragraphs Humboldt seems to suggest that true academic freedom and progress are not necessarily the result of the most favourable external circumstances, but rather of the institution itself and its commitment to science and research.

Such dedication within our institute has led us to catalogue successful translational research initiatives and their researchers. This effort has recently led to the establishment of a large internal CARIM-Heart+Vascular Center programme: CARIM+HVC Lighthouse. This programme is committed to curing a hereditary heart disease by 2030 through the use of CRISPR/Cas9 DNA correction on iPSC-derived patient-specific heart tissue, prior to implementing clinical interventions.

Never before has such a comprehensive and distinctive programme been launched within our institute, and never have the pieces of the puzzle been so clearly laid out for us to make this a success.

The atmosphere in the Lighthouse research team is energising; there is a buzz of enthusiasm, and everyone is motivated to commit fully to science. After all, let us not forget why we exist as researchers. It is our intrinsic drive to unravel nature and to understand and cure cardiovascular disease that has given us the opportunity to dedicate our lives to this beautiful field, alongside sharp, smart and pleasant colleagues. And even though our scientific world is currently filled with fashions and trends, we must never lose sight of our scientific aims. Conduct research, write grants, publish well, perform our academic duties, educate researchers, inform society, and above all, be a good mentor. Do it well and get better at it.

Our unique stronghold of cardiovascular research has paid off, making you realise what a relatively small gathering of founders have accomplished by strategic combination of basic and clinical disciplines and becoming translational *avant la lettre*. Our unique comprehensive niche originated from combining research on all cardiovascular tissues of blood, vessels, and heart. I must say that our founders did exceptionally well by creating a blueprint that challenged their contemporaries and has grown into one of the most successful cardiovascular research institutes in Europe.

In our current annual report, we look back on 35 years of CARIM, our fantastic 35th anniversary summer night party, and we compiled many interviews with established and coming leaders in our field to learn from their news and views. Our HS-BAFTA grants programme for the young and talented continues to be a success, and this year our first Anna Maria van Schurman Stipend will be awarded to a young female researcher. Each of our divisions showcases one of their highlights, clearly illuminating CARIM's strategy of early recognition, regeneration, and repair. We show our acquired personal grants and contracts, and all honours and prizes awarded to our fellow CARIM employees in this anniversary year.

All these topics lay in front of you, in our annual report that is packed with spirit, pictures, progress, and commitment, while looking back on 35 years of cardiovascular science, in which CARIM surely has made a difference.

This is CARIM 2023.

I hope you enjoy your reading.

Professor Tilman Hackeng
Scientific Director CARIM
Cardiovascular Research Institute Maastricht

[1] Wilhelm von Humboldt. Memorandum for the Ministry of the Interior: Über die innere und äussere Organisation der höheren wissenschaftlichen Anstalten in Berlin (1809/10).

INTERVIEW

IWAN VAN DER HORST AND BAS VAN BUSSEL

“We want to get every detail right”

With its creative and thorough approach, the Data & Monitoring group of the Intensive Care Unit (ICU) not only manages good papers to be published, but also attracts young research talents. And secretly, they feel the latter is more important than the former.
Iwan van der Horst and Bas van Bussel talk about this new CARIM group, which they jointly lead with great enthusiasm.

They both work at Maastricht UMC+ as intensivists, while Iwan is also a cardiologist and Bas is an internal medicine specialist. The initial impetus for this PI group, which is formally led by Iwan, but in practice by the two of them, was the COVID pandemic. It was during this hectic period at the ICU that they started an observational study. A key characteristic of this first study, as well as of their ongoing work, is that they do not like cutting corners to get quick results. “We were more like a diesel train”, says Bas. “We started by very thoroughly and neatly categorising four hundred ICU patients, based on daily monitoring. If you design that smartly, other researchers can then join in to address a wide range of questions. If the pie is big enough, there’s a piece for everyone. For example, we cooperated with a number of radiologists in writing a publication about the impact of atherosclerosis on COVID patients admitted to the ICU. Our study design enabled us to reveal such interrelationships by thinking: what is unique and how can I learn things? This one cohort alone yielded about fifty papers.”

Not one clinical picture

That became the start of the current research group. They do not focus on one clinical picture only, but use a study design that allows them to address many different research questions. Iwan: “Most patients do not have just one disease, but several, and we study this complexity as it develops over time in the ICU population. We unravel patients with a focus on the heart and blood vessels.” Bas confirms: “We have long since stopped dealing with ‘singular diseases’, as that’s not where the future lies. I think it lies in multimorbidity. While you can focus completely on your own little piece of the puzzle, which is very important for a particular disease, the question is whether that fits in with suitable care for everyone in the future. I’m not saying that everyone should work the way we do, but I do think we have some added value to offer to CARIM.” Iwan: “You can take an in-depth approach, but we’ve specialised in designing and conducting more generalist, broad-based research, yielding high-quality databases to which you can then link many research questions.”

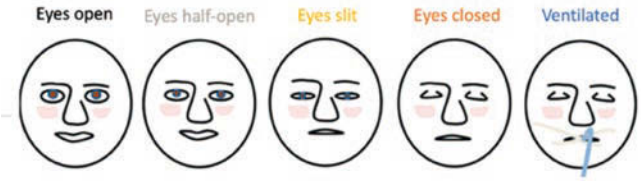
Using the same approach, the group compiled a database of patients admitted to the Maastricht ICU from 2023 onwards. Iwan: “You can use that to pose innumerable questions. For instance, it includes 37,000 ECGs of patients with inflammation. What are the coagulation factors like in this population? We ensure that the data are categorised really neatly and reliably, and we keep a close eye on the literature: what is really new? What questions have not yet been asked? That has helped us a lot in recent years.”

Expanding partnerships

At the same time, the group is carefully checking the different motivations of collaborative partners. Bas: “A young person who wants to earn a PhD benefits as the first author in a paper, while young specialists prefer to be listed last, so they can show they can supervise a scientific project which help them develop their career. Another collaborator may want to use a paper to achieve political ends, or to secure a grant. If you ask potential partners to explain their goals beforehand, you can often find a good basis for effective partnerships. Methodology is our business, while others are more interested in getting answers to their questions, so together we can engage in interesting research. That’s how we would like to expand collaboration within CARIM.”

What they are noticing is that young researchers and students are attracted by their research climate. Iwan: “They can do a lot of things with AI and other tricks, but they come to us because they’re interested in how we manage the

playing field and guard the limits of thorough scientific research. They like that and it yields nice results." For example, he designed a study that linked an ICU patient's facial expression with their degree of dysfunction of their inner organs. "I drew a series of pictures of eggs, showing eyes ranging from open to close in a number of steps, and with different intensities of the blushes on the cheeks. We then asked students to choose the image that they thought corresponded best with the ICU patient in the bed. When analysing this, it turns out that the face predicts the state of the organs." Bas: "So it's like a mother who looks at her child and says: 'You're not very well today.' This works exactly the same at the ICU. Many people have been saying this before, but we've now shown evidence."



Original question

Or take the study they undertook together with four medical students during COVID. They determined how many of the COVID publications in the PubMed database mentioned whether the authors had asked for informed consent, whether they had followed METC protocols, and suchlike. Bas: "We managed to get the article published in the *British Medical Journal Global Health*, with the four students as first authors. Because the research question was original and the study had been super-carefully designed."
Iwan: "We gather data with a lot of people, tidy it up, make it accessible and create a community. That appeals to young researchers, especially if you then also take the whole group along to a European conference of ICU physicians in Milan. Our group had the largest number of young people."
Each year, the group manages to get published a few times in one of the top five journals on epidemiology and ICU medicine, and the young researchers keep coming back. And this last aspect is what they think is really the most important. Bas: "Publications are important, but training new researchers will yield a larger critical mass. So we invest in people, preferably as diverse as possible. ICU nurses and laboratory staff also join in and are therefore listed in our papers as researchers, next to the PhD candidates and other researchers. This diversity strengthens your research."

Human ICU

In addition to the enjoyment of doing good research together, training young people and sharing results in publications, the group would also like to change the healthcare system. One example of such a project is the 'HumanIC'. Its aim: getting to know the person behind the ICU patient better. Who is this person, who is being subjected to so much technology and examinations in this bed? Bas: "What do they want in life? What is their profession, and what is important to them? What was their quality of life like before and what will it be like afterwards? Because we subject people to all kinds of procedures to make them better, but is that always desirable from the patient's perspective? We are carrying out this project together with the care providers, which also improves care. This way we try to create a circle of research that actually works for the care system. As a researcher, you are part of the system, you join in, your input matters; that's how you create synergy."

PROFILE

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PROFILE

Founded in 1988, the Cardiovascular Research Institute Maastricht (CARIM) has established itself over the last decades as a leading research institute in the field of cardiovascular disease in Europe. 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 applied in healthcare are evaluated, often in collaboration with private partners, and the results of scientific research are published in high-ranking international journals. Master students, PhD candidates and MD students are trained to become independent researchers, while postdocs are trained to become leading scientists in the field of cardiovascular disease.

CARIM is built around three research divisions, 'Blood', 'Vessels' and 'Heart', each consisting of two programmes:
1.1 Blood coagulation, venous thrombosis & bleeding;
1.2 Atherosclerosis, arterial thrombosis & stroke;
2.1 Vascular complications of diabetes & hypertension;
2.2 Regenerative & reconstructive cardiovascular medicine;
3.1 Structural heart failure and
3.2 Complex arrhythmias.
These six programmes together host 21 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 a team science setting that combines track record, expertise, and innovative content and disseminates results to scientific communities and to society.

All three divisions involve both basic and clinical programmes, and are led according to a shared governance principle, executed by the Division Leader together with basic and clinical scientists from the divisions. This governance system enables shared responsibility for the scientific progress of programmes, linking activities and seeking collaborations between PIs and divisions and mentoring of PhD candidates, postdocs and talent development tracks. The individual PIs are responsible for the financial management of their groups. Cardiovascular scientists from around the world join CARIM because they value CARIM's open communication, close cooperation, high ambitions, advanced technological facilities and a critical learning environment. CARIM is one of the eight research institutes 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 institute by the Royal Netherlands Academy of Arts and Sciences (KNAW) and recognised as an international training site for Early Stage Researchers by the European Commission. CARIM researchers have been very active in EU networking activities and the establishment of (inter)national alliances. In 2023, CARIM was involved in many European projects including six ITN/DN programmes with a total number of almost 30 Doctoral Candidates allocated to CARIM.

CARIM has a long standing tradition of executing programmes in collaboration with industry, sharing its expertise while maintaining its independence as reflected by the right to independently publish. Past and ongoing collaborations with industry include, among others, Medtronic, Bayer, Roche, Abbott, Siemens and Philips. Furthermore, CARIM researchers are involved in other public private collaborations in (inter) national networks such as CVON, Horizon 2020, Horizon Europe, ERA-CVD, Interreg and Leducq Transatlantic Networks. 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, including translational research and medical care. International training is provided by all three divisions, leading to three excellent and much acclaimed courses: the Certificate of Advanced Studies in Antithrombotic Management (CAS-AM: Division Blood); The European Vascular Course (EVC: Division Vessels), and the Diploma of Advanced Studies in Cardiac Arrhythmia Management (DAS-CAM: Division Heart).

KEY FIGURES 2023

ANNUAL BUDGET: **21.1** M€

NEW CONTRACTS AND GRANTS: **10.5** M€

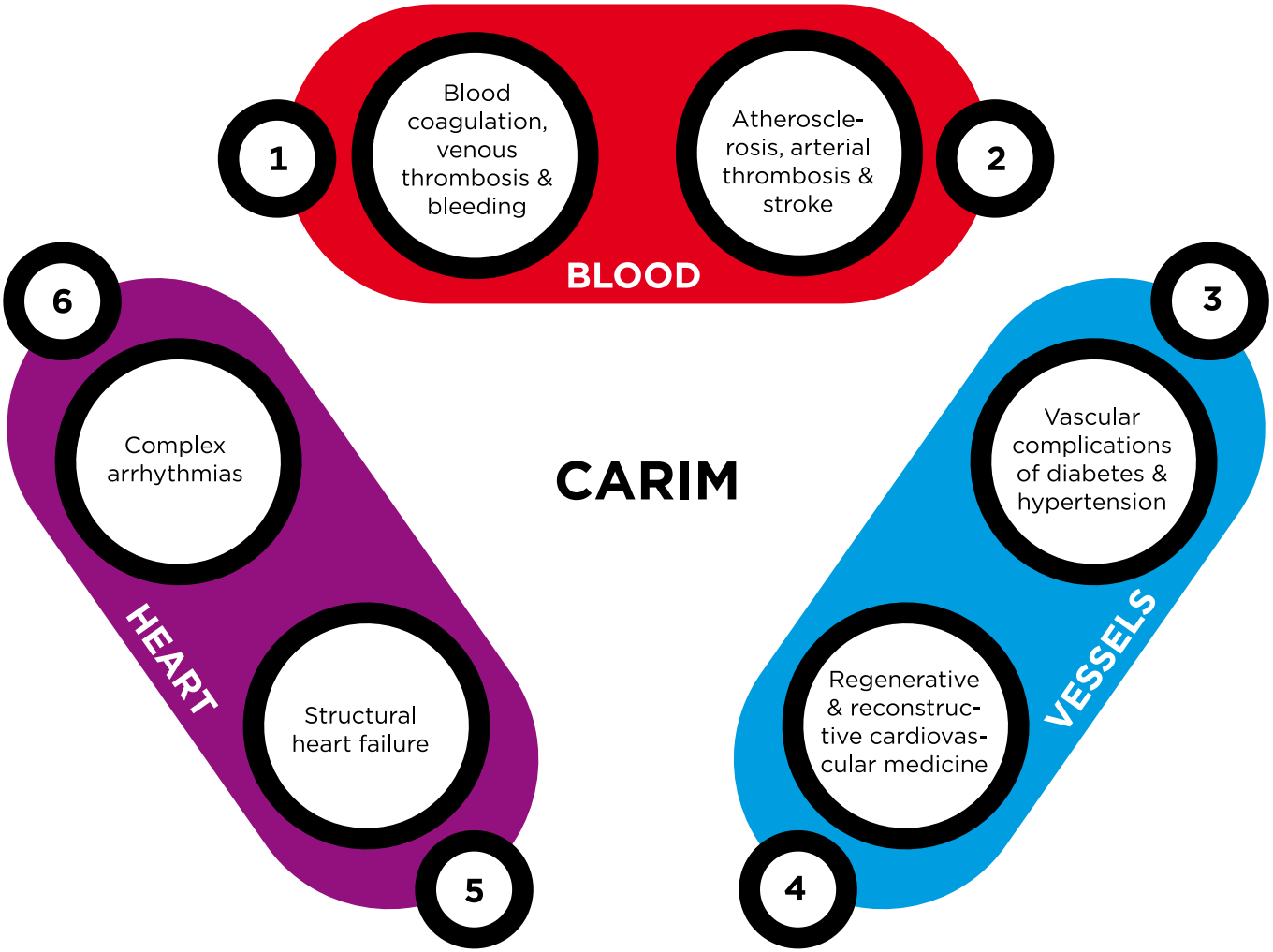
RESEARCHERS: **159.5** FTE (101 INTERNAL PHDS)

TECHNICAL AND SUPPORTING STAFF: **52.5** FTE

DEPARTMENTS/DISCIPLINES: **17**

INTERNATIONAL PEER-REVIEWED JOURNAL ARTICLES (SCI): **1,004**

PHD THESES: **63**


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
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INTERVIEW

FATMA KARAPINAR

Southern adventure

Fatma Karapinar had never thought about moving from the urbanised west of the Netherlands to Maastricht, until she was approached for a job there. Working as a hospital pharmacist and doing academic work, both within the same organisation, sounded very appealing. That, and of course the lovely countryside and the housing opportunities, and no more traffic-jams. In the end, “academic progress” was the main reason for her to embrace the adventure, as her partner called it. By now, she has secured two substantial research grants, and Fatma is well-settled in the south.

Fatma does not like to think in terms of 'islands'. To her, the question why she particularly joined CARIM and not another research institute, for instance one which focuses more on the organisation of health care, is not a very interesting one. "As a pharmacist, my brain doesn't look upon people as 'hearts and blood vessels', but most of my research projects do involve a cardiovascular component. Patients with cardiovascular disorders use a lot of medicines and there is room for improvement there. An example is that of prescribing cascades."

Such cascades arise when a patient starts treatment with medication A, is then prescribed medication B to counteract an adverse effect of A, and then, if they are unlucky, medication C to combat the adverse effects of B. "A classic example is amlodipine, a medication to reduce high blood pressure. Its use can lead to swollen ankles due to fluid retention, so the patient is prescribed diuretics, and we've seen cases where people were then prescribed medication against urinary incontinence." With older people in particular, who have the highest medication use, the full list of medicines is often a puzzle, and correct medication transfer to their GP, the community pharmacy, home care, and the thrombosis clinic is a challenge. No wonder then that medication is a major cause of rehospitalisation within thirty days after a patient is discharged. That is another challenge, which has to be addressed particularly by cooperation across care settings. One of the aspects that attracted Fatma at Maastricht UMC+ was that they acknowledge the importance of integrated care and are actively involved in shaping it.

MISCOMMUNICATION

"At the hospital, we often assume that the patient's GP, or their pharmacy, will understand what we mean, but that's not always the case. This can lead to patient harm that could potentially have been avoided. In addition, we may start a particular medication at the hospital, but we don't always know how it's going to be used after the patient is discharged. This is something that the community pharmacy or the home care nurse do know, so they're in a much better position to monitor adherence over time, and can identify when action needs to be taken. In order to bridge these two worlds, I intend to create an academic network of pharmacies in the region, the aim being to promote collaboration in the care process for people with cardiovascular disorders." Communication with patients themselves is another focal point. "Rehospitalisations also occur because care providers use difficult words or medication schemes, making things hard to understand for patients. If you were to show me a document on mortgage conditions, that would puzzle me too, as it's not a subject I've studied."

ONE WORK SITE

Her interest in integrated care, especially for older adults, arose during her PhD project. She investigated medication transfer in the chain of care after hospital discharge, and found a lot of room for improvement. For 16 years, she worked as a hospital pharmacist and epidemiologist at the OLVG hospital in Amsterdam, and also taught at Utrecht University. "Because you have to divide your attention over many different things, you're not always in the loop. Where I am now, it's great to be able to have the hospital and university next to each other and visit CARIM at any time. Now, after a year in Maastricht, she notices that she still does not know all the ins and outs of the organisation, and sometimes fails to fully understand why matters have been organised in a particular way between the university and the hospital. "But when I hear that even some people who've

been working here for ten years don't always understand it, it puts my mind at rest", she smiles. "And I also found it a friendly gesture how colleagues immediately gave me their phone number, in case I encountered any problems, even about personal matters. I really find Limburg people superfriendly."

RESEARCH

Maastricht also turned out to be a great place for her research work. Last year, she and her team won the 25,000-euro Marja van Dieijen Award. It is an award to support innovative ideas and projects of Maastricht UMC+ staff and students, and her research into identifying adverse effects fitted right in. The aim is to train hospital pharmacists in training and trainee doctors to recognise adverse effects of medication. "As we want to avoid unnecessary accumulation of medicines in the chain of care."

In the future, she intends to investigate how to help patients recognise adverse effects themselves. A pilot study found that people endure adverse effects for an average of four months, before consulting someone about it. "That's rather a long time, during which the medication can cause damage. I would like to shorten that period. For one thing, does it help if patients are contacted automatically by digital means after a month, to detect adverse effects? That might prevent them having to visit a doctor or even being admitted to hospital. This idea recently gained us the Hacking Health innovation award." Fatma also participates in a national consortium that was awarded a 1.44 million euro grant from the Dutch pharmacists' association KNMP to improve pharmaceutical care for heart failure. This project also concerns cooperation between primary and secondary care, the goal being to reduce the risk of rehospitalisation and to improve such aspects as adherence. Finally, she leads a research project of the Dutch Ministry of Health, Welfare and Sports into the current state of the national programme on medication transfer.

THE AIM IS TO TRAIN HOSPITAL PHARMACISTS IN TRAINING AND TRAINEE DOCTORS TO RECOGNISE ADVERSE EFFECTS OF MEDICATION

DISCOVERING LIMBURG

"I'm really enjoying my work, so that's a major motivation for me. But I also enjoy Limburg; together with my husband and our nine-year-old daughter we regularly walk the hills. One thing I've noticed is that children's farms around here are sort of small zoos compared to those in the west of the country. And there are so many nice places for kids to roam about. Before, all I knew about Maastricht was that it was a good place to shop and eat *'vlaai'*, a local speciality. Now I'm learning lots of new things about Maastricht and Maastricht UMC+, so I'm happy that this opportunity has come my way and that CARIM enables me to develop further academically."

INTERVIEW

ROB HOLTACKERS

The racing scientist

Rob Holtackers' scientific career already shifted into top gear when he was still a PhD candidate. So after he had defended his PhD with *cum laude* distinction, there was no reason to delay writing a Veni application. His CV was already impressive, and his research proposal proved to be too. An interview about performing while a deadline is looming, "the most wonderful imaging technology" (MRI), and fast cars. Because, let's not forget, he is not only a scientist but also runs his own company organising sports car events.

When the e-mail from NWO (Dutch Research Council) came in, announcing whether he had been awarded the Veni grant or not, the first thing Rob did was to close his mailbox again. He was busy with something else, and felt it was not the right moment. It wasn't until a few hours later that he opened the email, first checking the second paragraph – "That's where you find the real information" – and read that he had been awarded the grant. With these funds he will further explore the treatment of cardiac arrhythmias while the patient is lying inside an MRI scanner, a new form of ablation therapy which he successfully implemented together with a team of colleagues in Maastricht.

VENI PROPOSAL

During ablation therapy, a catheter is used to burn specific 'points' in the heart muscle tissue from the inside to block the electrical impulses that cause the arrhythmia. Carrying out this procedure in an MRI scanner enables detailed imaging of the heart and the treated tissue, both during and immediately after the therapy. "Wouldn't it be great if we could use these MRI images to predict, already during the procedure, whether the performed therapy will have the desired effect in the long term, by looking at the properties and state of the ablated tissue? That's what I hope to investigate with the help of this Veni grant."

THIS IS A PERFECT EXAMPLE OF AN EVERYDAY CLINICAL PROBLEM FOR WHICH A RAPID, EASILY IMPLEMENTABLE SOLUTION WAS FOUND

By making additional MRI scans of the heart at three and twelve months following the intervention, researchers can evaluate, in both successfully and unsuccessfully treated patients, what state the heart is in, how the tissue has recovered, and hence, what effect the ablation therapy has had on the cardiac tissue. "We would expect to see patterns – so-called imaging markers – which allow us to better understand the MRI images made immediately after therapy. We can then use these images to adjust and steer the ablation therapy already during the procedure, for instance by burning additional areas or burning the same areas again but then more thoroughly. Ultimately, we want more patients to undergo an ablation therapy that is successful the first time and thus not have to come back for further follow-up treatment."

STAGNATION IS EXASPERATING

It is a great example of the type of research that gets Rob going. No wonder then that the Biomedical Engineering programme he attended at Eindhoven University of Technology fitted him like a glove. The programme focused mostly on technology, with just a small medical component, which taught him to solve clinical problems in medical care by technological means, using his biomedical knowledge. He is driven by the ambition to help medical staff improve their work, and thereby improve the outcome of treatment for patients, preferably as soon as possible.

IT MAY SOUND CLICHÉ, BUT GET GOING IN TIME

In the final stages of his master's programme 'Medical Engineering', he did an internship at King's College London where he focused on better visualising scar tissue in the heart using MRI. The work yielded promising results, but the project was unfinished and was put on the back burner for a while. After his graduation, when he started his PhD project at Maastricht, the first 18 months were rather slow going. "The project was very ambitious, so it took a lot of time to get off the ground, and prospects were limited. I found that very frustrating, because if things show only little progress for months beyond my own control, I feel useless and would rather move on to something else. But of course, that's easier said than done during a PhD. I was then given permission to return to London for a few months to continue working on the project I had done during my internship. The discovery I made there changed my entire PhD track and eventually became the basis of my thesis."

COMBINED PHD CANDIDATE AND POSTDOC

Briefly, Rob developed a new method to distinguish between healthy cardiac tissue, blood and scar tissue to improve the visibility of small infarcts on cardiac MRI scans. The solution is so 'simple' that it is now being applied in numerous hospitals all over the world. This is a perfect example of an everyday clinical problem for which a rapid, easily implementable solution was found: the fact that clinicians are now able to detect even minute areas of scar tissue, and can determine their size and precise location, has made it possible to tailor diagnosis and potential treatment better to each patient. His thesis earned him, among others, the 2022 Frederik Philips Award for the best PhD thesis in Radiology, as well as the CARIM Dissertation Award for the best PhD thesis within CARIM.

In addition, Rob was offered a half-time research staff position at the Department of Radiology and Nuclear Medicine at a time when he was only 1.5 years into his PhD project. When his PhD contract ended in late 2019, this was converted to a full-time position even before he had received his doctorate. So, once he had finally defended his thesis after the COVID pandemic in early 2022, he saw no reason why he should delay applying for a Veni grant, "I wanted to make it clear that I showed initiative."

A TIP HE CAN ALSO TAKE TO HEART HIMSELF

One learning point for him in this lengthy application process is also a tip he would like to pass on to others: It may sound cliché, but get going in time. He is actually not very good at that himself. "I perform best under pressure." So, if you then find yourself in a hotel room somewhere in the US in the middle of the night trying to submit a proposal on the NWO website, three minutes before the deadline, and the submission system lets you down, that's a rather nerve-racking situation. Or if you have to put pressure on your closest colleagues to please have a look at your proposal at extremely short notice, preferably there and then. "One colleague gave me really useful feedback, but unfortunately it was after the deadline, which was a great shame. Another

tip: also approach colleagues beyond your own field of expertise for feedback, as often there's no-one from your specific discipline in the NWO jury, which leads to a totally different type of questions."

And finally: make use of the expertise of the FHML Grants Office. "The presentation skills training I had there made me do a complete overhaul of my presentation, making its structure so much better." In the end, applying for these grants is also a kind of 'jury sport', he realises. "You need a bit of luck too."

PAT ON THE BACK

Luck is something he has had plenty of so far. In recent years, he received not only the Veni grant, but also a Kootstra Talent Fellowship and a Niels Stensen Fellowship to do research abroad for a year. The Kootstra fellowship ended when he was awarded the Veni grant; the Stensen one has enabled him to work in Switzerland, where he is staying at the time of this interview. "I'm doing an exciting project on a brand-new 0.55 T (low-field) MRI scanner. The question is whether the current technology still enables us to produce high-quality images using an 0.55 Tesla scanner, a type of instrument we discarded 25 or 30 years ago, together with all the practical advantages of low-field."

He loves being able to switch between various projects, and the freedom to structure his work the way he prefers. "But I'll never just assume that things will always continue to run as smoothly with the grant applications as they do now. Competition is fierce, so I give one hundred percent each day. I regard being awarded such a grant not merely as a pat on the back to say I'm doing well, but mostly as proof that you're apparently doing something good for society. There's a need for it, and that's what matters most to me."

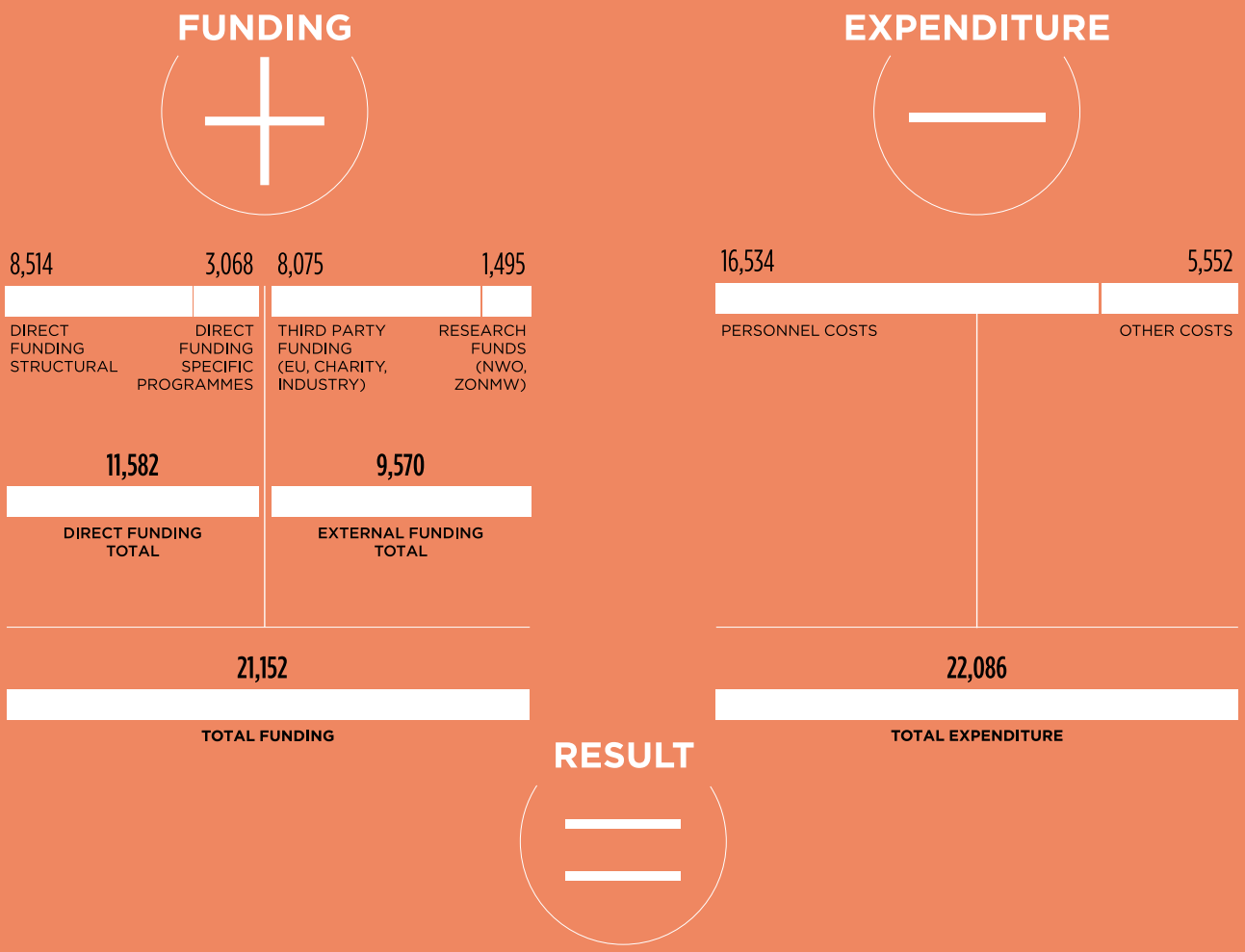
CAR ENTHUSIAST

The ultimate break-away from his scientific work is probably his own company, 'Wheels of Thrill'. "I'm a bit of a car enthusiast", he says with a sense of understatement. "I organise sports car events throughout Europe and, as of this year, also beyond. We have a rally event about six times a year, exploring the more attractive roads and landscapes with a maximum of twenty sports cars, for a weekend or even a week. We stay in charming hotels and enjoy great food. I take care of everything, from planning the entire route to booking all the hotels and restaurants, and from creating personalised name tags to arranging 'money-can't-buy' experiences. I do this for our 'own' group, with which we started back in 2016, but also on request from companies, which might, for instance, want to offer their customers an adventurous tour of the Swiss Alps. I regard it as a great combination, but also as a diversion that gives me a lot of fresh energy. As long as I manage to combine the two, I'll remain the 'racing scientist'."

FACTS AND FIGURES

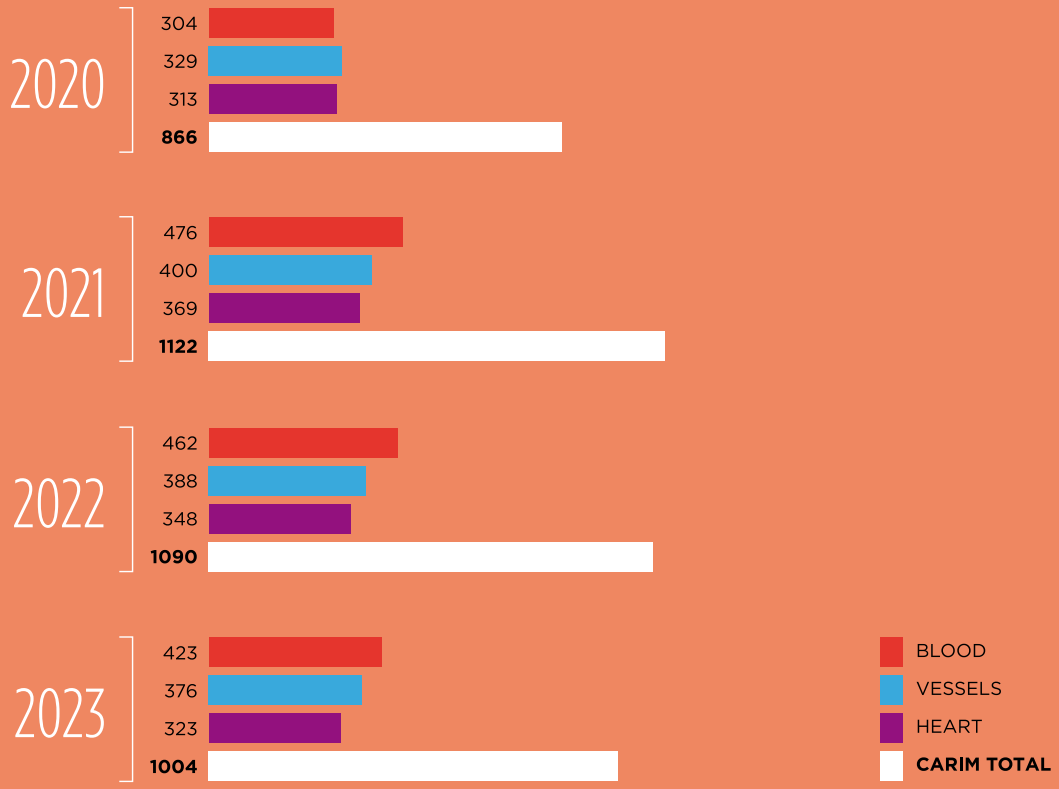
02

FUNDING AND EXPENDITURE (K€) AT INSTITUTE LEVEL 2023



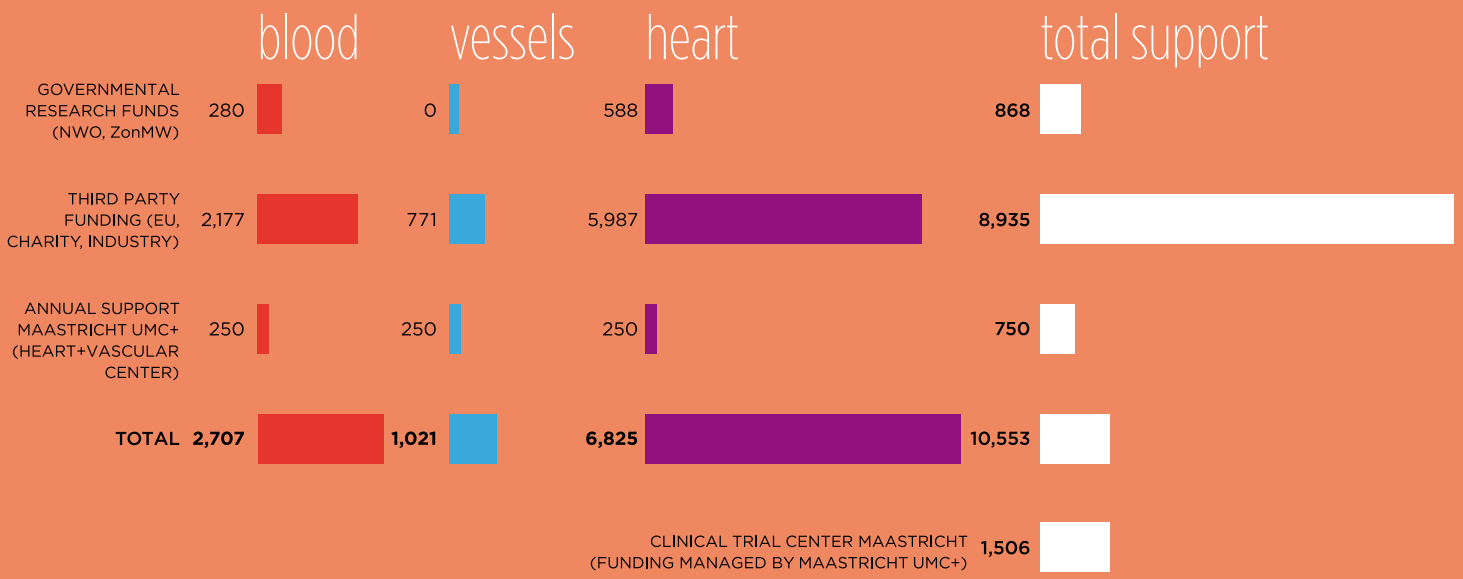
RESEARCH OUTPUT IN 2023

SCI JOURNAL ARTICLES

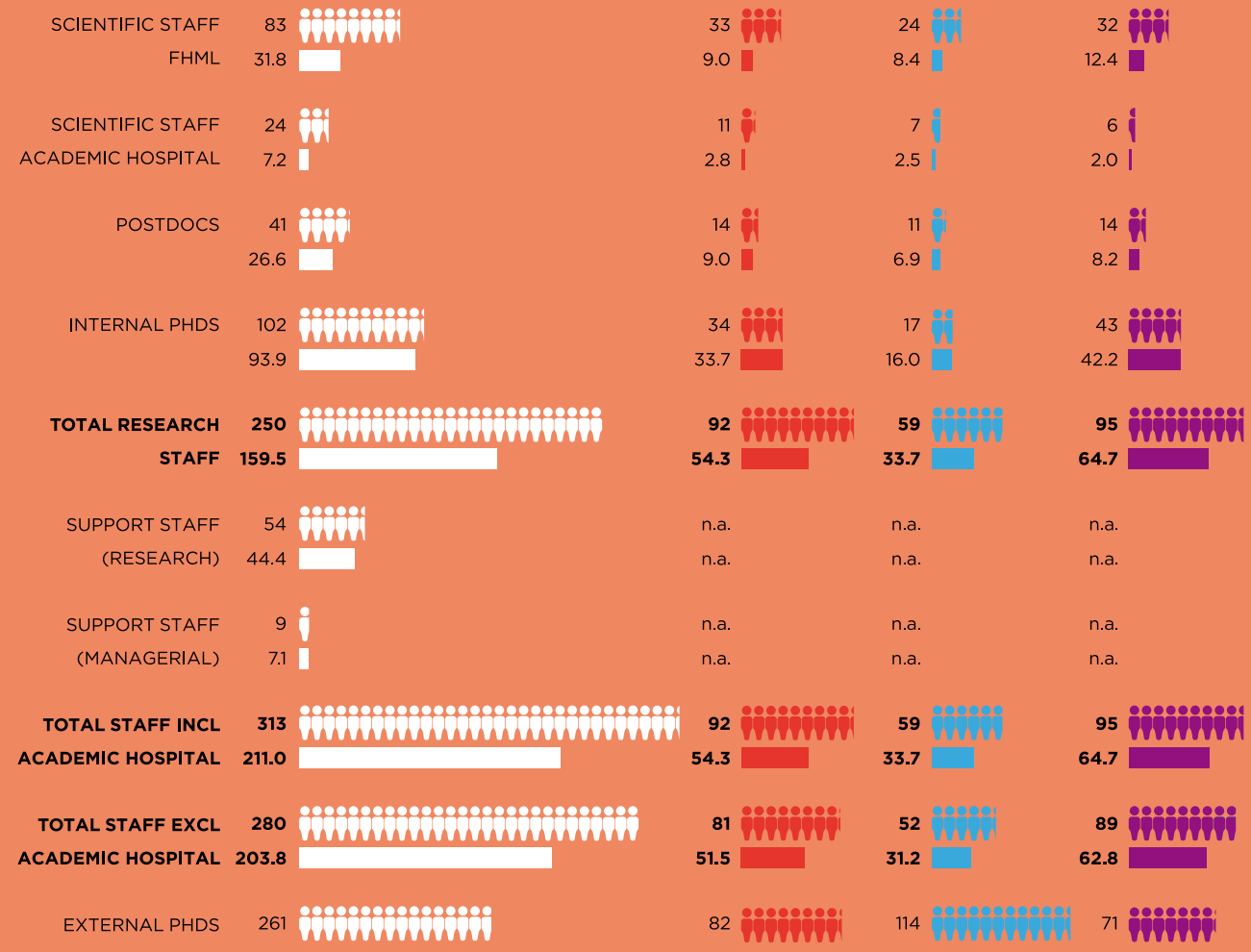


Note: the sum of publications in the divisions exceeds the total number of publications at Institutional level due to double counting of publications with authors from different divisions.

NEW CONTRACTS AND GRANTS (K€) CONCLUDED IN 2023



SUMMARY OF SCIENTIFIC AND TECHNICAL STAFF CARIM AT THE END OF 2023



Note: the sum of staff in the divisions does not add up to the number at institute level due to double affiliations and separate institute-central appointed staff

INTERVIEW

SAM HEUTS

Sam Heuts has a dream

The night before he was to have his interview at the Dutch Heart Foundation for the Dekker Clinical Scientist grant, Sam Heuts lay wide awake in a hotel in The Hague. “This represented nine months of work, which in my view would be wasted if I didn’t get the grant. My girlfriend and me had just had our first child and the preparation of the project took a considerable amount of time in that busy period, so I would have found it really hard to come home with the news of a rejection.” Sam did get the grant, with which he is hoping to clarify the grey area of peri-operative myocardial infarctions.

When Sam began working at the Department of Cardiothoracic Surgery in 2015, as a PhD candidate and physician-not-in-training, he briefly thought it was he who got it wrong. “During the morning handover, the postoperative blood values of the patients – which quantify the damage to the heart – were discussed, and one doctor would say: ‘There’s something wrong here’, while another said: ‘Oh no, not at all.’ After a couple of years, I realised that these blood values, which help decide whether someone has had a myocardial infarction after an operation, were interpreted differently by different doctors. Hospitals in the Netherlands use different biomarkers and cut-off values for certain breakdown products in the blood, and those in other countries often also check different compounds, so it’s impossible to compare centres and studies.”

WORK AS A HOBBY

The topic has kept him occupied ever since. A year after having received his PhD in 2019 on the topic of mitral valve surgery, he was given a trainee post in cardiothoracic surgery at Maastricht. His decision to go for this specialist discipline was partly the result of the research he had done as a student at this department during a scientific internship. “Now my work has also become my hobby and am fascinated by the heart. On the one hand, the heart is a beautiful organ, as it’s always in motion, but on the other hand it’s very complex.” Together with the Departments of Clinical Chemistry, Intensive Care and Cardiology, he has in recent years focused on the diagnostics of peri-operative myocardial infarctions. They have been trying to find out what are the best biomarkers to measure, such as CK-MB and cardiac troponins. This resulted in the application for a Dekker grant, drawn up together with the Department of Radiology and Nuclear Medicine. “All of these departments were already involved in CARIM, and this research project made their clinical ties even tighter, which is great.” In his view, this illustrates the added value offered by CARIM, by forming a bridge between scientific research and the clinic.

DETERMINING A CUT-OFF VALUE

He realises that cooperation has made all the difference for his grant application. “It’s a personal grant, but without all these people I wouldn’t have stood a chance of course. We want to standardise this diagnostic trajectory further. The first step towards this is to make MRI scans of 143 patients before and after their cardiac surgery, in order to objectively map the damage to the heart. We can then correlate this to the blood values; which compound best reflects this damage? This then allows us to determine a cut-off value for it. It’s something that has never been done in this way yet.” This should improve current practice, which currently still leads to underdiagnosis or overdiagnosis. In Sam’s view, the present practice, which causes patients to be told in one hospital that they have had a heart attack after the operation, while another hospital comes to a different conclusion based on the same blood values, is no longer tenable.

HELPFUL FEEDBACK

Since he had completed his research proposal in time, he had the opportunity to pitch it with the CARIM Research Council. “I would really recommend that to anyone, and after that, asking various external people for feedback also really results in improvements. Their answers are sometimes a bit hard to swallow, as you may get comments like ‘What on earth is this? Makes no sense at all.’ You have to be able to take that and accept it, as it really makes things better. There was a world of difference between the proposal that I thought was good enough to be submitted in December 2022 and what I actually submitted one month later.” One month after the interview, which he qualifies as ‘reasonably easy-going’, he

got the message that the grant was his. There was one condition: he should not make MRI scans only at the Maastricht hospital; at least one other hospital had to participate in the project, to ensure the generalisability of the results.

In addition to his diagnostic research, Sam will work together with a colleague from the University of Innsbruck (Can Gollman-Tepeköylü) to set up the world's largest international database, comprising about six thousand patients, and storing their post-operative biomarkers and their longer-term outcomes. "This allows us to combine diagnostic and prognostic research."

DREAM

A PhD candidate (Brian Swinnen) will work on the project for three years, while Sam himself will have a day a week available for research. "That really is a must if you want to collaborate with colleagues who are not medical doctors. For most people, it's not an option to plan meetings before seven in the morning or after seven at night, and rightly so", he laughs. At this time in his life, his days are dominated by his work and his family, which will soon welcome a second child. "I've temporarily set aside the other hobbies I used to have. But I derive a great deal of satisfaction from my research. It's my dream to solve this problem, which has been going through my mind for years. And I want to become a good cardiac surgeon; I've got another two years of training ahead of me."

I REALISED THAT THESE BLOOD VALUES WERE INTERPRETED DIFFERENTLY BY DIFFERENT DOCTORS

HIGHLIGHT
DIVISION BLOOD

FEMKE DE VRIES

Cracking the Code of Ageing: Multimodal Imaging in Multimorbidity

In recent decades, medicine and health care have made rapid progress, with evolving patient needs and transformative technologies. This is reflected in our average lifespan, which rose from 32 to 76 years over the past 200 years. This rise, however, also resulted in an increase in age- and lifestyle-related diseases, such as cardiovascular disease (CVD), cancer, type 2 diabetes, and neurological cognitive decline. A common denominator of these chronic diseases consists of changes in vascular remodelling, resulting in reduced elasticity of vessel walls and an impaired ability to control blood flow and pressure.

To comprehensively investigate the relationship between cancer and CVD, and their impact on mental health, our group focuses on *in vitro* and *in vivo* research and clinical studies, within a partnership involving the research institutes CARIM, GROW and MHeNs. We have initiated *in vitro* research to investigate the direct effect of breast cancer cell conditioned media on vascular smooth muscle cell (VSMC) function. Simultaneously, we are developing a multi-morbidity experimental animal model that allows us to study interactions between cancer and vascular diseases, and their influence on mental health. Additionally, the risk of thrombosis and vascular calcification in breast cancer patients will be assessed. Below we present the highlights of our research lines.

IN VITRO MODELS TO STUDY THE RELATIONSHIP BETWEEN BREAST CANCER AND VASCULAR REMODELLING

Breast cancer is the most common cancer in the world, and 12.5% of all new annual cancer cases concern breast cancer. Survival rate is greatly influenced by the stage and type of the tumour (e.g., luminal A, luminal B, and HER2 positive). Breast cancer survivors are at elevated risk of dying from CVD, compared to women without breast cancer. Additionally, the risk of breast cancer and CVD increases with age. Elucidating the relationship between breast cancer and CVD will provide molecular and cellular cues to improve current patient and preventive care.

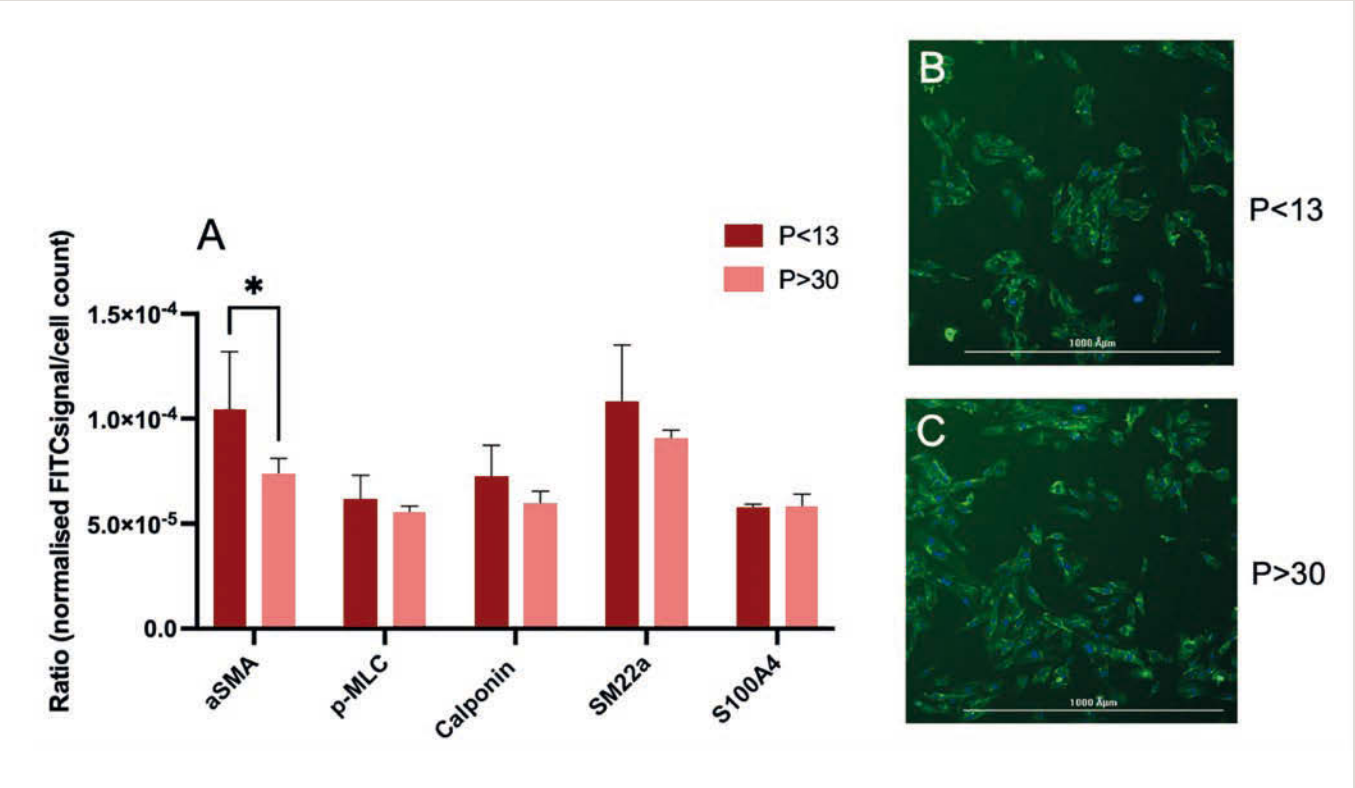


FIGURE 1 iVSMC phenotype was assessed using five different characterisation markers, namely α-SMA, p-MLC, calponin, SM22α, and S100A4. Panel A shows the different levels measured in young and aged iVSMCs. B shows the α-SMA levels measured using fluorescence in young iVSMCs. C shows the α-SMA levels measured using fluorescence in aged iVSMCs. α-SMA: α-smooth muscle actin; p-MLC: phospho-myosin light chain; SM22α: smooth muscle 22α.

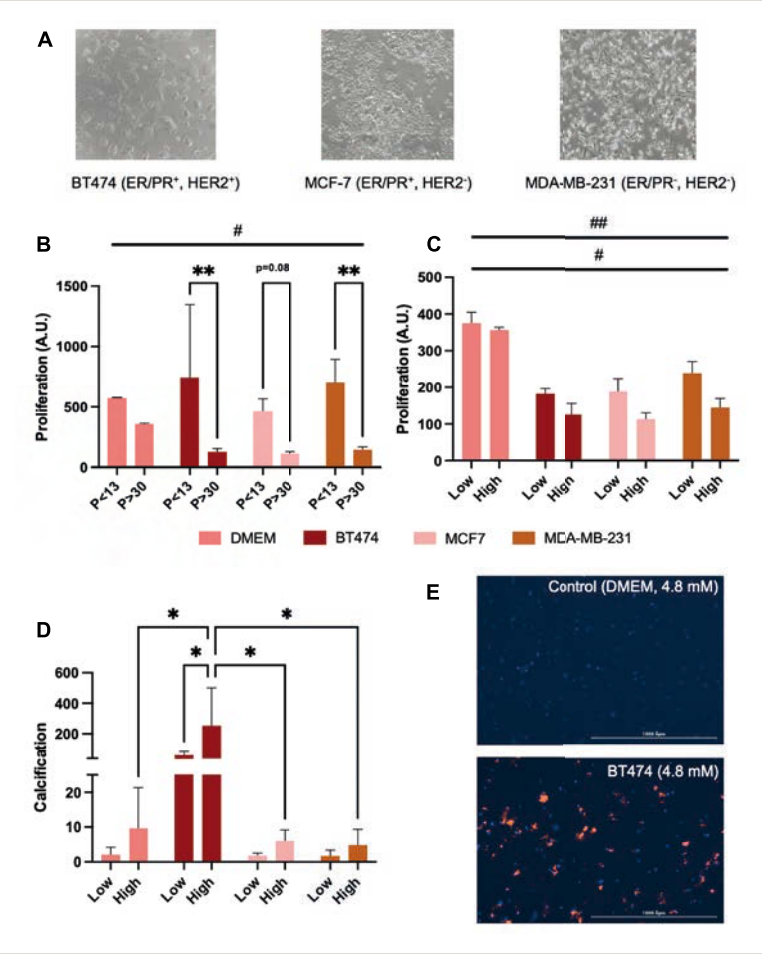


FIGURE 2 The effect of young and aged iVSMCs exposed to human breast cancer conditioned media on proliferation and vascular calcification.

Panel A: Microscopic images of BT474, MCF-7 and MDA-MB-231 in culture conditions.

B: Proliferation measured by xCELLigence of young and aged iVSMCs exposed to control (DMEM), BT474, MCF-7 or MDA-MB-231 conditioned media.

C: Proliferation measured by xCELLigence of aged iVSMCs exposed to control (Dulbecco's Modified Eagle Medium (DMEM)), BT474, MCF-7 or MDA-MB-231 conditioned media with normal or high levels of Ca^{2+}.

D: Calcification measured by Fetuin-A of aged iVSMCs exposed to control (DMEM), BT474, MCF-7 or MDA-MB-231 conditioned media with normal or high levels of Ca^{2+}.

E: * p<0.05 ** p<0.01 # significant age difference between conditions (p<0.001) ## significant calcium difference (p<0.0001)

Our research aims to investigate the influence of human breast cancer on vascular ageing, using induced-pluripotent stem cells (iPSC) VSMCs (iVSMCs, Stem Cell Research University Maastricht; SCRUM). For this research, we selected three breast cancer cell lines, each with its own phenotype, namely triple hormone positive BT474 (ER+/PR+ and HER2+), triple hormone negative MDA-MB-231 (ER-/PR- and HER2-), and HER2-negative MCF-7 (ER+/PR+ and HER2-). iVSMCs were cultured as either young (passage<13) or aged (passage>30) cells. To confirm iVSMC phenotype, we characterised expression levels of the smooth muscle markers a-SMA, p-myosin light chain (p-MLC), calponin, smooth muscle 22a and S100A4. As expected, aged iVSMCs showed a significant decrease in a-SMA levels (p=0.016) compared to young iVSMCs (**Figure 1**), in line with the literature.

To investigate the effect of breast cancer cell conditioned media on iVSMC proliferation and calcification, cells were exposed for 72h to ensure that transcriptional and translational changes took place. Aged iVSMCs conditioned with BT474 (p=0.004) and MDA-MB-231 (p=0.008) media showed a significant decrease in proliferation compared to

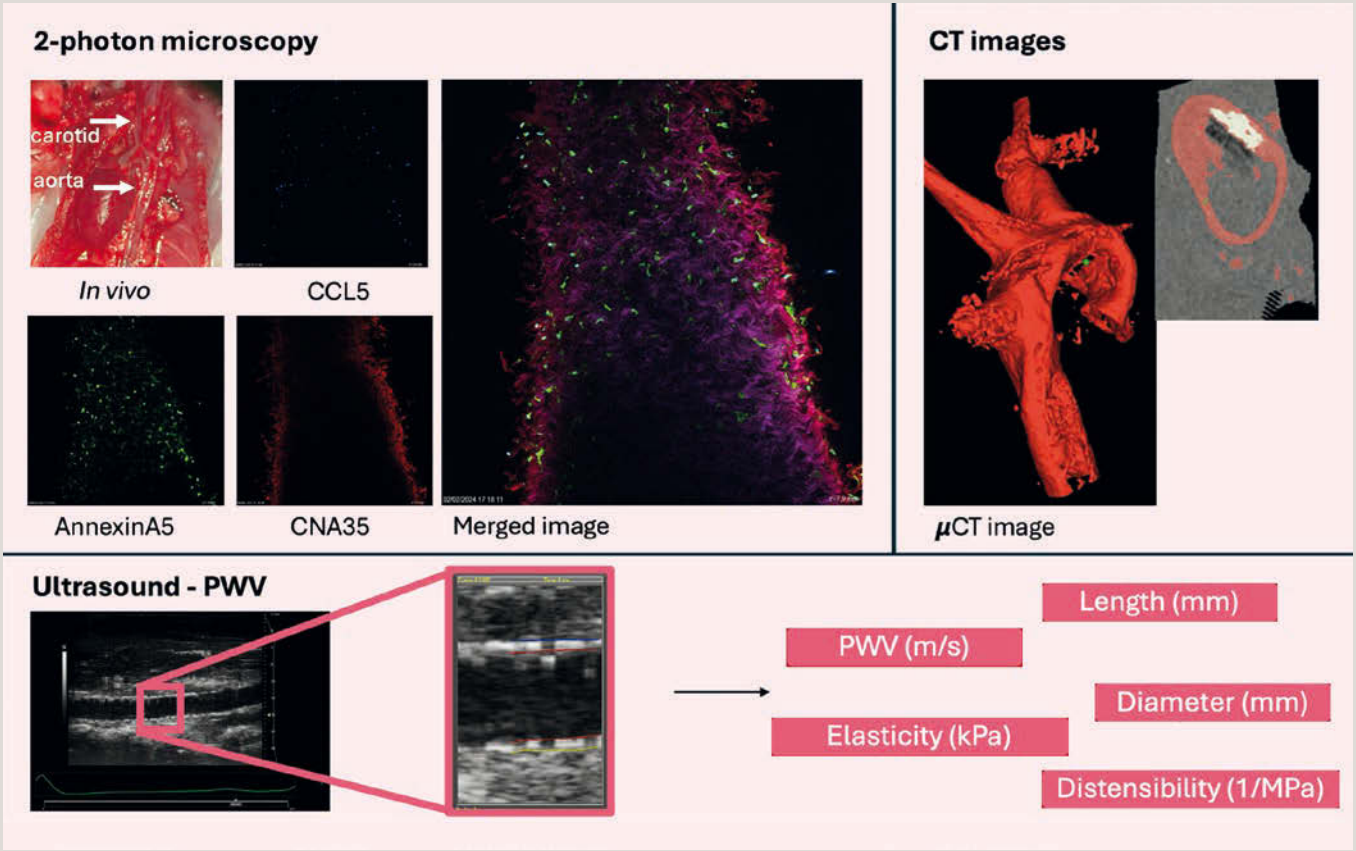


FIGURE 3 Examples of the different imaging modalities used for the *in vivo* animal model. PWV: Pulse Wave Velocity.

young iVSMCs, while iVSMCs conditioned with MCF-7 (p=0.08) only showed a trend (**Figure 2B**). When calcium conditions were raised, aged iVSMCs showed a significant decrease in proliferation (p<0.0001; **Figure 2C**). Aged iVSMCs exposed to BT474-conditioned media with high calcium levels showed a significant increase in calcification compared to control, MCF-7 and MDA-MB-231 conditions, with high calcium levels (p<0.05; **Figure 2D/E**).

MULTIMORBIDITY ANIMAL MODEL TO STUDY THE RELATIONSHIP BETWEEN CVD AND CANCER, AND THEIR INFLUENCE ON MENTAL HEALTH

Over the past years, increasing life expectancy has resulted in clinical care shifting from treatment to prevention and early detection. Interactions between morbidities and the consequences of these interactions for treatment are currently insufficiently understood. Additionally, studying the causal interaction between morbidities in the clinical setting is far from ideal, due to the complexity of the diseases and the specific expertise required. Therefore, developing and using a multi-modal animal model is of crucial importance to answer complex future research questions. As such, examining how comorbidities drive disease could reveal as yet unknown fundamental pathways and provide new therapeutic angles for future translation to the clinic. Several animal models for multi-morbidity have been developed in recent years, including models combining CVD and renal failure, CVD and chronic obstructive pulmonary disease (COPD), hypertension and stroke and CVD/COPD and smoking. However, these models do not combine CVD, cancer, and mental health.

In our approach, we will develop an atherosclerotic and vascular calcification model using ApoE knockout rats, in combination with rhabdomyosarcoma R1 cancer. Our multi-modal model will be evaluated using advanced imaging (**Figure 3**). The carotid artery will be assessed using 2-photon microscopy, staining for collagen (CNA-35-AF564), calcification (Fetuin-A-AF546), inflammation (CCL5-Pacific Blue), and apoptosis (Annexin-A5-AF488). Furthermore, the aorta will be assessed using μCT/PET; immunohistochemistry staining for collagen (CNA-35), calcification (Alizarin red), inflammation (CCL5/CD68/Mac3), apoptosis (Annexin-A5) and hypoxia (Pimonidazole); and tissue stiffness using the Pavone. Vessel properties (e.g., pulse wave velocity, vessel diameter, and vessel elasticity) are evaluated by ultrasound measurements at baseline and endpoint. Additionally, to assess the influence of CVD on mental health, five different behavioural and stress tests will be performed (e.g., Y-maze, sucrose preference test, object recognition test, and open field).

CLINICAL STUDY: THE INFLUENCE OF BREAST CANCER ON VASCULAR CALCIFICATION AND THROMBOSIS

To validate our research results obtained from *in vitro* models, we have initiated a partnership with the Department of Oncology at Maastricht UMC+. As mentioned above, the relationship between cancer (including breast cancer) and CVD has as yet been insufficiently studied. Our clinical study will focus on the relationship between breast cancer and CVD, specifically vascular calcification and thrombosis. This translational partnership will make it possible to initiate patient sample collection, including early-stage breast cancer patients, before treatment. In this line of research, patients will be analysed for the risk of vascular calcification and thrombosis. By elucidating which breast cancer patients are more prone to vascular calcification and thrombosis, and which factors cause an increased risk, we ultimately aim to provide preventive care for these patients.

INTERVIEW

PETER STENVINKEL

Collaborating on vitamin K and hibernating bears

His last visit to CARIM coincided with The European Fine Art Fair (TEFAF) in Maastricht. Apart from superior art (a little beyond his budget unfortunately), Prof. Peter Stenvinkel discovered new possibilities for cooperation between his group at Karolinska Institutet and Prof. Leon Schurgers' lab in Maastricht. They share a huge interest not only in vitamin K, but also in what we can learn from hibernating bears and other solutions found in nature.

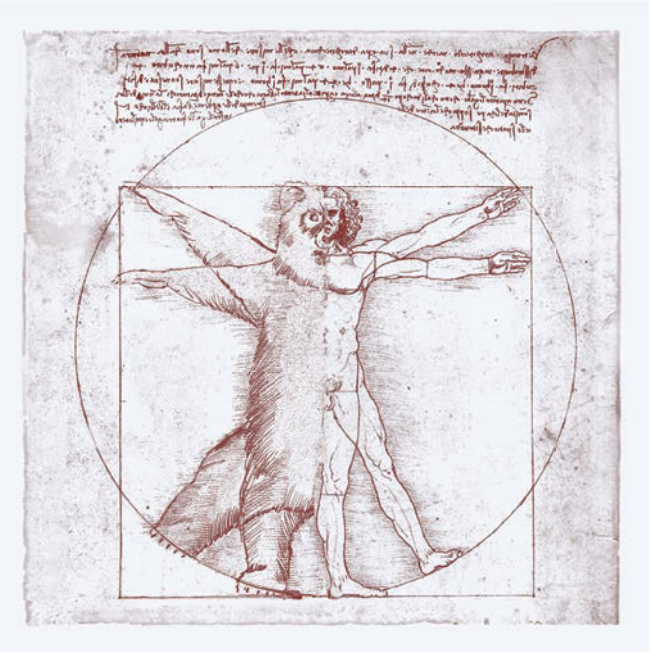
Peter has been a visiting professor at CARIM for about a year. He is a professor of nephrology at Karolinska University Hospital, focusing on risk factors for metabolic, cardiovascular and nutritional complications of chronic kidney disease. He has just published a popular science book called 'Nature's intelligence' about his interest in biomimetic studies, that is, solutions developed in nature that inspire scientists. How can naked mole rats grow to an extremely old age without developing cancer? How can bats escape disease from harmful viruses and how can a bear sleep for five months without losing most of its muscle, as humans would do in such a case?

But first, how did the cooperation with CARIM start?

"It started with me listening to one of Leon's lectures many years ago, where I recognised his interest in vascular disease, vascular aging and vitamin K. We wrote a couple of reviews together, we sent some samples from Sweden to Maastricht for analysis, and that resulted in a couple of collaborations. And I should add that during the last years we have been actively collaborating in two EU Marie Curie consortia, INTRICARE and CaReSyAn."

How exactly do Karolinska and CARIM complement each other?

"The researchers I've met in Maastricht have very similar mindsets to ours at Karolinska Institutet. We approach problems the same way and have fun working together, that's always a good thing. The competence and analyses on vitamin K that Leon is an expert at, we don't have here. And it's important in nephrology: our patients undergo premature aging, especially in their vasculature, and I would think Vitamin K plays a very important role in this



accelerated vascular ageing process. What we contribute to the cooperation is patient samples. We have small pieces of arteries from patients undergoing living donor transplantation, which can help in this research."

Do you also share your interest in biomimetics with the Maastricht colleagues?

"Yes, indeed. Leon and Tilman Hackeng visited us in Stockholm in late May, to brainstorm about lessons from nature and the animal world. I expect that the current environmental changes will accelerate biological aging processes, thus increasing lifestyle diseases in the future. I think we can learn how things are being solved in nature."

Can you name an example?

"There's a Greenland shark that can become more than 400 years old. What can this elusive creature teach us about premature aging in humans? For me as a kidney doctor, it's just amazing that a bear can survive many months during hibernation without peeing, and without getting ill. If we understand that, we hope to find opportunities to protect humans against osteoporosis, kidney disease, thrombo-embolic complications and muscle wasting. But we also try to learn from animals what to eat. I'm more and more concerned that the artificial ultraprocessed food that we humans now consume in such large quantities creates health problems. We need to eat more according to nature's original intentions, and I think we can learn from animals how we can improve our health with our food habits."

Nevertheless, you seem optimistic about the future

"Yes, there are reasons for hope, despite a long series of grim climate reports. In these challenging and uncertain times, marked by conflicts and environmental crises, it seems like we live in the 'worst of times'. After watching the news on TV it's easy to forget that in many ways life on our planet has never been as good as it is today. Four out of five children with cancer are cured and WHO believe AIDS can be eradicated by 2030. We have learned so much already and every dimension of human activity is rich with solutions that can help bring humanity back into balance with our natural systems. With former and present world leaders like Trump, Putin, Bolsonaro and even Geert Wilders in the Netherlands, we need to make our politicians realise: science is the only way forward if we want to solve health and environmental problems."

SCIENCE IS THE ONLY WAY FORWARD IF WE WANT TO SOLVE HEALTH AND ENVIRONMENTAL PROBLEMS

GRANTS, PRIZES AND HIGHLIGHTS

03

SCIENTIFIC HIGHLIGHTS

In 2023, the successful work of our researchers was reflected in 1,004 international peer-reviewed journal articles (SCI), 63 PhD candidates successfully defended their theses, and 9.57 million Euros were received in competition from national science foundations and from third money parties, charities, EU framework programmes and industry.

SCHOLARLY IMPACT

23% of CARIM's publications belong to the top 10% and 3.3% to the top 1% of publications in its field. With an overall CNCI (Category Normalized Citation Impact) of 2.3, CARIM's publications are cited 2.3 times more often – on average – than the expected average for comparable publications in their specific fields. All three divisions are above the global average in their contribution to the top 1% and top 10% of publications. The proportion of publications published open access has increased at CARIM, with 38% of the total output being available in a journal as open access in 2016 to 69% in 2023. Including green open access publications, 82% of CARIM's 2023 publications are available as open access.

	NUMBER OF DOCUMENTS*	AVERAGE CNCI	NUMBER OF PAPERS IN TOP 1%	NUMBER OF PAPERS IN TOP 10%	% OF PAPERS IN TOP 1%	% OF PAPERS IN TOP 10%
Blood	927	2.0	27	239	2.9	26
Vessels	826	1.9	26	153	3.1	19
Heart	728	3.3	37	177	5.1	24
CARIM total	3,999	2.1	131	921	3.3	23

*The number of documents and citation impact for separate divisions (2020-2021) and the research institute (2016-2021)

RESEARCH GRANTS AWARDED TO INDIVIDUALS

NHS DR E. DEKKER PROGRAMME

Within the framework of the Dr E. Dekker programme of the Dutch Heart Foundation, Dr **Sam Heuts** (Dept of Cardiothoracic Surgery) was awarded a Clinical Scientist grant. The k€ 264 grant facilitates the initiation of a multi-disciplinary research group, involving several CARIM divisions, focusing on the identification of clinically relevant myocardial injury after cardiac surgery in general, and coronary artery bypass surgery in particular.

During cardiac surgery, the heart is temporarily ceased, and its function is taken over by the cardiopulmonary bypass machine. As such, the procedure inherently causes some degree of cardiac injury. However, until now, the thresholds of cardiac injury (as quantified by biomarkers such as cardiac troponins) that negatively influence prognosis and warrant early recognition and treatment, remain unknown. Therefore, Sam and his team will apply several different study designs incorporating state-of-the-art imaging techniques and extensive biomarker follow up to determine the diagnostic and prognostic value of these modalities for clinically significant injury, in a multicentre setting. See pages 30-33 for a full interview with Sam.

NWO TALENT PROGRAMME

NWO has awarded a Veni grant worth k€ 280 to Dr *ir* **Rob Holtackers** (Dept Radiology and Nuclear Medicine). Rob receives the grant for his project 'Interventional cardiac MRI: a new treatment method for cardiac arrhythmias'. Recent developments made it possible to perform ablation therapy for cardiac arrhythmias in an MRI scanner. Due to the excellent soft tissue image contrast of MRI, the different tissues of the heart can be imaged in great detail and completely radiation-free. This study investigates whether the outcome of the treatment can be predicted based on specific findings in the images at the time of treatment, in order to immediately provide additional treatment if necessary to improve the outcome of the treatment in the long term. See pages 20-24 for a full interview with Rob.

DUTCH DIABETES RESEARCH FOUNDATION

Prof. **Casper Schalkwijk** (Dept of Internal Medicine) has received a grant worth k€ 275 from the Dutch Diabetes Research Foundation for the project 'The effect of pyridoxamine on microvascular dysfunction in type 2 diabetes; a randomized controlled trial'.

People with diabetes face a higher risk of small blood vessel malfunctions, which can lead to blindness and kidney failure. Current treatments do not specifically target these complications. Research has identified high glucose concentration as a key factor, leading to increased production of the reactive molecule methylglyoxal, which damages organs and tissues. It was found that methylglyoxal levels are elevated in both type 1 and type 2 diabetes and are linked to small blood vessel dysfunction. In animal studies, it was demonstrated that methylglyoxal causes direct damage to these vessels. Importantly, it was discovered that the vitamin B6 derivative pyridoxamine inhibits methylglyoxal formation and improves vascular function. A clinical trial showed that pyridoxamine is safe, reduces methylglyoxal, and may enhance vascular function. The next goal is to test pyridoxamine in people with type 2 diabetes and small blood vessel dysfunction. In an 8-week, placebo-controlled study, it

will be assessed whether pyridoxamine improves blood vessel function in the eye and kidney. If successful, this could lead to larger clinical trials and potential widespread use of pyridoxamine in diabetes care, possibly as an adjunct to existing treatments due to its unique mechanism of action.

JUNIOR FELLOWSHIP PHILIPPE VANGRIEKEN

The Belgian Foundation of Frans Janssen, together with the Dutch Diabetes Foundation, has decided to support the Junior Fellowship of Dr **Philippe Vangrieken**, awarded in 2022. The project, titled 'Methylglyoxal as a mediator of insulin resistance: novel mechanism and unique target', has received additional funding of k€ 75. The foundation, which is part of the Koning Boudewijn Foundation, aims to promote diabetes research. The project focuses on the role of methylglyoxal in the development of diabetes and its associated microvascular complications. This project aims to unravel how methylglyoxal causes insulin resistance and to evaluate whether lowering systemic methylglyoxal levels prevents the development of insulin resistance and subsequent type 2 diabetes. This additional financial support enables Philippe to include more detailed measures for (micro)vascular function and insulin sensitivity and to investigate the potential role of the microbiome in the association of methylglyoxal with (micro)vascular dysfunction and the development of type 2 diabetes.

HARRY CRIJNS RESEARCH GRANT QUIRIEN ROBBE

Quirien Robbe (Dept of Neurology) received the 2023 Harry Crijns Research Grant for the project 'Prognostic value of concomitant, choroid artery occlusion in acute ischaemic large vessel stroke', pioneering scientific research into dementia after stroke through a collaboration between radiology and neurology. The Harry Crijns Research Grant was first awarded in 2021 by the Cardiovascular Research Fund of Health Foundation Limburg (this year sponsored by Bayer and Amgen) to a promising young researcher in the field of cardiovascular disease. The grant was instituted as a tribute to Prof. Harry Crijns, who chaired the Department of Cardiology of Maastricht UMC+ until December 2020 and was a board member of CARIM. The grant was traditionally awarded during CARIM Symposium 2023, followed by a presentation of the winner.

EUROPEAN RESEARCH COUNCIL GRANTS

The iCARE4CVD (individualised care from early risk of cardiovascular disease to established heart failure) project, coordinated by Prof. **Hans-Peter Brunner-La Rocca** (Dept of Cardiology), has been granted M€ 22 in funding from the Innovative Health Initiative (IHI), a joint undertaking of the European Commission and the European life science industry. The international research project focuses on personalised prevention and treatment of cardiovascular diseases and aims to improve the understanding of these conditions and optimise future prevention. iCARE4CVD brings together 33 leading international partners from civil society, academia and industry, and is led and coordinated by Maastricht University and global healthcare company Novo Nordisk.

The project PRAETORIAN (Euro**P**ean Training Netwo**R**ks to T**A**rget DAMPs and N**ET**s: novel appr**O**aches in p**R**ecision Seps**I**s p**A**tie**N**t care), coordinated by Dr **Gerry Nicolaes** and Dr **Kanin Wichapong** (Dept of Biochemistry) has been selected for funding by the European Union within the Horizon Europe Marie Skłodowska-Curie research and innovation programme to train ten doctoral candidates. PRAETORIAN is an interdisciplinary and international consortium involving five partners from academia (universities of Maastricht, Paris, Münster, Uppsala, and Institute for Biomedical Research Barcelona), seven partners from industry, four organisations representing patient and societal perspectives, and two organisations for international dissemination and outreach. The goal of the PRAETORIAN is the establishment of a highly interdisciplinary research and educational training platform for doctoral candidates in the (bio)medical sciences to optimally design novel therapeutics and diagnostics and to increase their employability in both academia and industry. In this project, multidisciplinary approaches through a combination of computational (*in silico*) and experimental methods will be applied to investigate the molecular mechanisms of DAMPs and NETs in the pathogenesis of sepsis and immunothrombosis and to develop new bioactive compounds to regulate key drug targets involved in pathogenic pathways leading to sepsis and/or immunothrombotic disease. See pages 108-111 for a full interview with Gerry and Kanin.

Dr **Martina Calore** (Dept of Cardiology) is one of the partners of the international consortium that was funded with M€ 4 by the European Innovation Council for cardiogenomics for the research project titled 'IMPACT (Cardiogenomics meets Artificial Intelligence: a step forward in arrhythmogenic cardiomyopathy diagnosis and treatment)'. The international team, led by Professor Alessandra Rampazzo of the Department of Biology at the University of Padua, will study the development of new therapies for arrhythmogenic cardiomyopathy (ACM), a genetic disease that affects the heart and represents one of the main causes of ventricular arrhythmias and sudden cardiac death. With an incidence of one in 5,000, it can be considered a highly relevant cardiovascular disease. Within IMPACT, Martina will contribute to the identification of deregulated microRNAs that will be tested next as a novel therapeutic approach for the disease.

Prof. **Stephane Heymans** (Dept of Cardiology) participates in the DCM-NEXT consortium, funded with M€ 4.1 by the European Innovation Council. The DCM-NEXT consortium combines the multidisciplinary expertise and resources of eight leading investigators in the fields of dilated cardiomyopathy (DCM), deep clinical phenotyping, cardiogenomics,

cardiac transcriptomics, bioinformatics, artificial intelligence, and functional studies and unique access to an unparalleled cohort of DCM patients and relatives from these centers with extensive clinical data. DCM-NEXT aims to develop comprehensive genetic risk profiling, predict disease outcomes more precisely, and expedite treatment development by identifying specific genes, variants, pathways, and cell types involved in DCM pathogenesis. This is crucial for addressing unmet medical needs in DCM patients globally. Stephane is responsible for target identification and validation. He provides access to essential infrastructure for this project tasks, including genomics, transcriptomics, metabolomics, functional genomics and bioinformatics. This includes integrating clinical and molecular data in both unsupervised and supervised manners to develop of risk models for predicting events in patient groups.

Prof. **Erik Biessen** and Dr **Pieter Goossens** (Dept of Pathology) are partners within the international consortium awarded M€ 2.7 million for their MSCA Doctoral Network named MIRACLE (Multilevel inflammatory regulation in cardiometabolic disease). The international team, led by Prof. Menno de Winther of the Amsterdam Medical Centre, will employ cutting-edge single-cell biology and multi-omics analysis approaches to study inflammatory pathways in cardiometabolic disease, paving the way to replace generalized blocking of inflammation used in recent clinical studies by more precise interventions targeting disease-specific cellular subsets and mechanisms. Within MIRACLE, Erik and PhD candidate Isabel Encarnação will study metabolic signatures and biomarkers of atherosclerotic plaque macrophage subsets while Pieter and PhD candidate Moritz Reif will focus on the phenotypic and functional implications of interactions between plaque macrophages and extracellular matrix.

CONTRACT RESEARCH

Prof. **Stephane Heymans** (Dept of Cardiology) collaborates with CSL Behring to identify pathomechanism-directed strategies) that may offer a more targeted approach to mitigate unbalanced inflammation. This strategy could also help prevent or reverse severe cardiomyopathy and heart failure related to myocarditis. The primary objective of the project is to explore and develop targeted treatments that address the underlying mechanisms of myocarditis. In doing so, more effective therapies are aimed to be provided, with the goal of enhancing patient outcomes and slowing the progression of disease to advanced heart failure, thereby potentially reducing the need for transplantation. In this research collaboration, cardiac transcriptomics and O-link analysis in plasma will be performed to identify the best targets for the treatment of myocarditis patients.

Dr **Vanessa van Empel** (Dept of Cardiology) has initiated a successful collaboration with the French company Owkin, which specialises in understanding complex biology through AI. The Maastricht-HFpEF investigators started this collaboration to establish a federated research network aimed at maximising the value of their data and to reach their joint aim: to create a multimodal database for HFpEF to capture the full heterogeneity of disease, and eventually target the disease. Jerremy Weerts, postdoc on this project stated: “We worked with very tight timelines to complete the whole process of ethics review, data collection and data curation and upload. This was quite challenging. With the support from DataHub, MEMIC and CARIM we were able to achieve this”.

Gnosis by Lesaffre sponsors a four-year academic PhD programme called ‘the Vitamin K2 Industrial PhD Program’

to study the fermented bioactive vitamin K in cardiovascular health. The primary focus of the programme is to explore the role of vitamin K2, either as standalone or in combination with other food ingredients, as a senolytic to boost cardiovascular health and to delay senescence. This collaboration initiative aims to shed new light on the potential benefits of vitamin K2 and its impact on cardiovascular health, and to better balance lifespan and health span. The collaboration between Gnosis by Lesaffre and CARIM (group Prof. **Leon Schurgers**, Dept of Biochemistry) allows the PhD candidate to explore research in a pragmatic and applicable way, working closely with experts in both research and industry. Gnosis by Lesaffre is part of the Lesaffre group, a French company, with over 11,000 employees that has been a key global player in fermentation for over 170 years. Their goal is to find ever more relevant answers to the needs of food, health, and respect for our environment.

OTHER GRANTS, AWARDS AND PRIZES

Prof. **Rory Koenen**, Dr **Judith Cosemans**, (Dept of Biochemistry) and Prof. **Blanche Schroen** (Dept of Physiology), together with their colleagues from the University of Edinburgh and the Ludwig Maximilian University of Munich have received a grant from the Dutch Heart Foundation together with the British Heart Foundation and the Deutsches Zentrum für Herz-Kreislauf-Forschung e. V. for their MegaCardiocyte project. Heart failure is a debilitating and progressive disease that has no cure and is often fatal. For a particular type of heart failure which arises from an impaired ability of the heart's chambers to relax between beats, abnormal function of small blood vessels is likely to be an important triggering factor. The MegaCardiocyte consortium will explore the link between small blood vessel function and that type of heart failure. They suspect it may be attributed to malfunctioning blood platelets – normally responsible for clotting – that, together with an overactivation of immune cells in the blood, compromise the ability of small blood vessels in the heart to work normally. The research could lead to the development of platelet-targeted treatments in the prevention and management of heart failure. The project builds on research supported by the CARIM PhD call of 2019.

Five projects involving CARIM researchers have been awarded funding under the ERA4Health call CARDINNOV 'Research targeting development of innovative therapeutic strategies in cardiovascular disease':

- Prof. **Leon de Windt** (Dept of Cardiology): Non-coding RNA therapeutics to elicit cardiac regeneration in ischemic heart disease (RECREATE);

- Dr **Miranda Nabben** (Dept of Cardiology): O-GlcNAcase Inhibition in Acute Decompensated Heart Failure (GANDHI);
- Dr **Job Verdonschot** (Dept of Cardiology): A Blueprint of Inflammatory Drivers of Heart Failure with Preserved Ejection Fraction (ID-PRESERVED);
- Dr **Marleen van Greevenbroek** (Dept of Internal Medicine): REstoring balance: Specialized Proresolvin mediators for resolution of INflammation and VAscular Repair in humans at high cardiovascular risk (RESPIN-VAR);
- Dr **Vanessa van Empel** (Dept of Cardiology): Diverging HFpEF phenotypes: patient-tailoreD targeting of anti-Inflammatory pathways to limit Ventricular and Atrial remodelling (HFpEF-DIVA).

The ERA4Health partnership is a European partnership within the Horizon Europe programme for innovative treatments in the field of cardiovascular disease. The partnership aims to fund international research in the areas of cardiovascular disease, nanomedicine and nutrition, health and prevention over a seven-year period. See pages 68-71 for the full interview with Leon, Miranda, Job, Marleen en Vanessa.

Dr **Marleen van Greevenbroek** (Dept of Internal Medicine) received a k€ 100 grant from the European Foundation for the Study of Diabetes (EFSD). Resolution of inflammation is a highly orchestrated process mediated by Specialised Pro-resolving Mediators (SPM). The objective of this study is to investigate whether imbalanced plasma SPMs and/or SPM-subsets are related to development of cardiovascular disease (CVD) in individuals with type 2 diabetes (T2D). Restoring the SPM balance in T2D-related CVD may provide a new therapeutic option for this number one comorbidity of T2D. This research will be conducted in collaboration with CARIM postdoc Dr Elena Tore, Dr Ana Briones (Universidad Autónoma de Madrid) and Prof. Jesmond Dalli (Queen Mary University of London).

CARIM is a key participant in the sustainable research project CAREFREE. This six-year research consortium, led by Prof. Nicole Bouvy (NUTRIM), aims to make operating rooms more sustainable, serving as a model for broader hospital procedures and measures to reduce environmental impact. The project has been granted M€3.4 in funding from the Dutch Research Council (NWO). Several faculties and departments of Maastricht UMC+ are involved in various work packages, including WP1 (refuse), WP3 (reuse trocar), WP5 (recover pharmaceutical residues), life cycle assessment, and health technology assessment (HTA). CARIM's involvement is highlighted in WP5, which focuses on recovering pharmaceutical residues and is led by Dr **Ben Janssen** (Dept of Pharmacology & Toxicology). CARIM PhD candidate Saba Rafi has been appointed to this project to monitor and implement interventions aimed at reducing the environmental impact of medicinal preparations used during surgeries.

Four CARIM researchers have been awarded a k€ 250 grant from the Academic Fund Maastricht UMC+:

- Dr **Elham Bidar** (Dept of Cardiothoracic Surgery): The next step in the evolution of cardiopulmonary bypass: selective warm blood organ perfusion;
- Dr **Martijn Smulders** (Dept of Cardiology): Imaging mycocardial fibrosis using spectral photon-counting CT;
- Dr **Job Verdonschot** (Dept of Genetics and Cell Biology): *Preventie in de cardiogenetica: de juiste zorg voor de juiste persoon!*;
- Dr **Martine Truijman** (Dept of Neurology): Clinical impact and cost-effectiveness of a novel Individualized MRI-based plaque clinical decision tool for treatment of symptomatic patients with carotid artery disease (IMPACT).

The Academic Fund gives talented young staff members the opportunity to set up their first scientific line of research within an existing or new line of expertise at Maastricht UMC+.

Three research projects received a Public-Private Partnership (PPP) Allowance in 2023: DELIVERANCE, involving Prof. **Leon de Windt** (Dept of Cardiology); ORANGE-FORCE, involving Dr **Carla van der Kallen** (Dept of Internal Medicine); and TranslATe-NASH, involving Dr **Kristiaan Wouters**, Dr **Sander Rensen** and Dr **Sabine Daemen** (Dept of Internal Medicine).

Ischemic heart disease (IHD), often following a myocardial infarction, is the leading cause of mortality worldwide. Current treatments include interventional angioplasty and lifelong generic drugs that only stabilise the condition. There is a need for new concepts to promote cardiac self-regeneration, such as boosting cardiomyocyte proliferation. RNA therapeutics have emerged as a new approach for cardiac repair. Non-coding RNAs (ncRNAs) are powerful cellular regulators. **DELIVERANCE** partner UM, led by Prof. Leon de Windt, has shown that a microRNA, miR-106b, can stimulate cardiomyocyte proliferation using synthetic RNA-mimics. However, RNA is prone to degradation, limiting its bioavailability. Effective RNA delivery to the myocardium remains a challenge despite the development of various delivery tools. The DELIVERANCE project aims to test different formulation strategies for targeted RNA delivery to human heart muscle cells, complemented by 3D in vitro studies using cardiac organoids.

TranslATe-NASH aims to uncover immune-related mechanisms in Non-Alcoholic SteatoHepatitis (NASH), recently renamed to Metabolic dysfunction Associated Steatohepatitis (MASH), to develop new diagnostic and treatment options and address the lack of current treatments and simple diagnostic blood tests. Partnering with the Dutch Obesity Clinic, human tissues and blood samples will be collected to investigate immune cell involvement and activation in NASH. Flowview diagnostics will aid in bioinformatics analysis to identify new markers and pathways crucial for liver inflammation, a key step in disease progression. With an estimated 52 million people affected by a steatotic fatty liver, costing €35 billion annually, early diagnosis and new therapeutic targets are essential. TranslATe-NASH focuses on the immune cell role in the adipose tissue-liver axis in obese individuals, using flow cytometry and multivariate bioinformatics analysis to identify mechanisms and cross-talk with adipose tissue. The data will inform diagnostic tests and new treatments for NASH.

The ORANGEHealth.NL consortium, led by ACTA Amsterdam, received over M€ 1.8 from the Top Sector Life Science & Health. The aim is to improve dental care and oral health for the elderly in the Netherlands, with special attention to vulnerable groups, prevention, providing the right care at the right place, and collaboration between caregivers. ORANGEHealth.NL has received the grant for its first major joint project, **ORANGEFORCE**. The project focuses on more effective communication between the parties and the development of supportive technology and diagnostics for the elderly who are at higher risk for diseases, both in the mouth and in the rest of the body. Timely detection of diseases can prevent or reduce health complications and costs, and improve the quality of life for patients. The Maastricht Study is involved in researching the link between oral health and overall health, and the development of biomarkers.

The project **'PreCIS'**, addressing medication prescribing cascades, has won the Marja van Dieijen Award 2023, worth k€ 25. Prescribing cascades occur when side effects of medications are not recognised but are instead seen as a new complaint. This results in unnecessary new medication prescriptions to treat the complaint. This phenomenon is largely unknown to patients, physicians, and pharmacists. This project focuses on recognising and addressing side effects that cause prescribing cascades in healthcare and educating residents from the Departments of Internal Medicine and Clinical Pharmacy. See pages 16-19 for a full interview with Fatma.

Dr *ir* **Rob Holtackers** (Depts of Radiology and Nuclear Medicine) has won the Frederik Philips Prize from the NVvR (Dutch Radiology Society) for his thesis 'Visualising the Invisible: dark-blood late gadolinium enhancement MRI for improved detection of subendocardial scar'. The jury praised the technique for making scar tissue visible, which his research has yielded, and which can be easily and quickly applied in practice. Jury chairpersons Mathias Prokop and Arjon Hoekstra presented him with the prize and a check worth k€ 4 on behalf of Philips, as well as a beautiful statuette.

During the 7th Translational Cardiovascular Research Meeting, Dr **Michiel Henkens** (Depts of Pathology and Cardiology) received two awards for his research. Michiel was awarded the second prize of the Einthoven Dissertation Award 2022, which recognizes exceptional doctoral research conducted in the Netherlands in 2022 on cardiovascular topics. In addition, on behalf of the NLHI Heart Bank (*Hartenbank*), he received the Wiek van Gilst Collaboration Award 2023.

The CARIM Commitment Award of 2023 went to **Sandrine Seyen** for her contributions to the CARIM Strategic Board and SCRUM, her instrumental role in organising the support staff, for being CARIM photographer during several occasions and for being an involved and stimulating CARIM employee and ambassador.

Laura Kempen (Dept of Pathology) has received a Bourse de Fonctionnement (operating grant) from the Foundation Léon Fredericq. The aim of the Foundation Léon Fredericq, a university hospital foundation in Liège, is to support and strengthen medical and biomedical research in Liège in all fields of medicine, as well as to support innovative projects carried out by the University Hospital of Liège for the well-being of patients and the quality of care. This operating grant is intended to cover the operating or equipment costs of a doctoral student or postdoctoral researcher.

During the Annual Symposium of the Dutch Society on Thrombosis and Haemostasis (NVTH) (29-31 March 2023), **Alice Todaro** (Dept of Biochemistry) received the Jeanne Stibbe Trophy for the best oral presentation, which was entitled: '*In vitro* and *ex vivo* rescue of a nonsense mutation (F5 p.Arg1161Ter) responsible for severe coagulation factor V deficiency'.

Anouk Achten (Dept of Cardiology) received the prize for best oral presentation during the autumn meeting of the Dutch Association for Cardiology (NVVC) on 2 November.

OTHER HIGHLIGHTS

In 2023, CARIM celebrated its 35th anniversary with a grand celebration held on 7 September at *Kasteel de Hoogenweerth*, situated in a picturesque location along the rolling banks of the Maas. On a lazy summer afternoon, a sparkling aperitif was served in the castle gardens, where guests could enjoy lively and light-hearted discussions about this memorable milestone and the future of our esteemed and illustrious institute, musically supported by Francine & Romain in the background. Following a speech and retrospective by our current director, Tilman Hackeng, an excellent buffet catered to modern trends and offering something for everyone, was served. As evening fell, guests moved inside where a magnificent party unfolded in the bar and ballroom, and a professional casino where many successfully tried their luck. The celebration continued into the early hours, and upon departure, all received a beautiful, practical memento as a reminder of a delightful evening and everyone's contributions to a top cardiovascular research institute in Europe. We owe many thanks to Barbara Przybylski for the flawless and efficient organisation of this legendary evening.

As from 1 January, Prof. **Eline Kooi** (Depts of Radiology & Nuclear Medicine) succeeded Dr Marc van Bilsen as PhD Coordinator of CARIM. See pages 122-125 for a full interview with Eline.

On 11 June, a group of CARIM researchers participated in *Maastricht's Mooiste* run. The CARIM team competed in either the 5 km or 10 km race, with the 10 km runners finishing in 9th place out of 27 teams. After last year's success, CARIM researchers are eager to be at the starting blocks again for *Maastricht's Mooiste 2024*.

During the 7th lustrum celebration of the Dutch Society on Thrombosis and Haemostasis (NVTH), Prof. **Tilman Hackeng** (Dept of Biochemistry) was appointed honorary member for his outstanding contributions to the society over the past years - and for many more years to come.

A CARIM team, consisting of **Boy Houben, Eline Berends, Lele Han, Koen van der Laan, Shaiv Parikh, Koen Reesink** and **Philippe Vangrieken** participated in the 'Prominentenroeien', organised by MWC Maastricht (*Maastrichtsche Watersportclub*). Our CARIM team traded lab coats for rowing gear and hit the water with enthusiasm for charity. They rowed alongside formidable competitors, all in the spirit of fun and teamwork.

Prof. **Roberto Lorusso** (Dept of Cardiothoracic Surgery) has been elected chairman of the Extracorporeal Life Support Organization (ELSO) Research Committee. He will be coordinating all the scientific and research activities of the ELSO worldwide organisation.

After two terms of six years each, Prof. Tilman Hackeng handed over the chairmanship of the Department of Biochemistry to Prof. **Leon Schurgers**. Leon took over the chair on 1 September 2023 and he aims to safely navigate the department though the roaring twenties, among other things, by implementing iPSC technology and vascularised micro-organs on a chip in current research strategies. Leon

has worked as staff member at the Department of Biochemistry since 2008, bridging the Division Blood with the Division Vessels (and Heart). As a vascular biochemist, his cardiovascular work includes a close collaboration with the Heart and Vessel Center at Maastricht UMC+ to study vascular remodelling on a cellular and molecular level.

PROFESSORSHIPS

- 1 March 2023: Rory Koenen (Dept of Biochemistry) - Professor of Biochemistry of Vascular Inflammation and Thrombosis
- 1 December 2023: Ingrid Dijkgraaf (Dept of Biochemistry) - Professor of Biomimetic Chemistry
- 1 December 2023: Miranda Schram (Dept of Internal Medicine) - Professor of Diabetes epidemiology, particularly focusing on Cardiovascular and Mental Health

CARIM COMMITMENT AWARD

This Commitment Award is intended for any CARIM member who has devoted his or her heart and soul to CARIM in an exceptional way, be it on an academic, managerial, service or community level. The award consists of a bronze coin by the sculptor Marina van der Kooi (www.marinavanderkooi.nl) and an exclusive restaurant dinner voucher for two.

CARIM COMMITMENT AWARD LAUREATES

2015	Rob van der Zander
2016	Frits Prinzen
2017	Peter Leenders, Agnieszka Brouns-Strzelecka, Nicole Bitsch, Helma van Essen, Jacques Debets (MF)
2018	Koen Reesink
2019	Kristiaan Wouters; Tara de Koster
2020	Carla van der Kallen; Harry Crijns
2021	Stella Thomassen
2022	Myrthe van der Bruggen, Renée Tillie, Valeria Saar-Kovrov, Kim Maasen, Adele Ruder (I'mCARIM); Marc van Bilsen
2023	Sandrine Seyen

ROB RENEMAN AND TILMAN HACKENG

INTERVIEW

Each era presents its own challenges

There is a lot of mutual respect between the first and current scientific directors of CARIM. Rob Reneman founded the institute 35 years ago. Now, at the age of 89, he still keeps close tabs on all developments. "Whenever a new message is posted on the CARIM website, the first reaction I receive comes from Rob", says Tilman Hackeng. Together, they look back on, and ahead to, the first, largest and perhaps best research institute at Maastricht.

The interview takes place at the Maastricht apartment where Rob and his wife Wijnanda live with their dog Femke. Coming to the university is unfortunately no longer an option, so he also had to skip last year's CARIM symposium, the first time he has missed it. "A great loss to our annual get-together", says Tilman. Rob concurs, but also counts his blessings. "A good friend of mine, whom I've known since secondary school, has lost his short-term memory; so compared to that I'd rather have mobility problems."

ACTIVE IN SCIENCE

Although ten years ago, when he was interviewed on the occasion of 25 years of CARIM, he already said he was embarking on his final scientific exploit, it turns out that Rob is still active in science. At the time, he was talking about two papers on free fatty acid uptake by the cardiac muscle, written together with Ger van der Vusse, Theo Arts and Jim Bassingthwaighte from Seattle.

The authors' average age: 82 years. Unfortunately, Bassingthwaighte died in the week it was published. At present, Rob is working together with Ger van der Vusse, as first author, and Theo Arts, on a review of fatty acid transport from the blood circulation to the cardiac muscle. "It's the last part of a four-part series. I can't stop researching." Nor can he stop his association with CARIM, as it turns out during the

interview. He closely follows the website, brainstorms with newly appointed professors about their inaugural lecture ("I pick up new things from that too") and, 'off the record', poses a few pertinent questions to Tilman about the current state of affairs. The institute is in his heart.

DARING FEAT

"It was not until last year that I really understood what a daring feat the founding of CARIM was", says Tilman. "It basically meant regarding the very structure of the Medical Faculty, and it required permission from the Ministry of Education." "That's right" says Rob. "It had never been done before, and when in 1988 it became legally possible to set up a more independent institute within a university, we were the first to do it, together with Leiden. And yet, we had it relatively easy, compared to nowadays, as there was no pressure of time and money was available. There have been such huge changes since then. I don't envy today's young researchers. The way they have to scrape funds together and how they compete on the work floor. That wasn't necessary in my days, there was enough money around. Tilman has to do his best to keep the people together. I think I've had a relatively easy time of it, compared to my successors." Tilman: "I don't know about that, because what you did, setting up such an institute, would be impossible today." Rob: "But I had no trouble getting several PhD places a year within the faculty, that was something I could use as a stimulus. They were deployed in research between clinic and preclinic." Tilman: "The choices you made at the time, like going for translational research, are what has made CARIM great today. That's why we're now at the top in Europe."

SOMETHING TO BE PROUD OF

One of the things Tilman is referring to is the publication analysis from 2016-17. Of the 200,000 articles published worldwide on the subject of cardiovascular research, 0.5% came from CARIM. And of the top 5% of the articles, it was even 1.5%. "That's an excellent result; something to be proud of", he says. "It's a missed opportunity that the university is only looking at whatever generates money, whereas no-one in the world cares about how many PhDs we produce, and how many grants we secure. They world cares about publications with impact."

FEWER PI GROUPS

Right from the start, Rob established the three main research lines that have formed the basis of the unique selling point of the institute today: Blood, Vessels and Heart. Tilman: "There are many very good institutes working in two of these three domains, but we've got all three, and there's also a lot of cooperation among the three." Rob: "My PhD supervisor used to say: a medical doctor on his own can't do research. They need a biochemist and a biophysicist to get anywhere. I've tried to introduce that idea at Maastricht. Collaborating is something you do on the basis of your own strength, not from a position of dependence." Tilman: "That was team science *avant la lettre*. Within the three divisions, we now have six research programmes in which a group of PIs work together with their teams. In the old days, we had over fifty research programmes and PIs within the institute. Way too many."

DIVERSITY

And, as the current director freely admits, even ten years ago, it was a predominantly male team. "Hidden away at the bottom of a drawer in my desk, I still keep an invitation card for a CARIM symposium held ten years ago, featuring a photograph of the 29 PIs: all men! Fortunately, the situation is now shifting." Rob remembers an important lesson in this respect which he once learned from a new female staff

member. “I’m married to a staunchly feminist lady, but I still used to make the odd mistake. Once I appointed the lady to the vacancy, and after having been employed for three weeks, she told me she was pregnant. I heaved a deep sigh, and asked her why she hadn’t told me this at the interview. ‘Would you have taken me on?’, she asked. That was a learning moment.”

NEW DEVELOPMENTS

Whereas research once used to be an occupation that seemed to know no fixed working hours, young researchers these days do care more about their private lives. Tilman: “Those stories about how it used to be make some young people feel insecure about their academic career. ‘I don’t think about my work when I’m at home’, some say. That's obviously allowed, but it shows the scientific climate is shifting. Regardless, we still manage to do very well at CARIM.”

The reason why he accepted the post of Scientific Director seven years ago was to be able to facilitate research and researchers. “Giving people opportunities and exploring interesting new research directions, while keeping the good things you have, is a joy. Look at the current development towards stem cell research. That’s caused a huge breakthrough. We can now develop patient-derived cells into tissues at the lab, test therapies on them and then apply the successful therapy to the patient. I think that’s the holy grail of cardiovascular research.” Rob compliments him on this.

GREAT JOB

“And yet I still think it was easier in my days. It’s obvious you’re doing a wonderful job leading the institute, but I think it’s costing you more energy now that it did me at the time. I didn’t have to prevent competition between our staff members.” Tilman: “Each era presents its own challenges. Nowadays it’s very hard to secure grants; colleagues spend a lot of time writing proposals, are invited for an interview and then still narrowly miss getting the grant. That’s making it ever harder, and thus also more difficult to make a life in academia attractive to people. We support them as much as we can, but the low-hanging fruit is gone. And yet there’s a lot of good stuff too. The interactions between basic research and clinical research are getting closer all the time. We are moving towards a situation where there is one Board for the clinical CARIM and Heart+Vascular Center, turning them into one center: CARIM+HVC. We are, and will remain, a great CARIM community; an organisation where people are genuinely supportive of each other. In the end, this is a great job.”

COLLABORATING IS SOMETHING YOU DO ON THE BASIS OF YOUR OWN STRENGTH, NOT FROM A POSITION OF DEPENDENCE

HIGHLIGHT
DIVISION VESSELS

ARMAND JAMINON

ReGen – the next level

Some years ago, CARIM wanted to create a platform to connect the PI groups working in the various CARIM divisions. To this end, each division was partly supported by a postdoc, in order to horizontally connect the different PI groups. In June 2023, I was appointed as a CARIM postdoc for the Division Vessels. In this highlight article, I present my research plans.

SCIENTIFIC BACKGROUND

Vascular regenerative medicine aims to repair damage and enhance vessel functionality, thereby improving cardiovascular health. Traditional clinical interventions, often involving surgery, are demanding and expensive. Transitioning towards the reuse or regeneration of vascular specimens offers promising alternatives that could reduce the need for major surgeries, ultimately lowering the morbidity and mortality associated with cardiovascular disease (CVD). While coronary artery bypass graft surgery is commonly performed to treat coronary artery disease, its long-term effectiveness is often impeded by occlusion (restenosis), despite ongoing advancements in surgical techniques and medical management.

Restoring the functionality of a diseased vessel requires targeted intervention aiming at multiple cell types, including endothelial cells (ECs; intima), vascular smooth muscle cells (VSMCs; media), and various cells within the adventitial layer (adipocytes, fibroblasts, macrophages, and lymphocytes). Our research at CARIM has achieved significant progress in this field by developing innovative pluripotent stem cell lines in collaboration with Stem Cell Research University Maastricht (SCRUM) and the Heart+Vascular Center (HVC), creating CRISPR/Cas9 mediated knock-out pluripotent stem cell lines. Furthermore, we established a comprehensive framework for generating diverse populations of vascular cells, including ECs, cardiac fibroblasts, epicardium (smooth muscle and fibroblasts), VSMCs (specific to aortic root, aortic arch, and descending aorta), as well as mesenchyme-like stromal cells.

Mechanisms such as oxidative stress, senescence, apoptosis, and mechano-transduction are at the forefront of our targets in vascular regeneration. In addition, the use of stem cell technology and pathological specimens obtained from surgery at the HVC provides a unique complementary tool to support the clinical relevance and robustness of our findings. Furthermore surgical biopsies, combined with relevant clinical data, aid in identifying personalised mechanisms of arterial diseases that affect CVD outcome. Modulation of these molecular pathways will help us design and develop vascular regeneration strategies.

HIGHLIGHT DIVISION VESSELS

This postdoc research project of the Division Vessels will focus on the regenerative development of all vessels within the cardiovascular system and will study pathological disease processes affecting them. To this end, this research proposal comprises three main research pillars:

RESEARCH STRATEGY

Research pillar 1: Biobank management

To study the pathology of vessels, we receive vascular specimens from HVC and from the Departments of Cardiothoracic and Vascular Surgery. Specimens obtained cover a wide variety of CVDs, such as thoracic and abdominal aneurysms, coronary artery disease (CAD), peripheral artery disease (PAD) and aortic valve calcification (AVC).

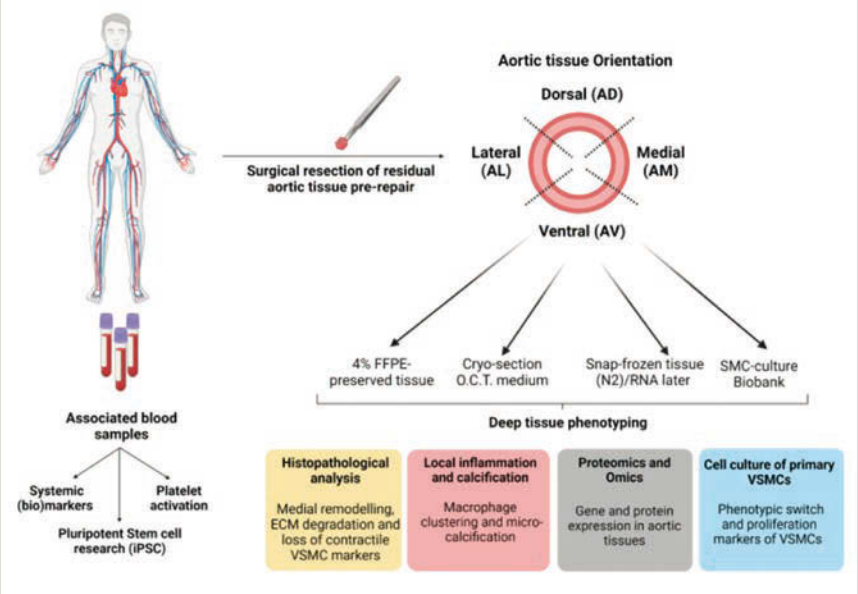


FIGURE 1 Tissue processing; obtained from Ganizada et al. Biomedicines 11, no. 8: 2095. https://doi.org/10.3390/biomedicines11082095. Location-specific characterisation of aortic aneurysm tissue as well as systemic arterial blood, enabling correlation with local differences in mechanical stresses.

Within this research pillar, we continue to support the management of vascular tissue and blood collected during routine corrective surgery. This involves coordinating the logistics and sample preparation to ensure that additions to the biobank meet standardised quality levels. Post-surgery, blood is processed for biomarker assessment and stored as serum and plasma for subsequent use. Vascular tissue is categorised by the surgical team according to pathology and anatomical classification; a section of the tissue is preserved in paraformaldehyde for histological analysis and in RNAlater for transcriptomic studies. An overview of the aortic tissue processing is displayed in **Figure 1**. If there is excess tissue, it will be utilised for primary cell isolation, decellularisation, or biophysical phenotyping using the Flexcell system, all conducted at the the Department of Biochemistry. An overview of the workflow of the HVC biobank is displayed in **Figure 2**.

In collaboration with the Department of Biomedical Engineering, we are developing and acquiring advanced platforms to characterise cellular mechanobiological signalling and responses related to tensile, compressive, and shear stress, in conjunction with biochemical markers of cell phenotype.

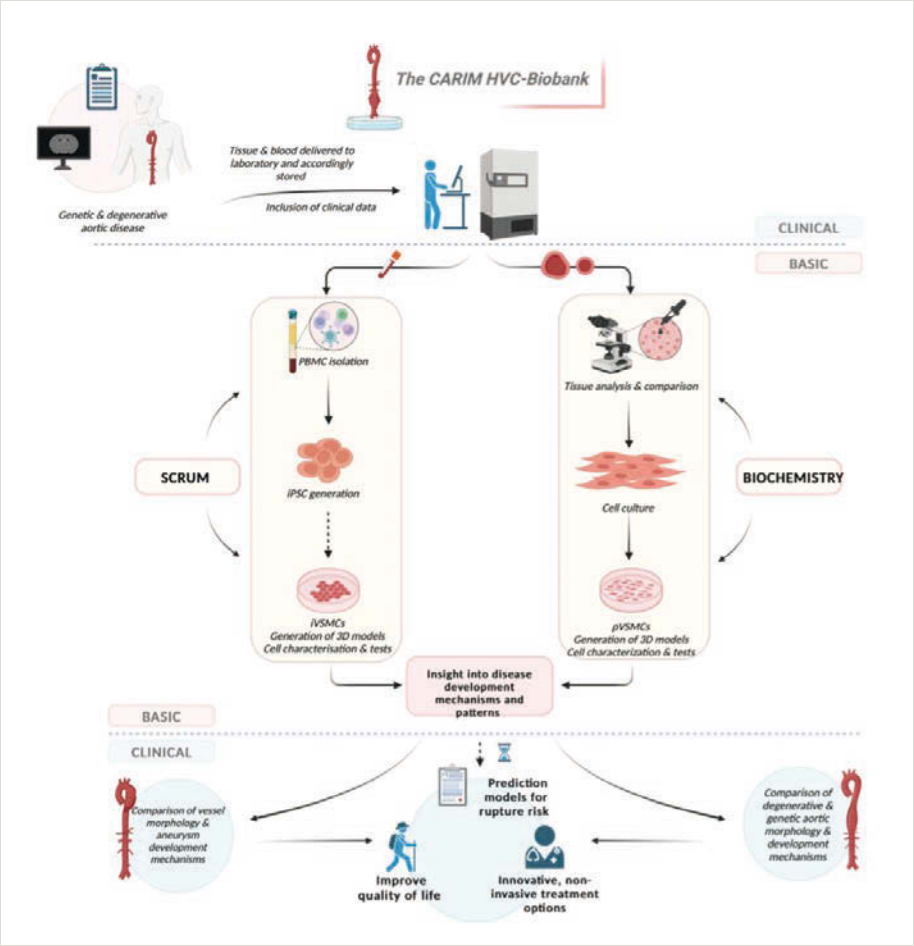


FIGURE 2 The CARIM+HVC Biobank.
Cardiothoracic and vascular surgery will deliver tissues upon inclusion of genetic and degenerative vasculopathy. Depending on the available tissue, different processing routes will be followed. All tissues will be extensively phenotyped for morphology (chemical and histochemical staining), stiffness (nano-indentation) and expression (cytochemistry/live imaging/omics). If abundant material is available, primary cells will be isolated from vascular specimens obtained, which can be applied in the cellular models. In certain cases (monogenetic disorders), PBMCs will be isolated and stored for later iPSC generation with subsequent differentiation of iVascular cells. These reprogrammed cells can then be directly compared with primary (exposed/diseased) cells, or assessment of differences between healthy and diseased cells can be conducted. All measurements can be correlated with clinical data from these patients, ultimately leading to improved quality of life or innovative treatment options.

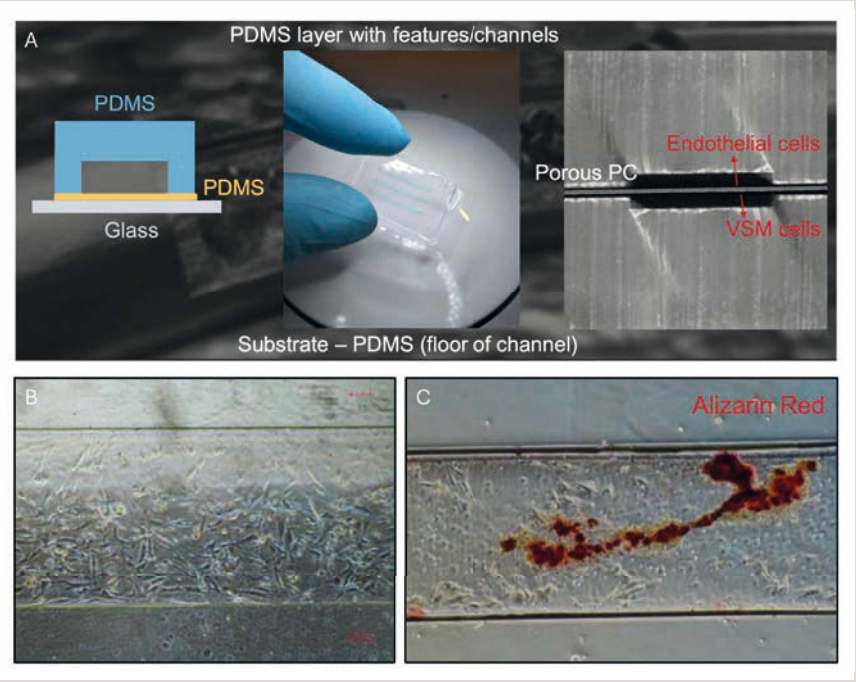


FIGURE 3 Vascular graft.
A. Schematic design of the graft, which is made from thermoplastic (PDMS) and can simultaneously culture multiple cell types. B. Attached VSMCs inside the channel cultured for multiple days, forming a confluent layer. C. After calcification induction (high calcium conditions), there is Alizarin Red positivity, indicative of the presence of calcification.

To this end, we have acquired a nano-indentation device (Optics11) which is coupled with a confocal microscope to follow fluorescent markers (Confocal.nl). With this platform we can measure tissue and/or cellular stiffness while simultaneously analysing fluorescent reporter expression.

Patients presenting with congenital aortic pathologies are another highly interesting patient population within the HVC, and will be identified by medical staff. These congenital patients will be invited to donate blood for pluripotent stem cell research. Supported by the existing ethical research framework at Maastricht UMC+, consent and blood tissue donation will be obtained in conjunction with standard patient care procedures. Peripheral blood mononuclear cells (PBMCs) will be isolated from whole blood samples and stored along with clinical and genetic information for the generation of induced pluripotent stem cell (iPSC) lines. These iPSC lines will be incorporated into the CARIM+HVC BioBank. Within SCRUM, we will facilitate the generation of novel iPSC lines for the purpose of studying congenital aorto–pathies, including Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, and other connective tissue disorders.

Research pillar 2: Differentiation of vascular cells

In this research pillar we aim to develop vascular grafts that can be used to study ‘vascular disease in a dish’. For this purpose, we collaborate with the MERLN Institute for Technology-Inspired Regenerative Medicine and have developed a device that can culture cells in a tubular structure and under flow. The first ideas centred around the development of such a model, after which diseases such as vascular calcification could be induced. **Figure 3** shows some pilot results, where we successfully produced and cultured the VSMCs in a tubular structure and were able to perfuse the system, which was performed in the context of the Regenerative Medicine crossing border consortium (RegMed XB) and in collaboration with MERLN. VSMCs were cultured under flow and were stimulated to calcify. Staining with Alizarin Red (calcification) showed positivity located in proximity to the VSMCs, which is indicative of pathological calcification build-up.

HIGHLIGHT DIVISION VESSELS

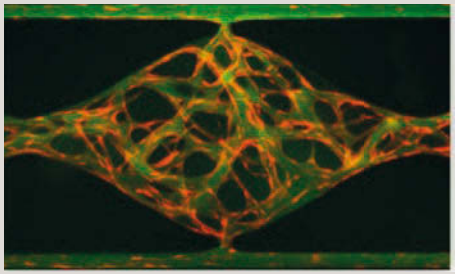


FIGURE 4
Vascularised micro-organism
A representation of spontaneous vessel formation in the VMO.

Additionally, smaller vessels, such as the 'vessel on a chip model', have been developed in collaboration with Prof. Hughes (visiting professor at CARIM; UC Irvine). The vascularised micro-organ (VMO) requires the use of stem cells which develop into spontaneously arranged microvessels (**Figure 4**). Our iPSC biobank can be used to differentiate towards the development of vascular cells (iVascular cells). iVascular cells will be applied in the VMO system to study disease development. iVascular cells that we aim to develop include iECs from different vascular beds (i.e arterial, venous and capillaries) as well as iVSMCs of different embryonic origins to investigate characteristics in relation to coagulation (in collaboration with the Division Blood), stiffness, functionality, and remodelling of the scaffold.

The 'vascular grafts and VMO' can be directly used to study molecular or pathological pathways affecting vascular disease. Furthermore, this research will connect researchers studying small vessel disease linked to pathologies such as chronic kidney disease (Dr Ed Eringa), The Maastricht Study (Dr Marleen van Greevenbroek) and type 2 diabetes (Prof. Casper Schalkwijk).

Research pillar 3: Improving functionality of regenerative vessels

In this final work package, we will initiate work on CRISPR/Cas9 technology to enhance its use in studying vascular biology and disease mechanisms. CRISPR/Cas9 genetic engineering will enable the creation of isogenic controls, providing a more thorough understanding of the role of mutations and molecular mechanisms in monogenic aortopathy. Additionally, CRISPR/Cas9 gene editing will be employed to disrupt functional pathways or modify specific genetic targets involved in vascular disease.

Using this technology, we will be able to assess the functionality of the scaffolds developed (from RP2), using techniques that evaluate vessel compliance and integrity, including myograph measurements, nano-indentation and two-photon microscopy (in collaboration with Dr Koen Reesink, Biomedical Engineering). This research will investigate how modulation of molecular pathways impacts vascular graft viability. Larger scaffolds will be used to explore their properties concerning vessel, tissue, and cellular stiffness. A recently developed mechanosensor (YAP/TAZ sensor) incorporated into iVSMCS will facilitate the study of interactions between cells and the extracellular matrix.

Ultimately, diseased vascular specimens obtained from vascular surgery will be used to study regenerative processes. Removing diseased cells or decalcifying vascular tissue is crucial for reimplantation of host tissue or graft development. Reusing patient vascular tissue is advantageous because it eliminates the need for donor tissue and avoids immune system activation. Radiobiochemical cardiovascular imaging will be applied, using various ex vivo techniques, such as tonometry (to measure vessel compliance), development of novel PET/CT tracers (^{18}F-NaF), and imaging with fluorescently labelled tracers (such as annexin A5, fetuin-A, and CCL5) to assess apoptosis, calcification, and inflammation, respectively.

INTERVIEW

5X CARDINNOV

ERA4HEALTH PROGRAMME

5x CARDINNOV

Five projects involving CARIM researchers have been awarded a grant within the ERA4Health programme CARDINNOV: ‘Research targeting development of innovative therapeutic strategies in cardiovascular disease’. The ERA4Health partnership is a European partnership within the Horizon Europe programme for innovative treatments in the field of cardiovascular disease. The partnership aims to fund international research in the areas of cardiovascular disease, nanomedicine and nutrition, health and prevention, over a seven year period.

GENETIC CHANGES IN THE BLOOD

Dr Job Verdonschot, researcher and trainee clinical geneticist, is going to investigate the genetic changes in blood cells in order to improve the understanding of heart failure. Heart failure means that the heart no longer manages to adequately pump the blood throughout the body. He investigates how changes in these genes contribute to an inflammation in the body which ultimately affects the cardiac muscle. As Job explains: “What we see is that patients with heart failure often have a latent inflammation, but as yet we know little about the causes. Recent research found that changes in the genes of blood cells might play a role. Although such genetic changes occur in many people without causing problems, we think that major changes cause inflammations and so are part of the disease mechanism.” Job will therefore use a large database of patients with diastolic heart failure to investigate how frequent these genetic changes are. He will also examine the inflammation in mice with this genetic change. “This way we hope to find out whether anti-inflammatory drugs could help to reduce symptoms in people with this mutation in their blood cells and slow down the deterioration due to their heart failure, and what anti-inflammatory drugs we should use.”

VARIOUS TYPES OF INFLAMMATION

Dr Vanessa van Empel, cardiologist and researcher, will be investigating how heart failure can be prevented or slowed down. She too will look at the role of inflammatory reactions. “What we want to know is whether there are subgroups of patients each with their own inflammatory mechanism, and whether this affects the way the heart functions. If the inflammatory reactions differ, the treatment effects may also differ. Vanessa previously set up a large cohort and database containing data of patients with heart failure, for the purpose of scientific research. It is this database that Job hopes will provide answers to his research questions as well. Both Job and Vanessa will collaborate in these projects and will now be further expanding the database: “We will be inviting back all patients in our database and collect blood samples from them. We will extract the white blood cells from these samples to further investigate the inflammatory reaction.” The ultimate goal is to find a better way to treat heart failure.

ENABLING THE CARDIAC MUSCLE TO REPAIR ITSELF

Prof. Leon de Windt, professor of molecular vascular biology, aims to help the cardiac muscle repair itself after a heart attack. “In a heart attack, the cardiac muscle gets damaged because it doesn’t receive enough oxygen, which is usually due to a blocked blood vessel”, explains Leon. “The problem is that the cardiac muscle cannot repair itself, which means that a heart attack causes permanent damage to the heart. But some animals, such as zebrafishes and African spiny mice, do have this ability.” Leon will try to understand which genes are responsible for this ability of the cardiac muscle to repair itself. He wants to use this knowledge to develop a gene therapy and find out if this can improve the natural capacity of the human heart to repair itself. He is going to test this on organoids, small versions of the human heart developed from human stem cells, as well as on thin slices of human cardiac muscle tissue.

SUDDEN EXACERBATION OF HEART FAILURE

Dr Miranda Nabben, assistant professor specialising in cardiac metabolism, is concentrating on the treatment of sudden exacerbations of heart failure. If patients with heart failure feel symptoms like dyspnoea rapidly worsening, this is called acute decompensation of the heart failure. These people often need to be admitted to hospital, but there is as

yet no effective treatment available. That is because the cause of the exacerbation is unclear, although there are some indications. As Miranda explains: “It seems that changes in certain metabolic proteins play a major role in the exacerbation of heart failure. A new drug that counteracts these changes has been shown to improve cardiac function in test animals.” Her research on rats with heart failure focuses on understanding the disruptions in these proteins. “We first want to understand the way the disease develops and find out how drugs can counteract these changes. We do this at various moments in time, to determine when the treatment is most effective.” In addition to her research on rats, Miranda also uses organoids to study heart failure in human cells. “This way we hope to find a drug that can reduce the exacerbation of heart failure.”

RESTORING THE DISRUPTED INFLAMMATORY RESPONSE

Dr Marleen van Greevenbroek, medical biologist and epidemiologist, will investigate how the body restores its balance after an inflammatory response. A latent inflammatory response appears to play a part in people who, despite being effectively treated for risk factors like hypertension or a high cholesterol level, still develop a cardiovascular disorder. “Although there are drugs that can reduce the inflammatory response, thereby preventing or repairing vascular damage, they can increase the risk of infections”, explains Marleen. “That’s why we don’t focus on suppressing the inflammation, but on resolving the inflammatory response after it’s done its job.” To this end, she investigates special compounds in the blood that promote the restoration of balance after inflammations. These substances are called ‘specialised proresolvin mediators’. “Using data from The Maastricht Study, we aim to find out whether people who have higher levels of these substances in their blood are at lower risk of cardiovascular disease. We also investigate whether genes that are involved in the production and functioning of these substances, influence the risk of cardiovascular diseases.” Understanding the mechanism the body uses to resolve an inflammatory reaction can help to further reduce the risk of cardiovascular disease.

ERA4Health promotes international research by granting subsidies to European partnerships, including those in the field of cardiovascular disease.

EDUCATION AND TALENT DEVELOPMENT

04

INTRODUCTION

CARIM offers a flexible and integrated education and training programme that suits the individual ambitions of its students and PhD candidates. The clinical and preclinical staff of CARIM is intricately involved in the development and execution of the education programmes of the FHML bachelor and master studies of Biomedical Sciences, Medicine, and the Physician-Clinical Investigator Programme (MSc/MD). CARIM also contributes to the education programme of the Faculty of Science and Engineering. In addition, CARIM's staff is involved in the design of a contiguous and state-of the-art PhD (doctoral) training programme. The content of the PhD education programme has been developed by CARIM's leading researchers, while its framework has been created by senior educators at Maastricht University, who have earned an excellent international reputation for their didactic system based on problem-based learning.

RESEARCH MASTER

In the master programmes offered at FHML, students are informed about CARIM and the programmes of the other FHML research institutes during the start of the master phase. CARIM staff members actively participate in the design and execution of the teaching programme in master programmes. Students can attend institute specific lectures and parallel programmes organised by researchers. In the second year, students who are attracted to cardiovascular research can do their senior research internship and master thesis at CARIM. These internships are also accessible for students from other master programmes, provided that they have an adequate background. Successful master students can subsequently pursue 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 Basic Sciences masters. At the beginning of 2023, a total of 355 PhD candidates (both internal as well as external) were enrolled in our PhD programme. In 2023, 57% of our PhD candidates came from abroad, creating an exciting multicultural and international atmosphere. To advance cardiovascular knowledge and the treatment of cardiovascular disease, CARIM considers basic and clinical research equally important, and thrives on research at their interface. 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 PhD training programme is to support PhD candidates in developing into independent and mature 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 institute specific courses, to attend seminars and master classes, and provide support from a buddy (a senior PhD candidate) and a coach (an independent senior faculty member). PhD candidates are encouraged to visit symposia to present their own research on national and international podia. In 2023, 37 new internal PhD candidates began their trajectory at CARIM.

POSTGRADUATE PROGRAMMES

The expertise of the three CARIM divisions is transferred to international colleagues through three clinical postgraduate programmes in strong collaboration with the Heart+Vascular Center: CAS-AM (Blood), EVC (Vessels) and DAS-CAM (Heart). CAS-AM (Certificate of Advanced Studies in Antithrombotic Management) is designed specifically for physicians who are active in the management of patients with thromboembolic diseases and have the ambition to improve their knowledge and skills in order to become leading professionals in antithrombotic management. The EVC (European Vascular Course) aims to provide outstanding training and education for specialists in arterial, venous, vascular access and cardiovascular fields. DAS-CAM (Diploma of Advanced Studies in Cardiac Arrhythmia Management) trains future leaders in cardiac electrophysiology by integrating state-of-the-art cardiac arrhythmia management with leadership skills, biostatistics and health technology assessment. All three professional development courses are supported by international societies. CAS-AM is endorsed by the International Society on Thrombosis and Hemostasis (ISTH) and the European Congress on Thrombosis and Haemostasis (ECTH); EVC is endorsed by the Aortic Association and Vascular International; and DAS-CAM is endorsed by European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC).

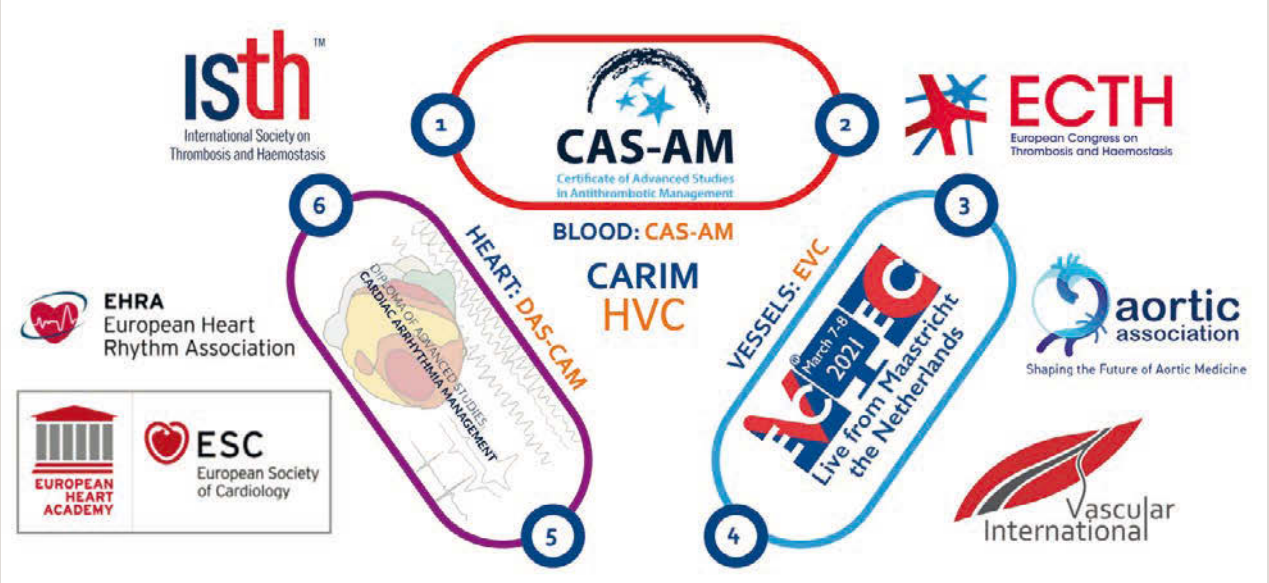
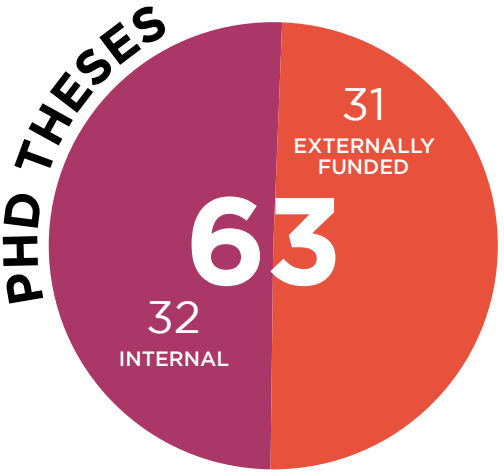
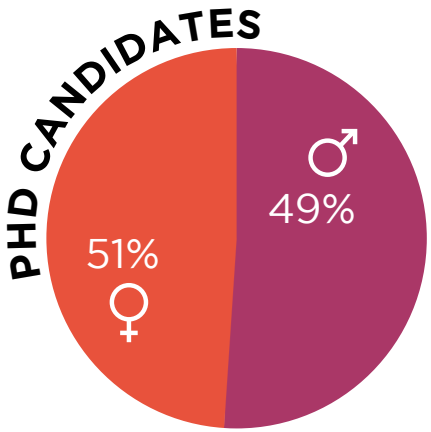


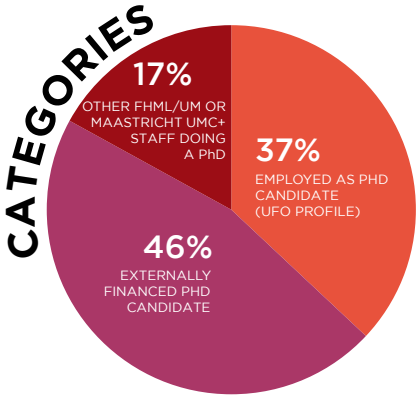
FIGURE CARIM divison structure with professional education

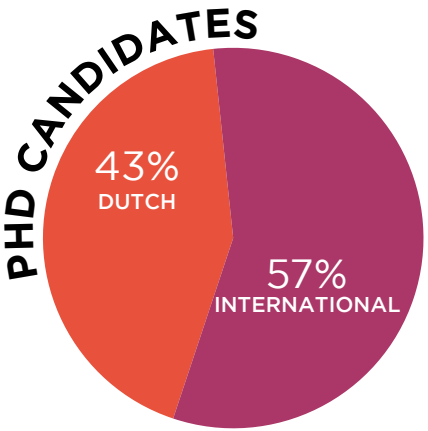
PHD STATISTICS

In 2023, 32 internally funded and 31 externally funded PhD candidates defended their theses at our institute. The male-to-female ratio within the group of PhD candidates appointed to CARIM at the start of 2023 is nearly 50/50. Almost 60% of our PhD candidates come from abroad.









CARIM THESES 2023

Rachel Schreurs
Title: Towards improved organisation of care: Improving compression therapy for patients with DVT and CVD (CEAP3-5)
Supervisors: Dr A.J. ten Cate-Hoek, Prof. M.A. Joore, Prof. H. ten Cate
18 January

Sibel Altintas
Title: Mechanisms of cardiovascular disease as defined by cardiac computed tomography
Supervisors: Prof. H.J.G.M. Crijns, Prof. J.E. Wildberger
Co-supervisor: Dr B.L.J.H. Kietselaer
18 January

Mirko Belliato
Title: The use of extracorporeal life support systems in patients with acute respiratory insufficiency
Supervisors: Prof. R. Lorusso, Prof. J.G. Maessen
19 January

William van Doorn
Title: Rethinking biomarkers. Innovations in laboratory medicine
Supervisor: Prof. O. Bekers
Co-supervisor: Dr S.J.R. Meex
20 January

Meike Ploeg
Title: Stretch, stiffness, sensing, signaling & speed. Mechanical activation of cardiac fibroblasts
Supervisors: Prof. F.W. Prinzen, Dr F.A. van Nieuwenhoven
24 January

Jana Hegenbarth
Title: The transcriptomics of the ever-changing heart: From development to senescence
Supervisors: Prof. L. de Windt, Prof. M. Stoll
1 February

Guiseppe Nasso
Title: Minimally invasive epicardial ablation for atrial fibrillation: From unipolar to hybrid bipolar treatment with a new treatment line
Supervisors: Prof. R. Lorusso, Prof. J. Maessen
8 February

Anke Keijbeck
Title: Protocol biopsies after kidney transplantation: Emphasis on interstitial fibrosis/tubular atrophy and peritubular capillary loss in relation to clinical parameters
Supervisor: Prof. E. Biessen
Co-supervisors: Dr M. Christiaans, Dr C. Peutz-Kootstra (Gelre Hospital, Apeldoorn)
14 February

Natalie Jooss
Title: Targeting GPVI: impact of modulating platelet-collagen interactions on receptor signalling and thrombus formation
Supervisors: Prof. J. Heemskerk, Prof. Y. Henskens, Prof. S. Watson (University of Birmingham, UK)
Co-supervisor: Dr N. Poulter (University of Birmingham, UK)
16 February

Marco Moscarelli
Title: Advancements in minimally invasive cardiac surgery
Supervisors: Prof. R. Lorusso, Prof. J. Maessen
28 February

Camilla Soragni
Title: Next stop: screening-on-a-chip. Where biology meets scalability development of assays for placenta-on-a-chip models
Supervisors: Prof. L.J. de Windt, Prof. P.A. da Costa Martins
Co-supervisor: Dr C. Ping Ng (MIMETAS BV Oestgeest)
2 March

Alexandru Florea
Title: Sodium [18F]Fluoride positron emission tomography for non-invasive identification of micro-calcifications as marker of atherosclerotic plaque vulnerability
Supervisors: Prof. F.M. Mottaghy, Prof. M.E. Kooi, Prof. L.J. Schurgers
Co-supervisor: Prof. J. Bucerius (RWTH Aachen University)
8 March

Nicolò Mangraviti
Title: LncRNA Bigheart in cardiac disease and development
Supervisors: Prof. L.J. de Windt, Prof. M. Stoll
13 March

CARIM THESES 2023

Renske Olie
Title: Personalized antithrombotic treatment in high-risk patients with coronary artery disease
Supervisors: Prof. H. ten Cate, Prof. J.M. ten Berg
Co-supervisor: Dr P.E.J. van der Meijden
20 March

Alexander Gombert
Title: Applications of new specific biomarkers for organ damage after open and endovascular thoracoabdominal aortic aneurysm surgery as model for more accurate perioperative patients' surveillance
Supervisors: Prof. M.J. Jacobs, Dr B.M.E. Mees
Co-supervisor: Prof. G.W. Schurink
27 March

Isabella Provenzale
Title: The modulatory roles of collagen and endothelial cells on platelet function
Supervisors: Prof. J.W.M. Heemskerk, Prof. J.M. Gibbins (University of Reading, UK)
Co-supervisors: Dr P.E.J. van der Meijden, Dr C.I. Jones (University of Reading, UK)
28 March

Pieter Glerum
Title: Generic interchangeability: between science and regulation
Supervisors: Prof. C. Neef, Prof. D.M. Burger (Radboud University)
Co-supervisor: Dr M. Maliepaard (College ter beoordeling van geneesmiddelen, Utrecht)
29 March

Shunxin Jin
Title: The alternative pathway of the complement system in vascular comorbidities of obesity and type 2 diabetes
Supervisors: Dr M.M.J. van Greevenbroek, Prof. C.D.A. Stehouwer, Prof. C.G. Schalkwijk
3 April

Renée Brüggemann
Title: Unraveling hypercoagulability in COVID-19 and optimizing VTE management in the frail nursing home population
Supervisor: Prof. H. ten Cate
Co-supervisors: Dr A.J. ten Cate-Hoek, Dr B.P.A. Spaetgens
4 April

Anouk Gentier
Title: GLAmorous Protein S
Supervisors: Prof. T.M. Hackeng, Prof. L.J. Schurgers, Prof. F. Kiessling (RWTH Aachen University)
Co-supervisor: Dr S. Agten
4 April

Alicia Veninga
Title: Platelet heterogeneity: a colourful palette of populations
Supervisor: Prof. J.W.M. Heemskerk
Co-supervisors: Dr P.E.J. van der Meijden, Dr C.C.F.M.J. Baaten
20 April

Tobias Meßmer
Title: Decoding cultured meat production. The transcriptomic landscape of bovine satellite cells in proliferation and differentiation
Supervisors: Prof. M.J. Post, Dr J.E. Flack
21 April

Stefano Navarro
Title: Novel platelet glycoprotein VI and CLEC-2 targeting strategies: studies in humanized mouse models
Supervisors: Prof. J.W.M. Heemskerk, Prof. B. Nieswandt (University of Würzburg)
Co-supervisors: Dr M.J.E. Kuijpers, Dr H. Hermanns (University of Würzburg)
25 April

CARIM THESES 2023

Ilaria De Simone
Title: Novel mechanisms of platelet activation and sustained signalling through GPVI and PAR1
Supervisors: Prof. H. ten Cate, Prof. J.M. Gibbins (University of Reading, UK)
Co-supervisors: Dr P.E.J. van der Meijden, Dr C.I. Jones (University of Reading, UK)
26 April

Julia Wirth
Title: Uremia-induced effects on cardioregulatory mechanisms in the context of the cardiorenal syndrome
Supervisors: Prof. E. Biessen, Prof. J. Jankowski (UM/RWTH Aachen University)
Co-supervisor: Dr H. Noels (UM/RWTH Aachen University)
8 May

Yee Lai Lam
Title: Extending the frontiers beyond heat: Non-Thermal varicose vein treatments
Supervisor: Prof. C.H.A. Wittens
9 May

Vishnu Suresh Babu
Title: Identification of metabolic dysregulation and transcriptional networks in retinoblastoma reveals novel therapeutic targets. Functional insights and novel therapeutic strategies using a correlative multi-omics approach
Supervisor: Prof. S.R.B. Heymans
Co-supervisor: Dr Arkasubhra Ghosh (Narayana Nethralaya Eye Hospital, Bangalore, India)
15 May

Nikolas Rapp
Title: Chasing the perfect storm: Vascular calcification in chronic renocardiac syndrome
Supervisor: Prof. L. Schurgers
Co-supervisor: Dr A. Jaminon
16 May

Anne Willers
Title: Bleeding-related conditions and complications in extracorporeal life support
Supervisors: Prof. R. Lorusso, Prof. J.G. Maessen
Co-supervisor: Dr J. Swol
25 May

Thomas Bergmeijer
Title: Antiplatelet treatment in acute myocardial infarction from routine treatment to genotype guided personalized medicine
Supervisor: Prof. J.M. ten Berg
Co-supervisors: Dr V.H.M. Deneer (Universiteit Utrecht), Dr C.M. Hackeng (St. Antonius Ziekenhuis, Nieuwegein)
30 May

Ard van Veelen
Title: Treatment optimization in patients with non-small cell lung cancer
Supervisor: Prof. V.C.G. Tjan-Heijnen
Co-supervisors: Dr S. Croes, Dr P.C. Souverein (Utrecht University), Dr R.M.J.M. van Geel
1 June

Alessandra Sala
Title: Isolated tricuspid valve regurgitation: assessment, timing and surgical treatment
Supervisors: Prof. R. Lorusso, Prof. J.G. Maessen
Co-supervisor: Prof. M. De Bonis (IRCCS, Vita-Salute San Raffaele University, Milan, Italy)
6 June

Delia Fernández de la Fuente
Title: High throughput assessment of platelet signaling, function and inhibition
Supervisor: Prof. J.W.M. Heemskerk
Co-supervisors: Dr M. Kuijpers, Dr A. García (Universidade Santiago de Compostela, Spain)
19 June

CARIM THESES 2023

Evelien Vandercappellen
Title: Physicial activity, sedentary behaviour and markers of cardiovascular and brain diseases; Does one size fit all?
Supervisors: Prof. C. Stehouwer, Dr. A. Koster
Co-supervisor: Dr Ronald Henry
3 July

Maurice Halder
Title: Dissecting mechanisms of heart failure and in-stent restenosis using fate tracing and scRNA-seq
Supervisors: Prof. L.J. Schurgers, Prof. R. Kramann (RWTH Aachen University)
5 September

Mohamed Rahouma Ahmed
Title: In-depth clinical investigations over cardiac tumors in adult patients
Supervisors: Prof. R. Lorusso, Prof. J.G. Maessen
Co-supervisor: Prof. M. Gaudino (Weill Cornell Medicine, USA)
5 September

Robin Colpaert
Title: Of mice and men in ACM: novel models and biomarkers for arrhythmogenic cardiomyopathy
Supervisor: Prof. L.J. de Windt
Co-supervisor: Dr M. Calore
7 September

Robert Dzhanaev
Title: Fetuin-a-based theranostics in ectopic calcification
Supervisors: Prof. L.J. Schurgers, Prof. W. Jahnen-Dechent (RWTH Aachen University)
12 September

Matteo Nardin
Title: Implications of genetics and major risk factors on platelet morphology, platelet aggregation and their relationship with coronary atherosclerosis
Supervisors: Prof. A.W.J. van 't Hof, Prof. J.M. ten Berg
Co-supervisor: Prof. G. De Luca (University of Messina, Italy)
15 September

Hilaire Cheung
Title: Deciphering glycoprotein VI signalling in platelet activation: integration of functional and computational modelling data
Supervisors: Prof. J.W.M. Heemskerk, Prof. S.P. Watson (University of Birmingham, UK)
Co-supervisor: Dr N.S. Poulter (University of Birmingham, UK)
27 September

Jayaprakash Shenthar
Title: Right ventricular angiography in permanent pacemaker implantation and in management of cardiac perforations
Supervisors: Prof. T. Delhaas, Prof. K. Vernooy
3 October

Christophe Kuppe CUM LAUDE
Title: Unlocking the Complexities of Human Kidney and Heart Disease: An Integrative Single Cell and Spatial Analysis
Supervisors: Prof. L.J. Schurgers, Prof. R. Kramann (RWTH Aachen University)
4 October

Joana Alves da Silva
Title: MiR-199b and the hypertrophic heart: a journey across species
Supervisors: Prof. P.A. da Costa Martins, Prof. L.J. de Windt
4 October

Samantha Pasca
Title: An overview in acquired hemophilia A: a rare but complicated disease
Supervisors: Prof. H. ten Cate, Prof. P. Mannuccio Mannucci (University of Milan, Italy)
Co-supervisor: Dr E. Zanon (University of Padua Medical School, Italy)
9 October

Abdulrahman Mohamed
Title: Contribution of genetic and environmental factors to a prothrombotic phenotype in native Saudi population with a focus on thrombin generation
Supervisors: Prof. H. ten Cate, Prof. B. de Laat
Co-supervisor: Dr M. Ninivaggi
11 October

CARIM THESES 2023

Cecilia Tetta
Title: Lung metastases from soft tissue sarcoma
Supervisors: Prof. S. Gelsomino, Prof. J.G. Maessen
Co-supervisor: Dr M. Rocca
16 October

Luuk Heckman
Title: Pacing the heart: one site fits all?
Supervisors: Prof. F.W. Prinzen, Prof. K. Vernooy
Co-supervisor: Dr J.G.L.M. Luermans
26 October

Bart van Sloun
Title: Modelling of postprandial glucose and insulin dynamics: the role of amino acids
Supervisors: Prof.*ir* I.C.W. Arts, Prof.*ir* N.A.W. van Riel (Eindhoven University of Technology)
Co-supervisor: Dr G.H. Goossens
27 October

Jules Olsthoorn
Title: Personalized Treatment in Mitral Valve Surgery
Supervisor: Prof. J.G. Maessen
Co-supervisor: Dr P. Sardari Nia
27 October

Adele Ruder
Title: Origin versus Context Defining Key Determinants of Human Macrophage Function in Health and Disease
Supervisors: Prof. E.A.L. Biessen, Prof. J.C. Sluimer
Co-supervisor: Dr L. Temmerman
31 October

Amée Buziau
Title: Combatting the Fructose Epidemic Fruitful or Fruitless?
Supervisors: Prof. M.C.G.J. Brouwers, Prof. C.D.A. Stehouwer, Prof. C.G. Schalkwijk
13 November

Sofia de la Puente Secades
Title: Vascular calcification in chronic kidney disease: vitamin K deficiency and new mediators
Supervisors: Prof. L. Schurgers, Prof. J. Jankowski (RWTH Aachen University), Prof. J. Floege (RWTH Aachen University)
14 November

Dominique Verhaert
Title: Integrating novel care approaches for atrial fibrillation patients undergoing ablation
Supervisors: Prof. K. Vernooy, Prof. U. Schotten
Co-supervisors: Dr D.L. Linz, Dr R.J. Beukema (Radboud University)
16 November

Uyen Chau Nguyen
Title: Multi-modality imaging in cardiac resynchronization therapy: *In silico* and *in vivo* analyses
Supervisors: Prof. F.W. Prinzen, Prof. K. Vernooy, Prof. A. Auricchio (Università della Svizzera Italiana, Switzerland), Prof. R. Krause (Università della Svizzera Italiana, Switzerland)
22 November

Bram Kremers
Title: Defining atherothrombotic risk in peripheral artery disease
Supervisor: Dr H. Spronk
Co-supervisors: Dr A.J. ten Cate-Hoek, Dr B.M.E. Mees
24 November

Elena Caporali
Title: Assessment of different interventional treatments of aortic valve diseases
Supervisors: Prof. R. Lorusso, Prof. J.G. Maessen
6 December

CARIM THESES 2023

Eva Harlacher
Title: Increased cardiovascular risk in patients with chronic kidney disease: Insight into mechanisms and mediators of kidney-heart crosstalk
Supervisors: Prof. E.A.L. Biessen, Prof. J. Jankowski (UM/RWTH Aachen University), Prof. L.M. Blank (RWTH Aachen University)
Co-supervisor: Dr H. Noels (UM/RWTH Aachen University)
12 December

Mohamed Kassem
Title: Intraplaque Hemorrhage on carotid MRI in stroke patients: on the road towards clinical application
Supervisors: Prof. E. Kooi, Prof. R. van Oostenbrugge
12 December

Xiaodi Zhang
Title: Interplay of methylglyoxal and immune cells: implications for type 2 diabetes?
Supervisor: Prof. C.G. Schalkwijk
Co-supervisor: Dr K. Wouters
13 December

Anne-Marije Hulshof CUM LAUDE
Title: Innovative applications of global assays of hemostasis
Supervisors: Prof.*ir* Y.M.C. Henskens, Prof. H. ten Cate
Co-supervisor: Dr B.C.T. van Bussel
15 December

Jennifer Monereo-Sánchez
Title: Segmenting the human brain in population-based studies: Methodological considerations and clinical applications in diabetes, depression, and dementia
Supervisors: Dr M.T. Schram, Prof. D.E.J. Linden, Dr J.F.A. Jansen
18 December

Nikki Werkman
Title: Type 2 diabetes beyond glycaemic control: the impact of disease severity and therapy
Supervisor: Prof. C.D.A. Stehouwer
Co-supervisors: Dr J.H.M. Driessen, Dr J.T.H. Nielen
21 December

Ozan Yazar
Title: Fenestrated and Branched Stent-grafts for Treatment of Complex Aortoiliac Aneurysms
Supervisor: Prof. G.W.H. Schurink
Co-supervisor: Dr B.M.E. Mees
22 December


CARIM 35TH
ANNIVERSARY
LUSTRUM PARTY


PHOTOS


PHOTOS











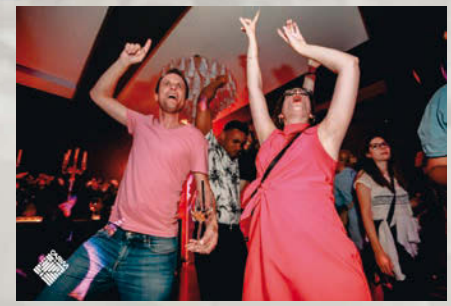


VanMelick










PHOTOS










































DISSERTATION PRIZE 2022

The CARIM Dissertation Prize 2022 has been awarded to Dr *ir* **Rob Holtackers** (Depts of Radiology and Nuclear Medicine) for the thesis 'Visualising the Invisible: Dark-Blood Late Gadolinium Enhancement MRI for Improved Detection of Subendocardial Scar'. In his PhD thesis, Rob describes the physical principles of magnetic resonance imaging and, in particular, the development of a novel method that increases the scar-to-blood contrast in the heart, called 'dark-blood late-gadolinium enhancement'. The dissertation contains many aspects of excellence: Rob examined feasibility issues, provided histological validation in a translational manner, developed clinical applications, and included four clinical case reports in which his methods were used. In most of these studies, he was the leading researcher, and through his efforts, his novel approaches became directly applicable on MRI scanners worldwide, without the need to adapt local systems or install software. Not only did he prevail individually, but he also proved to be a team player. As an example: the introduction of interventional MRI at Maastricht UMC+, to which Rob contributed significantly, was awarded the 2022 NWO Team Science Award. Additionally, he has received many more scientific awards, fellowships and recognitions.

KNOWLEDGE TRANSFER

CARIM COURSES

In 2023, the CARIM Courses were scheduled in two consecutive weeks. From 12 until 16 June the course 'Heart Failure research' was organised by Dr Vanessa van Empel, Prof. Blanche Schroen and Dr Twan van Stipdonk. This course delved into clinical and preclinical methodologies essential for advancing our understanding and treatment of heart failure. It emphasised the intricacies of translational research, extending beyond the foundational knowledge of heart failure.

The course 'Non-invasive Cardiovascular Imaging was organised by Dr *ir* Rob Holtackers and Prof. Joachim Wildberger from 19 until 23 June. The aim of this course was to provide insight into the basic principles and cardiovascular applications of various non-invasive imaging methods. The course focused on the most frequently applied imaging modalities, including ultrasound, CT, PET and SPECT, X-ray angiography, MRI,

and hybrid imaging modalities. Aspects covered during this course were the basic physical principles, the imaging characteristics, the requirements for human and animal studies, and the possibilities and limitations of each imaging modality in relation to specific cardiovascular research questions.

Furthermore, a workshop on Science Communication was arranged for all CARIM PhD candidates and a social activity was organised by I'MCARIM. In total, nearly 40 PhD candidates participated in this year's CARIM courses.

CARDIOVASCULAR GRAND ROUNDS MAASTRICHT

The Cardiovascular Grand Rounds are a lecture series organised since 2010 by CARIM researchers. In recent years, the scientific organisation is in the hands of a broad committee representing the CARIM divisions and the range of clinical to basic research. Additionally, I'MCARIM plays a vital role in involving younger researchers by promoting lectures and organising workshops with the speakers. We continue to be excited about offering engaging lectures and featuring excellent speakers.

In 2023, a total of 18 speakers were hosted, including excellent lectures from CARIM researchers and more than half from other institutes, primarily abroad. We are grateful for the financial support from *Stichting Annadal* and *Stichting ter Bevordering van Cardiovasculair Onderzoek en Onderwijs*. Special thanks go to Jordy Heijman for his outstanding organisational support. Additionally, Miranda Nabben and Vanessa van Empel are welcomed as the new daily organisers, joining Blanche Schroen and Lilian Skiba.

Since the start, the lectures have been held on Friday mornings from 8 to 9 AM. To make the series more accessible to the broader CARIM community, starting in September 2024, they will be moved to lunchtime on Tuesdays from 12 to 1 PM.

CARIM SYMPOSIUM 2023

The CARIM annual scientific symposium was held on Wednesday 29 November. The morning session featured presentations from recent laureates on their research projects, followed by a discussion on the Ministry of Education, Culture, and Science's Topsector Plan for Medical & Health Sciences. In the afternoon, Prof. Paul Shiels from the University of Glasgow delivered a lecture on the exposome of ageing. This was followed by a presentation from the Harry Crijns Research Grant winner and the results of the CARIM survey on employee experience conducted earlier this year. As in previous years, a significant portion of the programme was dedicated to a poster session, where CARIM scientists showcased their latest research findings.

This year's Robert Reneman Lecture, in honour of the founding Scientific Director of CARIM, was delivered by Prof. Mary Cushman. Prof. Cushman is University Distinguished

Professor of Medicine and Pathology & Laboratory Medicine at the Larner College of Medicine at the University of Vermont. With over 27 years of continuous NIH funding, her research focusses on the causative factors for heart disease, stroke, cognitive impairment and venous thrombosis using molecular epidemiology approaches. More recently, she has been involved in designing and conducting treatment trials in COVID-19. She is the inaugural Editor-in-Chief of *Research and Practice in Thrombosis and Haemostasis*, a journal of the International Society on Thrombosis and Haemostasis. Prof. Cushman has mentored over 30 research students, most of whom have continued in academic careers. She has been an invited speaker or visiting professor at various universities and other organisations more than 130 times. In 2020, she received the AHA's Award of Meritorious Achievement for her efforts in encouraging women to pursue careers in science, technology, engineering, and math (STEM) fields.

Finally, the CARIM prizes were awarded and the CARIM priori were drawn by lot. As of January 2023, Nynke van den Akker and Job Verdonschot have joined the CARIM Executive Board for a one-year term. The following posters received awards:

- Division Blood: Titus Lemmens - Native Vascular Extracellular Matrix Coating for in vitro Cardiovascular Models;

- Division Vessels: Sabine Daemen - In-depth immunophenotyping of immune cells in cardiometabolic disease with spectral flow cytometry;

- Division Heart: Job Stoks - Multimodal image integration can improve management of ventricular tachycardias.

OTHER CARIM LECTURES, SEMINARS AND SYMPOSIA 2023

Complementary to the Cardiovascular Grand Rounds Maastricht and the CARIM annual scientific symposium, several lectures, seminars and conferences were organised by our staff in 2023. Some of them are presented below.

The **Cardiorenal Seminars** is a joint lecture series of CARIM and the Institute of Cardiovascular Research (IMCAR) of RWTH Aachen University (headed by Prof. Joachim Jankowski) and provides a platform for international top scientists in the fields of vascular biology and nephrology to present their recent work. The lecture series alternates between Aachen and Maastricht. In 2023, six keynote lectures were given by Jaap van Buul (Amsterdam UMC, 16 March), Stefan Rudloff (University of Bern, 20 April), Ferdinand le Noble (Karlsruhe Institute of Technology, 15 June), Candice Roufosse (Imperial College London, 11 August), Carolin Schneider (RWTH Aachen University, 21 September) and Marcela Ramos (Federal University of ABC, 16 November).

On 28 March, the **workshop 'Science Communication'** was organised in collaboration with the the Departments of Marketing & Communication of FHML and Maastricht UMC+. The workshop featured interactive discussions on translating research into accessible language, using social media to share research, and effectively engaging with the media.

The **Maastricht Immunology Seminar Series** brings together researchers from Maastricht who are interested in immunology and inflammation. These informal meetings are ideal for expanding local networks, and to share research techniques and experiences. Each seminar features an external speaker and two PhD candidates or postdocs from Maastricht

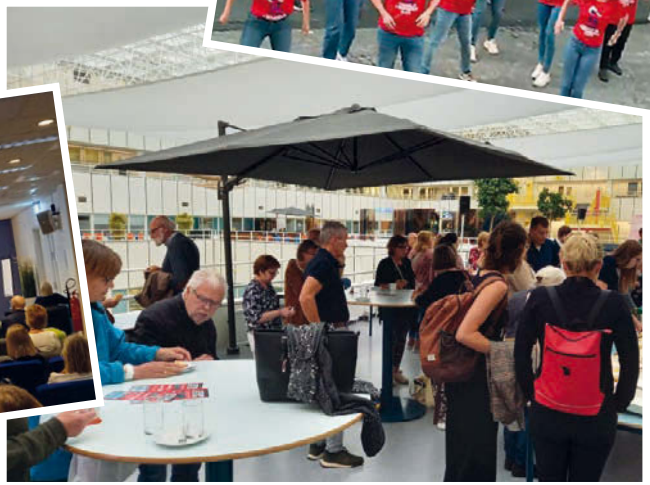
present their research. The meetings are organised by Dr Kristiaan Wouters (Dept of Internal Medicine) and Dr Lotte Wieten (Dept of Transplantation Immunology). The organising committee also includes young researchers from different research institutes: Dr Sabine Daemen (Dept of Internal Medicine), Dr Denise Habets (Depts of Transplantation Immunology), and Dr Marina Damas (Dept of Psychiatry and Neuropsychology). In 2023, two meetings were held. In June, a special edition focussed on the use of flow cytometry in research, with presentations by Dr Kristiaan Wouters, Denise Habets (Dept of Transplantation Immunology), and Meike Thijssen (Dept of Pathology). In October, Dr Emiel van der Vorst (Aachen) was invited speaker, local speakers included Laura Kempen (Dept of Pathology) and Michelle Koster (Dept of Psychiatry and Neuropsychology).

The workshop **'Crowdfunding@UM: How to create a successful campaign?'** was held on 11 April. In this workshop Guido Vanderbroeck, Senior Advisor at the University Fund Limburg/SWOL, provided a general introduction to crowdfunding along with tips and tricks for launching a successful campaign.

On 1 October, the 15th edition of the event **'Loop met je Dokter'** was organised by the Health Foundation Limburg, in collaboration with doctors from Maastricht UMC+, Zuyderland and regional general practitioners. The walking event allows patients to engage in a different, informal way where doctors show the importance of a healthy lifestyle by setting a good example themselves. Several CARIM members acted as team captains. In total, € 60,368 was raised for groundbreaking research into cardiovascular diseases.

On 12 October, Dr Kristiaan Wouters, Dr Lieve Temmerman and Erwin Wijnands (Dept of Pathology) organised a **Flow Cytometry course**. The participants were first-time users with little or no experience in flow cytometry. The morning session consisted of a theoretical course covering a general introduction to flow cytometry, the latest technological advances in the field, and information on the flow cytometry capabilities available at Maastricht. In the afternoon, participants engaged in hands-on practical sessions to learn how to operate the flow cytometers and to become familiar with data acquisition, analysis, and troubleshooting.

CARIM, in collaboration with the HVC, orchestrated a programme for **World Thrombosis Day** on 13 October for the tenth year, aiming to shed light on thrombosis. This year, special attention was given to exercising against thrombosis. The event started with a well-attended information market in the hall of the Maastricht UMC+. Subsequently, several speakers provided insight into various factors related thrombosis.
Dr Renske Olie, a vascular medicine internist, provided information on 'hereditary and acquired risk factors for thrombosis.' Aaron Iding, a medical researcher, discussed what you can and cannot do after thrombosis. Dr Jelle Posthuma, a trauma surgeon in training at Amsterdam UMC, addressed the intersection of elite sports and thrombosis consequences. Eline Boer, a journalist, and online marketer, alongside Noa Smolenaars, an industrial designer, both co-founders of Thrombosis Survivors, shared insights into the journey to recovery. Finally, Tom van de Berg, an internist in training, engaged in a dialogue with a patient. To draw attention to thrombosis and the event, a flash mob took place on 6 October in Maastricht's Grote Staat (https://rtvmaastricht.nl/nieuws/artikel/flashmob-voor-aandacht-trombose-in-centrum).



On 30 October, the annual scientific meeting of **The Maastricht Study** took place at Maastricht UMC+. Pairs of senior and junior researchers showcased a diverse array of topics investigated within The Maastricht Study. Prof. Tilman Hackeng opened the meeting with an update on the study's progress, highlighting its origins in diabetes research and addressing financial challenges. This set the stage for fruitful discussions during the symposium. Prof. Martijn Brouwers discussed the impact of fructose on nonalcoholic fatty liver disease (NAFLD), followed by Zhewen Ren's examination of socioeconomic factors' association with liver health. Dr Sebastian Köhler and Jens Soeterbroek presented research on air pollution's effects on cognitive function and brain structure, utilising data from The Maastricht Study and the GECCO study. Dr Annemarie Koster and Jeroen Albers explored health inequalities in type 2 diabetes, focusing on the role of environmental factors. Dr Miranda Schram and Magdalena Beran discussed the Netherlands Consortium of Dementia Cohorts' aim to prevent dementia through pooled analysis of Dutch cohorts. Their presentation highlighted associations between plasma biomarkers of endothelial dysfunction and cognitive performance. Dr Marleen van Greevenbroek provided an overview of The Maastricht Study's current status and future plans, including a new data application app and a new data collection center. Prof. Andre Dekker delivered a keynote address on AI's potential in healthcare, emphasising its role in improving treatment decisions across various medical conditions. He advocated for a decentralised approach to data infrastructure, heralding a future of personalised and effective healthcare interventions.

Following the Cardiovascular Ground Rounds lecture of Dr Marit Westerterp on 3 November, a **Q&A session 'Beyond Dutch Borders: Exploring the World of International Research'** was organised.

On 6 November, a **CARIM+HVC guest lecture** titled 'Heart Rate Modifications in Aging Hearts - HFpEF, AF and Pieter Bruegel the Elder' was given by Dr Markus Meyer, University of Minnesota.

On 30 November, The CARIM working group on Diversity, Inclusivity & Social Safety organised the **lunch session 'Shining the Light on Gender Bias in Scientific Publishing: an Editor's Experience'** by Prof. Mary Cushman, to learn from her when it comes to equity, diversity and inclusion in scientific practice. As editor of the journal 'Research and Practice in Thrombosis and Haemostasis', Mary Cushman took a pro-active role to promote equal opportunity for women in scientific publishing.

On 11 December, Prof. Luca Saba, University of Cagliari, Italy, gave a **seminar on 'Carotid plaque imaging: What are the targets for the next future?'**

In 2023, several newly professors delivered their inaugural lectures, showcasing groundbreaking research in their respective fields. On 17 May, Prof. **Judith Sluimer** from the Department of Pathology presented her lecture titled 'A Breath of Fresh Air in Cardiovascular Research'. On 6 June, Prof. **Joost Lumens** from the Department of Biomedical Engineering delivered his inaugural lecture, 'Computational Cardiology: The Sensation of Simulation'. Finally, on 24 November, Prof. **Rory Koenen** from the Department of Biochemistry delivered his lecture, *'Ontsteking en trombose, eindelijk herenigd!'*.

CARIM'S DEVELOPMENT 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 fellowships at each step of their career, be it at bachelor, master, postgraduate, PhD or postdoc level. These grants will be enabled through our 'Harry Struijker-Boudier Award for Talented Academics' (HS-BAFTA). The HS-BAFTA programme 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 to 12 months during their Bachelor phase.

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

c. Talented future PhD candidates in Health, Medicine or Life Sciences, Postgraduates to bridge the time between graduation and the start of an official contract as a PhD candidate within CARIM. The fellowship must start within the first year after graduation and is open to students not yet contracted by or enrolled in a PhD programme.

The fellowship covers the candidate's full salary for 6 to 12 months including bench fee. For bachelor and master students the regular curriculum should be interrupted to perform the research project within CARIM.

2017 William van Doorn

2018 Jasper Demandt

2019 Mohamed Kassem

2020 Anne-Marije Hulshof, Yentl Brandt

2021 Daniek Meijs

2022 Peter Deissler

2023 Daria Majcher, Yesim Kaya

2. HS-BAFTA TALENTED PHD CANDIDATES

The fellowship is meant to support PhD candidates who want 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 up to 6 months supplemental living allowance per month and travel costs.

2018 Mueez Aizaz, Jens Posma

2019 Federica de Majo, Cengiz Akbulut, Walid Chayoua, Rogier Veltrop, Valeria Lo Coco, Rob Holtackers

2020 Stefan Reinhold, Anouk Geraets, Job Verdonschot, Raquel Videira, Jorik Simons, Anne Willers

2021 Kim Maasen, Job Stoks, Jordi Kocken, Renée Tillie, Rachel van der Velden

2022 Jerremy Weerts, Shaiv Parikh, Mitch Ramaekers, Deepak Balamurali, Vanessa Bröker, Bob Knapen, Maurits Sikking

2023 Aaron Iding, Eline Berends, Ellen Denessen

3. HS-BAFTA TALENTED POSTDOCS

The fellowship is intended for recently graduated CARIM PhD candidates. The fellowship is meant to keep top CARIM talents connected to our institute by giving the opportunity to go abroad, thereby establishing international cultural and scientific exchange and 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 fellowship covers the candidate's full salary for 12 months including bench fee. 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 either to acquire or increase international research experience, to broaden the laureate's professional network, and to enhance 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

2020 Federica de Majo

2021 Jens Posma

2022 Mohamed Kassem

2023 Amée Buziau

HS-BAFTA winners 2023

ROBERT RENEMAN LECTURE

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

1993	M. Verstraete	Leuven, Belgium
1994	J. Sixma	Utrecht, NL
1995	P. Vanhoutte	Courbevoie, France
1996	W. Schaper	Bad Neuheum, Germany
1997	P. Davies	Philadelphia, USA
1998	M. Pfeffer	Boston, USA
1999	Y. Nemerson	New York, USA
2000	V. Fuster	New York, USA
2001	M. Schneider	Houston, USA
2002	F. Rosendaal	Leiden, NL
2003	A. Zeiher	Frankfurt, Germany
2004	P. Poole-Wilson	London, UK
2005	D. Wagner	Boston, USA
2006	S. Wickline	St. Louis, USA
2007	J. Molkentin	Cincinnati, USA
2008	B. Furie	Boston, USA
2009	K. Walsh	Boston, USA
2010	J. Lusis	Los Angeles, USA
2011	W. Ouwehand	Cambridge, UK
2012	D. Kass	Baltimore, USA
2013	J. Yudkin	London, UK
2014	P. Reitsma	Leiden, NL
2015	S. Hatem	Paris, France
2016	S. Laurent	Paris, France
2017	J. Griffin	San Diego, USA
2018	M. Giacca	Trieste, Italy
2019	V. Ramachandran	Boston, USA
2020	H. Büller	Amsterdam, NL
2021	B. Casadei	Oxford, UK
2022	P. Stenvinkel	Stockholm, Sweden
2023	M. Cushman	Vermont, USA

PROFESSORSHIPS

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 (1935-2020), 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
2020 - 2023	Th. Münzel	Mainz, Germany

CARIM+HVC CHAIR

The programme is founded and funded by the CARIM together with the HVC and aims at strengthening the translational cardiovascular axis.

2020 - 2025	C. Hughes	University of California at Irvine

STICHTING TER BEVORDERING VAN CARDIOVASCULAR ONDERZOEK EN ONDERWIJS

2020	P. Kirchhof	University Heart and Vascular Center UKE Hamburg
2022 - 2023	P. Stenvinkel	Karolinska Institute Stockholm, Sweden

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

OTHER VISITING PROFESSORSHIPS

2016 - 2022	A. Baker	University of Edinburgh

INTERVIEW

GERRY NICOLAES AND KANIN WICHAPONG

Biochemists in the lead

‘Three times is a charm’, says the proverb, and the coordinators of the EU-funded PRAETORIAN training network can only agree. Gerry Nicolaes and Kanin Wichapong from the Department of Biochemistry received a grant from the Horizon Europe Marie Skłodowska-Curie research and innovation programme. “Our proposal was rejected twice and we got the chance to resubmit one year later”, Wichapong says. “Now I understand why the project coordinators I used to work with in these types of consortia were looking so stressed at times”, Nicolaes laughs.

'PRAETORIAN: EuroPean Training NetwoRks to TArget DAMPs and NETs: novel apprOaches in pRecision SepsIs pAtieNt care' is the full project title. It involves five academic partners (the universities of Maastricht, Paris, Münster, Uppsala, and the Institute for Biomedical Research Barcelona), seven partners from industry, four organisations representing the perspective of patients and society and two organisations for international dissemination and outreach. The topic: systemic inflammation and sepsis. "Many septic patients develop thrombosis. Until about seven years ago, people did not realise that these are two sides of the same coin. Inflammation and sepsis, or other types of atherosclerosis, have a lot in common with what we traditionally regarded as cardiovascular disease or thrombosis", Gerry says. He and Kanin have in fact been working on immunothrombosis and thrombo-inflammation for years. Their group at the Department of Biochemistry uses computational techniques to find and optimise new molecules, and studies how proteins involved in coagulation and inflammation interact.

NO DRUG AGAINST SEPSIS

The fact that there is to this day no cure for sepsis is what triggered their interest many years ago. Gerry: "There's not a single drug on the market aimed purely at sepsis. Treatment usually consists of antibiotics or fluids to raise the blood pressure, because if you go into shock, your blood pressure drops, which is an extremely serious and deadly medical condition. There are many factors that contribute to the disease. Everybody can get it and people can die within a matter of a few days, while having been perfectly healthy until then." Kanin: "The research group had been working on some proteins that are involved in sepsis, called extracellular histones, since 2010, and I then joined the group in 2013. We realised these proteins are important targets for sepsis and inflammation too. Within this consortium, we at Maastricht will focus on how these histones enter your circulation." Gerry adds: "Diagnostics is also a problem. There are several methods to detect a bacterial or viral infection, but these generally take a couple of days. And you don't have that time."

TRAINING FUTURE RESEARCHERS

Content-wise, the aim of PRAETORIAN is to find new treatments, and new diagnostic tools, for sepsis. While researching these, the project will also train ten PhD candidates from all over Europe: the next generation of researchers. Each one of the five participating universities will employ two PhD candidates, who will also do placements at other participating universities or companies. Kanin: "They can broaden their research scope, learn additional techniques, expand their network and so on." And the fact that the universities are not allowed to employ candidates who have been in their country for more than six months in the previous two years stimulates selecting students from abroad.

LITTLE SCIENCE SO FAR

At the time of the interview, the two are very busy arranging administrative matters for the consortium. "Little science so far. It takes quite some time to find our way around university regulations, but also looking for funding for the fourth year of the PhD projects, since the EU only funds for three years", Gerry says. In September, they plan to have all ten PhD candidates together on their first training session, and they are already looking forward to the annual meetings with the entire consortium. Gerry: "We did all the work for the grant, but we don't get more money than the others. So on an hourly basis, we get far less, but it's worthwhile anyway. You learn a lot and work with the people you've

selected yourself. That's fun. But I do understand now why the coordinators of the networks I participated in were always a bit stressed. We're very happy with the support from the CARIM office, which has experience coordinating these kinds of projects."

THE GOLDEN TIP

When asked for a tip on how to obtain a grant like this, they start with "having a good idea and a very clear aim. Find people with types of expertise that contribute to the goal and don't overlap. Make sure the proposal is written around the theme of educating new researchers, since it's a training network fund. And make sure plans are realistic". And then they reveal the golden tip. Gerry: "The first proposal we wrote all by ourselves, and we scored 92%. That wasn't good enough: you need to be in the top 5%. The research plans are probably of good quality in every proposal the EU receives, but they also want you to describe how you will set up the administrative side, how you guarantee equal opportunities and so on. You should not only organise it well, but also write it down well. In the end, we hired a company for the latter, which checked our application and advised us. It's a circus, and without a little luck you'll not succeed", he concludes.

IT'S A CIRCUS, AND WITHOUT A LITTLE LUCK YOU'LL NOT SUCCEED

HIGHLIGHT
DIVISION HEART

CAMILLA SORAGNI

Towards an hiPSC-CMs derived model of the heart

Cardiovascular diseases (CVDs) remain the foremost cause of death worldwide, based on WHO statistics. Due to the scarcity of human-derived material and the limitations of maintaining these samples due to the non-proliferative nature of cardiomyocytes, research to elucidate the mechanism underlying pathological conditions as well as to develop new therapeutics for cardiac diseases often relies on non-human models. Although these models have been a useful source of information to understand the aetiology and pathophysiology of cardiac diseases, differences between humans and these models in terms of the genetic background, cardiac morphology [1], action potential [2] and contraction capabilities [3] have limited the translational power of the non-human models.

Advancements in new techniques like culturing human-induced pluripotent stem cells (hiPSCs) have overcome these limitations, as these cells are patient-derived materials which use non-invasive techniques for sample collection to generate hiPSCs. This enables the generation of patient-specific cell lines to establish models with high disease specificity [4], [5], [6]. Thanks to the ability of hiPSCs to differentiate into the three germ layers, these cells are an infinite source of different cell populations.

hiPSCs have already proved to be an extremely valuable tool to study human patho-physiology at cellular level, also in the cardiac field [2], [6].

The first example of cardiomyocytes differentiated from hiPSCs (hiPSC-CMs) dates back to 2011 and utilised BMP4 and FGF2 to generate beating embryoid bodies [7][8]. A few years later, hiPSC-CMs cultured in monolayer form were prepared via temporal modulation of canonical Wnt signalling [9], which has become the leading way to generate hiPSC-CMs in a monolayer fashion. Multiple protocols, which differ in terms of complexity, type of inhibitors or exposure time, have been developed since the first examples. These protocols generally require around 12 days or more to establish hiPSC-CMs, and they can be followed by a phase in which the CM population is purified, which also facilitates the maturation of the cells. Overall, the procedure from hiPSCs to fully differentiated hiPSC-CMs can take up to 20-25 days.

Since hiPSC-CM differentiation and culture are expensive and lengthy processes, it seems reasonable to maximise data collection by exploiting non-invasive techniques that do not require cell collection or treatment. Acquisition of video

images of the culture using a camera and a bright-field microscope is an example of non-invasive data collection to evaluate the beating of cardiomyocytes without interfering with the experiment or the need for special equipment.

Together with other advanced cell-culture techniques such as spheroids, organoids, on-a-chip, 3D engineered tissue and bio-printed scaffolds, hiPSC-CMs aim to generate highly physiological in vitro models to mimic the human environment as closely as possible. In this context, it is not only the source of the cells which is important, but also the way in which the culture is maintained and the microenvironment in which this is done. The extracellular matrix (ECM) defines the microenvironment in vivo and is also a key factor for in vitro modelling. Indeed, ECM plays a role in the migration, differentiation and maturation of cardiac cells[10] and it has been shown that, in vivo, ECM goes through a series of chemical modifications after birth, which affect the electrophysiological properties of cardiac muscle [11], [12]. The gold standard for the culturing and differentiation of hiPSCs into cardiac lineage is the use of Matrigel, a basement membrane extracted from murine tumor [13] as the ECM [12]. Few studies have investigated the effect of physico-chemical properties of Matrigel on cell behaviour, in particular the stiffness of the matrix. In this regard, the literature has reported contradictory results, with certain studies reporting that intermediate to moderately high stiffness (around 50 kPa) promotes differentiation and contraction in CMs [14], [15], [16], while others have suggested that low (around 34 kPa) [17] or even super-low stiffness (around 0.6 kPa) [18] is ideal for the culture. Apart from the debate regarding the preferred stiffness of the Matrigel, it seems obvious that identifying the **optimal microenvironment** for culturing and differentiating hiPSC-CMs should always be considered.

Due to their nature as a patient-derived in vitro model, hiPSC-CM cultures find their most useful application in disease modelling and drug development, especially in the field of personalised medicine. In this research area, parallel testing of different conditions, or new or previously developed drugs, is a common procedure, which requires the use of multiple technical replicates per experiment. Generally, hiPSC-CMs are produced in 6- or 12-well plates [19] or culture dishes [9], but these platforms are not considered to be easily scalable, while 48- and 96-well plates constitute the right compromise between high-throughput need and manual handling feasibility. Scaling down the hiPSC-CMs culture from traditional flasks or 6-well plates to higher-throughput platforms makes the model a better tool for medium-scale testing, which fits in with the purpose of disease modelling and personalised medicine.

Here we present some data regarding the maximisation of data collection, finding the optimal microenvironment for hiPSC-CM differentiation and scaling down the process to proceed in the direction of generating a reliable hiPSC-derived in-vitro model of the heart.

MAXIMISING DATA COLLECTION

Acquisition of data throughout non-invasive or end-point assays is always a valuable option, especially in research that employs expensive high-maintenance models. An example of this in the context of in-vitro models is differentiated hiPSCs.

In Prof. Leon de Windt's group, we establish hiPSC-CMs by inducing the canonical Wnt signalling through GSK3 inhibition for mesodermal germ-line specification, followed by Wnt inhibitors to restrict the differentiation to cardiac lineages and a chemically driven metabolic selection to

purify the culture [20]. The entire protocol takes 25 days in total and requires different mediums and active compounds.

Possible approaches to collecting data without intervening in the culture are medium collection to investigate the release of biomarkers, metabolites to monitor physiological parameters, and image-based techniques which do not require labelling or incubation with fluorescent substances, such as bright field or phase-contrast microscopy. The latter is particularly suitable for hiPSC-CMs, thanks to the spontaneous contraction of these types of cells, which makes it possible to record video images of the beating cells for later analysis of the images, in order to extract important parameters regarding contractility.

There are various examples of the use of specific platforms developed to quantify the beating with expensive high-speed cameras [21], the use of Matlab codes [22] as well as specific software to analyse the videos [23].

Here we report a simple and cheap method to acquire video images of beating CMs (Figure 1.A) by using a standard camera and a bright-field microscope, and then to analyse the images by using a macro developed by Grune et al. [24] for use in the opensource imageJ program to extract information about beat time [sec], frequency [1/sec] and amplitude of the contractions [a.u.], as well as to allow certain parameters like the diastole and systole portions of the beating to be derived (Figure 1.B).

The analysis of the frames is used to generate a graph with the beating profile (Figure 1.C), with green and red indicating the local minimum and maximum for each individual peak, representing a beat. From this plot, various parameters are extracted and calculated (Figure 1.D). This non-invasive analysis can be used as a standard quality control (QC) to monitor and evaluate the success of the differentiation as well as the perpendicular or parallel assay to be used in the experiments.

OPTIMAL MICROENVIRONMENT

Identifying the optimal microenvironment for the culture and differentiation of hiPSC-CMs is crucial to establish reliable and physiologically relevant in-vitro models.

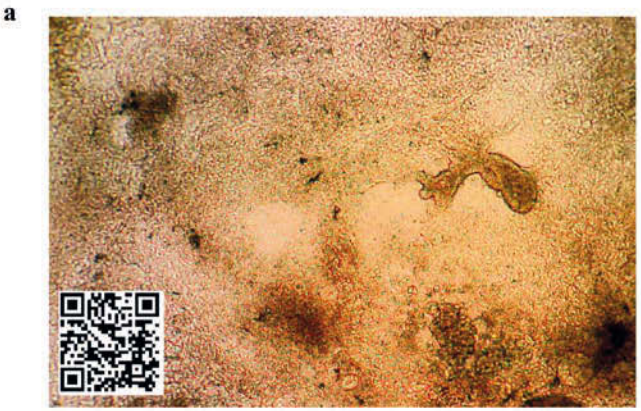
We tested the effect of storing the Matrigel on the differentiation outcome, in terms of the expression of cardiac markers and the contractile capability of hiPSC-CMs. We also decided to evaluate the expression of inflammation, to exclude the possibility that storing the Matrigel could be detrimental to the culture. We noticed a massive increase in GATA4 and NKX2-5 [25], [26], both capable of activating genes driving cardiac lineage differentiation, as well as cardiac troponin expression, which indicates the presence of functional CMs (Figure 2.a-c). Storing the Matrigel does not seem to affect the culture, as the inflammatory markers were considerably decreased, as in the case of ILB1, or were comparable, as the differences in IL6 and TNF-alpha were not statistically significant Figure 2.d-f). Video images of beating CMs were also acquired, and parameters were extracted using the MYOCETER macro for ImageJ (Figure 2.g-k). One observation is the number of beating CMs that could be extracted from the two conditions tested, and in fact, the same number of video images of beating hiPSC-CMs was acquired. The graphs depicted in Figure 2.g-i show the discrepancy in terms of numbers of datapoints per condition, with each data (dot) representing beating cells. Next to this, hiPSC-CMs cultured on stored Matrigel had shorter* beat times and higher frequency, characteristics generally linked to increased maturation [27]. The video

presented in Figure 2.j-k (by scanning the QR code) shows that in the stored version there is a bed of beating hiPSC-CMs with synchronised contractions.

Overall, this indicates that storing the Matrigel has a beneficial effect, and it is a promising parameter to tone to improve hiPSC-CMs cultures.

SCALING DOWN THE CULTURE TO INCREASE THROUGHPUT

Improving the throughput of in-vitro models is always preferable and in line with the tendency to develop complex models suitable for drug development. In any case, it is not a straightforward process, and always requires some optimisation. Here we report some preliminary results regarding the culture and differentiation of hiPSC-CMs in 48-well plates versus the traditional T25. The aim was to reliably replicate the model established in T25 in a platform with higher throughput/capable of hosting multiple technical replicates. Unlike IRX4, which showed lower expression in the 48-well plate compared to T25, the markers TNNT2, GATA4 and NKX2-5, investigated with qPCR to evaluate the quality of the differentiation were comparable between platforms (Figure 3.a-d). The same can be said for the contractile capability of hiPSC-CMs, which was also comparable (Figure 3.e-g). A qualitative difference in favour of the 48-well plate condition is the formation of larger patches of hiPSC-CMs compared to T25, based on the video images acquired (Figure 3.h,i). These preliminary results indicate the suitability of generating hiPSC-CMs on a high-throughput-friendly platform.



	Min	Max	Mean	StdDev
Beattimes [sec]	1.15	1.25	1.1818	0.03371
Frequency [1/sec]	0.8	0.8696	0.8468	0.02385
Amplitudes [a,u,]	19.325	21.0484	20.2602	0.6106
Peaktimes user [sec]	0.35	0.4	0.38	0.02582
Systoles user [sec]	0.1	0.1	0.1	2.46E-09
Diastoles user [sec]	0.25	0.3	0.28	0.02582
Peaktimes Thr10% [sec]	0.45	0.5	0.485	0.02415
Systoles Thr10% [sec]	0.1	0.15	0.1136	0.02335
Diastoles Thr10% [sec]	0.35	0.4	0.37	0.02582
Peaktimes Thr50% [sec]	0.25	0.3	0.275	0.02635
Systoles Thr50% [sec]	0.05	0.1	0.09091	0.02023
Diastoles Thr50% [sec]	0.15	0.2	0.185	0.02415
Peaktimes Thr90% [sec]	0.1	0.15	0.145	0.01581
Systoles Thr90% [sec]	0.05	0.05	0.05	1.23E-09
Diastoles Thr90% [sec]	0.1	0.1	0.1	2.72E-09

FIGURE 1 Maximising data collection: (a) Video of beating hiPSC-CM acquired with a standard camera and a bright-field microscope. (b) Data extraction from the peak profile. (c) Plot of beating profile of the hiPSC-CM shown in a, with green and red indicating the local minimum and maximum of each peak. (d) Example of data extracted from a video of beating CMs, generated with the MYOCYTER macro for ImageJ.

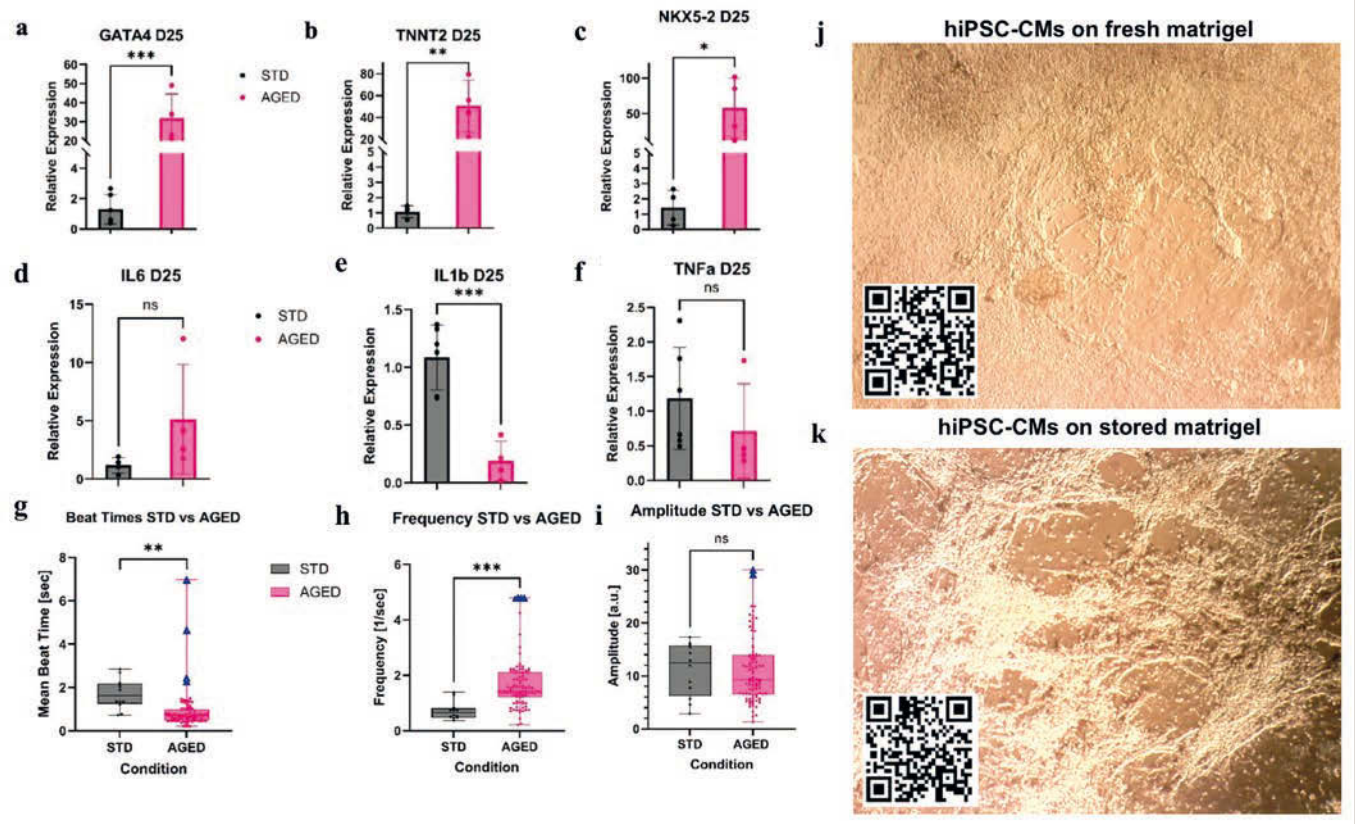


FIGURE 2 hiPSC-CMs culture on fresh and stored Matrigel. RNA expression (quantified with qPCR) of cardiac markers: (a) GATA4, (b) TNNT2 (c) NKX5-2; inflammatory markers: (d) IL6, (e) ILb1 and (f) TNF-alpha (values normalised against the standard condition of hiPSC-CMs on fresh Matrigel); Contractile properties: (g) beat time [sec] (h) frequency [1/sec] (i) amplitude of the contraction. Images extracted from the video of beating hiPSC-CMs cultured in (j) fresh (STD) (k) stored (AGED) Matrigel (scan the QR code to watch the video). In graphs (a)-(i), data in grey show the fresh Matrigel condition, while those in pink show the stored version. In all graphs, data are expressed as mean ± standard deviation. Data were analysed with unpaired student's t-test: *** p< 0.001, ** p < 0.01 * p < 0.05. In graphs (g) to (i), data points highlighted with a blue triangle were identified as outliers based on the ROUT method.

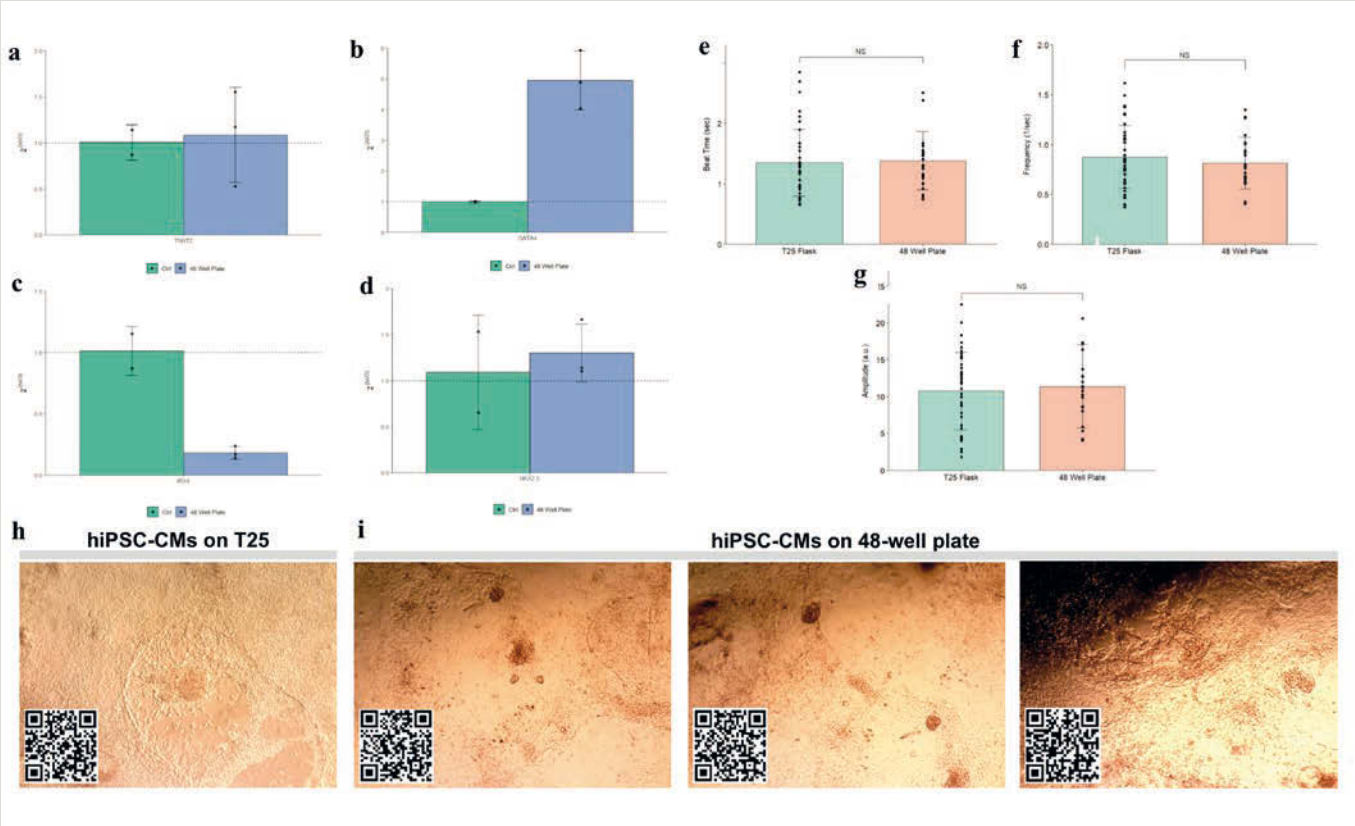


FIGURE 3 hiPSC-CMs culture on T25 and 48-well plates: RNA expression (quantified with qPCR) of cardiac markers: (a) TNNT2 (b) GATA4, (c) IRX4 (d) NKX5-2, with values normalised against the standard condition of hiPSC-CMs in T25. Contractile properties: (e) beat time[sec] (f) frequency [1/sec] (g) amplitude of the contractions. Images extracted from the video of beating hiPSC-CMs cultured on (h) T25 (i) 48-well plates (scan the QR code to watch the videos). In graphs (a)-(d), T25 and 48-well plates are shown in green and blue, respectively, while in graphs (e)-(g) they are shown in light green and salmon, respectively. Data shown are mean ± standard deviation. Data in graphs (e)-(g) were analysed with unpaired student's t-test.

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INTERVIEW

ELINE KOOI

A well-oiled machine

When Eline Kooi herself received her PhD in 1999, the supervision of PhD candidates was not quite what you can expect nowadays. "Still, I can look back on a wonderful time, as during your PhD project you can focus entirely on your research", she says. Just over a year ago, she succeeded Marc van Bilsen as CARIM's PhD coordinator.

I REALLY INHERITED A WELL-OILED MACHINE

For years, Eline had been a member of the CARIM Educational Programme Committee, which advises the Board on PhD-related matters. In January 2023, she became its chair: “A great honour”. In addition to advising on policies and programmes for PhD candidates, she has a number of other tasks. For one thing, she organises a welcome meeting for new PhD candidates every three months, together with I’MCARIM. She is the approachable contact person and source of information, and she consults colleagues of similar committees elsewhere in the university. From an annual science day to a one-week course, CARIM’s more than three hundred PhD candidates are offered numerous tools to help them develop into independent researchers, ready for their next career step.

FOND MEMORIES

She still remembers how as a physics PhD candidate – at the time she was only the second female PhD candidate for her supervisor – she was more or less thrown in at the deep end when it came to her first major presentation. “I think the present generation have better presentation skills than my generation during their PhD”, she laughs. “But mostly I have fond memories of that time, even though in those days we didn’t have a PhD coordinator, nor a coach or welcome meetings.” Nowadays, CARIM assigns to each PhD candidate a staff member as a coach for four years. “A wonderful initiative of my predecessor. I really inherited a well-oiled machine.”

Of course, she can add some personal touches to that well-oiled machine. For instance, she gets to choose a theme for a workshop each year. This year, the focus is on diversity and inclusivity, “such as to enable the new generation of leaders that we are training to recognise talents without bias. As the PhD coordinator, I enjoy the opportunity to contribute to that. CARIM has a long-standing tradition of taking the PhD programme very seriously. Fortunately, the vast majority of our PhD candidates are very satisfied with the supervision they are offered.”

FUTURE

In the final stages of their project, the PhD candidates also focus on the future, whether within or outside the academic community. “The industry is also in need of independent researchers to contribute to innovation, so our supervision also considers that aspect. Another thing is that PhD candidates must learn to deal with setbacks. I can well remember that from my own PhD project, 25 years ago. The word ’perseverance’ frequently came up in a training course on qualities. Not surprising, of course, as without that attitude you can’t succeed in science. If you wish to be innovative, there is never a clear-cut path and things always develop differently from what you expect. You can then mope for an evening, but then you have to pull yourself together and just get on with it. We like to assist our PhD candidates in all these matters as best we can.”

I'MCARIM 2023

I'MCARIM 2023

I'MCARIM is a committee formed by a group of enthusiastic PhD candidates who represent all PhD candidates at CARIM. We organise social and networking activities, provide input to improve the PhD programme and advise the CARIM Executive Board and Faculty Board on related issues.

During the last year, I'MCARIM continued to work to reinforce the social cohesion within the CARIM PhD community. Even though the COVID pandemic and restrictions already lie two years behind us, we still feel that social life within the university has not been completely restored.

In 2023, we went and played minigolf together with all the PhD candidates participating in the CARIM course week, got together to discuss science during several editions of the Young Investigator Rounds, and organised a workshop on how to design a beautiful thesis. These events provided opportunities to casually socialise and network, thereby contributing to the social interaction within our research institute. To help CARIM PhD candidates find their career paths post-PhD, we organised our annual Career Event in collaboration with the NUTRIM PhD council. Hosting this event online was a great success and meant that we were able to invite speakers from all over the world and increase the accessibility of the event for many PhD students. Our participants provided enthusiastic feedback, and inquired about organising a follow-up event.

Well-being at the workplace is closely linked to physical exercise. Therefore, I'MCARIM started an official CARIM running team, which was represented at several running events in 2023, such as the *Maastricht's Mooiste* and the Campus Run. We also supported the promotion of the *Prominentenroeien* rowing event. More group running and other sports events are planned for the new academic year.

This year, the second edition of the CARIM PhD guide booklet was launched and distributed by the members of I'MCARIM. It serves as a useful tool at all stages of the PhD track at CARIM. We have also improved our visibility on social media by sharing our events on X and Instagram through the official I'MCARIM account (@imCARIM).

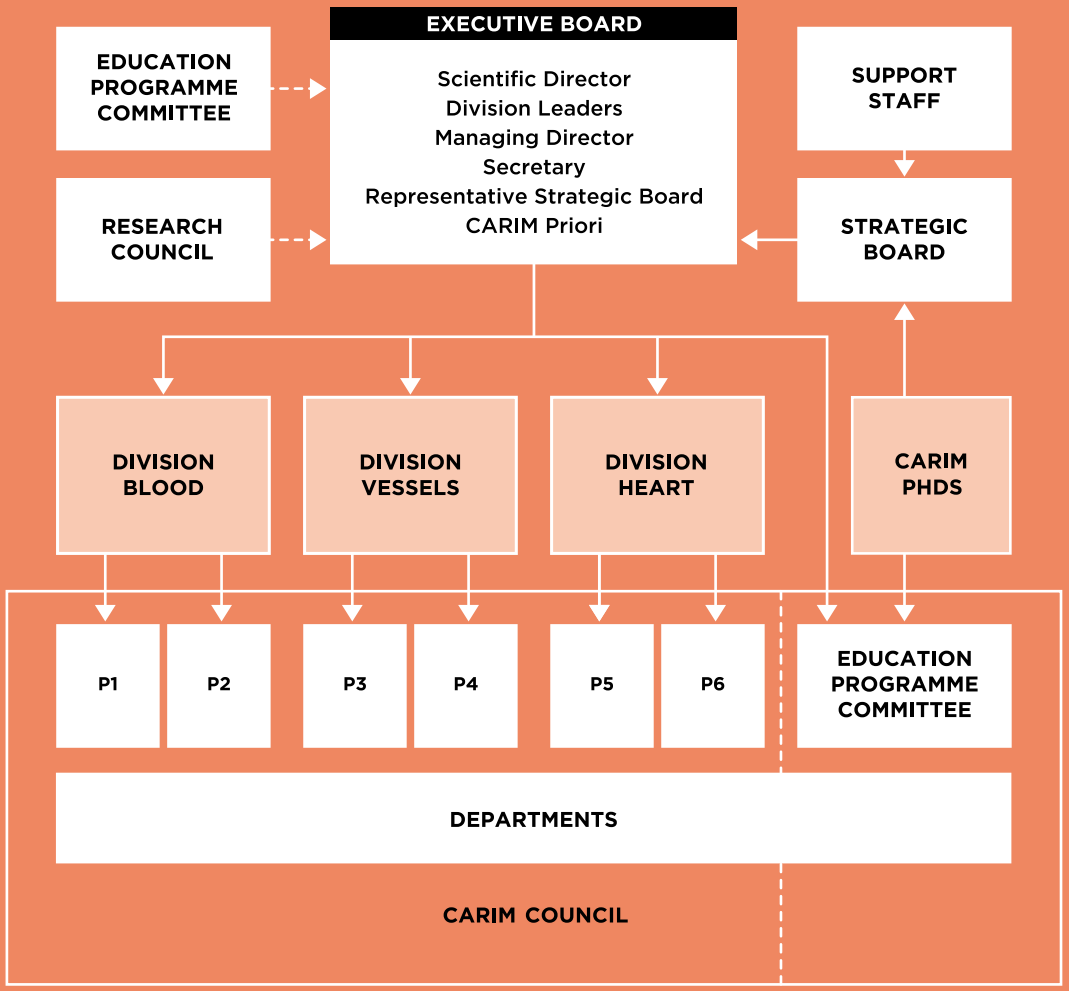
We are eager to work towards providing these events to offer social and professional networking opportunities, promoting the professional development of fellow PhD candidates and, more importantly, offering a structure for support in other matters than the research activities. Furthermore, we think it is important to stimulate social interaction between CARIM PhD candidates in a fun and educational way. If you share this enthusiasm, do not hesitate to contact us, as I'MCARIM is always open to new members and initiatives! Here's to a fulfilling and active 2024!

I'MCARIM 2023
Elias Wieland
Minke Rijpkema
Laura Kempen
Eline Berends
Lisa den Brok

ORGANISATION

05

ORGANISATION



The Scientific Director has the final responsibility for the research institute, including the organisation and management of its research programme, the scientific output, the training of bachelor and master students, PhD candidates and postdocs, the financial management and the public relations of the institute. The Scientific Director is assisted by the Managing Director, who handles the financial, legal and human resource issues, and by the secretary to the Board, who together represent the Management Team (MT). The MT meets weekly to discuss daily matters. Together with the three leaders of the divisions, a representative from the Strategic Board and the CARIM Priori board members, the MT constitutes the Executive Board (EB) of the institute. The EB meets monthly to discuss and decide on issues at strategic and operational level. The EB is advised by the Strategic Board, Education Programme Committee (EPC) and the Research Council.

The Strategic Board (SB) is in place to advise and support the Scientific Director in developing long-term policy. The SB serves as a discussion forum and generates written visions of the future of CARIM and its sustainability in an increasingly competitive international scientific environment. The SB meets monthly to discuss issues such as grant programmes, national and international collaboration networks, trends, interdisciplinary communication and CARIM's visibility in the national and international cardiovascular fields.

The EPC coordinates both the PhD and master training programmes and advises the EB on all issues regarding these educational programmes. The chairperson is also CARIM's PhD Coordinator and advises the EB about all issues regarding the PhD programme. Within CARIM, the PhD Coordinator works closely with the CARIM Office and Scientific Director.

The Research Council advises the PIs, researchers and EB on the quality of research proposals and meets regularly to discuss and guide grant applications. The Research Council trains applicants for their personal interviews with funding bodies and evaluates applications for the HS-BAFTA Pre-PhD and postdoc fellowships.

The Grants & Incentives Team was established to boost grant acquisition by activating researchers and research teams, keeping track of submitted, granted and rejected applications and discussing calls and opportunities.

The Institute Council consists of all PIs and Department Heads and meets four times a year. The Institute Council is informed by the EB on ongoing matters and advises the Scientific Director on research within the institute and the related education programmes.

EXECUTIVE BOARD

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- Dr Boy Houben
- Dr Aaron Isaacs
- Sandrine Seyen
- Prof. Paul Volders
- Danny Luciana
- Tara de Koster

PRINCIPAL INVESTIGATORS

- Prof. Erik Biessen, Dept of Pathology
- Dr Matthijs Blankesteijn, Dept of Pharmacology & Toxicology
- Prof. Martijn Brouwers, Dept of Internal Medicine (from 1 December 2023)
- Prof. Hugo ten Cate, Dept of Internal Medicine
- Dr Judith Cosemans, Dept of Biochemistry
- Prof. Tammo Delhaas, Dept of Biomedical Engineering
- Prof. Tilman Hackeng, Dept of Biochemistry
- Prof. Stephane Heymans, Dept of Cardiology
- Prof. Iwan van der Horst, Dept of Intensive Care
- Prof. Bram Kroon, Dept of Internal Medicine
- Prof. Jos Maessen, Dept of Cardiothoracic Surgery
- Prof. Robert van Oostenbrugge, Dept of Neurology
- Prof. Mark Post, Dept of Physiology
- Prof. Uli Schotten, Dept of Physiology
- Prof. Leon Schurgers, Dept of Biochemistry
- Prof. Coen Stehouwer, Dept of Internal Medicine (until 1 July 2023)
- Prof. Monika Stoll, Dept of Biochemistry
- Prof. Kevin Vernooy, Dept of Cardiology
- Prof. Paul Volders, Dept of Cardiology
- Prof. Christian Weber, Dept of Biochemistry
- Prof. Joachim Wildberger, Dept of Radiology
- Prof. Leon de Windt, Dept of Molecular Genetics

GRANTS AND INCENTIVES TEAM

- Prof. Frits Prinzen, chair (until September 2023)
- Prof. Judith Sluimer, chair (from September 2023)
- Dr Stijn Agten
- Dr Constance Baaten
- Dr Matthijs Blankesteijn
- Dr Mark Hazebroek (until October 2023)
- Dr Marleen van Greevenbroek
- Dr Gwynned de Looijer
- Dr Daniel Molin
- Danny Luciana

RESEARCH COUNCIL

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- Dr Constance Baaten, secretary
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- Prof. Paula da Costa Martins
- Prof. Ingrid Dijkgraaf
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- Dr Ed Eringa
- Dr Pieter Goossens
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- Prof. Chris Reutelingsperger

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- Dr Matthijs Blankesteijn, Coordinator Biomedical Sciences master
- Dr Boy Houben
- Dr Marleen van Greevenbroek (from January 2023)
- Adele Ruder (until March 2022)
- Joanna Alves da Silva (until April 2023)
- Valeria Saar-Kovrov (until April 2023)
- Minke Rijpkema
- Elias Wieland
- Laura Kempen (from February 2023)
- Lisa den Brok (from May 2023)
- Eline Berends (from May 2023)

CARIM OFFICE

The CARIM Office consists of specialists who support the institute and its researchers with administrative, financial and legal issues, including HRM and funding. Tara de Koster, Esther Willigers and Barbara Przybylski are responsible for administrative issues, including supporting the EB. The controller of CARIM is Lynn Lemeer, assisted by Hans Slenter. The Finance Department of Maastricht University provides support for accounting related to CARIM research projects with Henny Kerckhoffs, Johan Noordijk and Jacqueline Roufs-Scheepers involved. Petra Suurmond and Anke Neekmann of the Department of Human Resources of Maastricht University are dedicated to CARIM. In legal affairs, Paul Bohnen and Suzanne ten Hoeve provide support to CARIM. Gwynned de Looijer offers Faculty support for funding acquisition. Managing Director Danny Luciana is the head of the CARIM office. The research within CARIM's divisions involves the research activities of employees working in 17 departments of Maastricht UMC+ (six basic and eleven clinical).

6
BASIC DEPARTMENTS

- Biochemistry
- Biomedical Engineering
- Epidemiology
- Genetics & Cell Biology
- Pharmacology & Toxicology
- Physiology

11
CLINICAL DEPARTMENTS

- Anesthesiology
- Cardiology
- Cardiothoracic Surgery
- Clinical Chemistry
- Clinical Pharmacy
- Internal Medicine
- Intensive Care
- Neurology
- Pathology
- Radiology & Nuclear Medicine
- Vascular Surgery

INTERVIEW

CARLA VAN DER KALLEN

New: CARIM Clinical Research Unit

Between 2010 and 2020, over nine thousand people were included in The Maastricht Study, forming a unique cohort of individuals from the province of Limburg, focusing on type 2 diabetes, cardiovascular diseases and other chronic disorders. Almost half of these participants have now returned for a second series of measurements. “In all, we hope to include six thousand people in the second phase”, says Carla van der Kallen, who leads the research unit. Now that the last major grant is coming to an end, this is one more challenge.

Whereas The Maastricht Study was previously housed in a building near the hospital and the university, it moved to the Maastricht UMC+ itself a few months ago. The research facility is now called CARIM Clinical Research Unit (CARIM CRU) and is available to all CARIM researchers. For the past ten years, Carla van der Kallen has led The Maastricht Study research centre, and she now leads CRU. “These fifteen rooms used to belong to CARIM, but were not used intensively. We’ve redesigned them and done them up. Researchers can use these spaces for all kinds of activities, from blood sampling and cardiac ultrasound to eye measurements, spirometry and the Xtreme CT-scanner. We can also provide them with the staff to perform the measurements.” Managing the team is what gives her the greatest satisfaction. “Working together in a pleasant atmosphere and gathering useful data for science, that’s what makes me happy. Although hardly any of the team have a permanent appointment, people like working here. The often very tight planning means they’re working hard, and coffee breaks are sometimes skipped, but being appreciated and working in a good atmosphere make up for that. We give our staff a lot of responsibility, plus room to develop themselves further, if possible. I’m very proud of our staff members.”

ENRICHED DATASET

In the past fourteen years, the team has included nine thousand individuals in the first series of measurements for the cohort study, and another four thousand for the second phase. “That means a huge enrichment of our dataset. You’re better able to study the timeline and distinguish between the chicken and the egg.” One of the findings of the study so far is that a third of adults in Limburg have diabetes or pre-diabetes. Other findings were that having a large social network is associated with less diabetes, that damaged blood vessels can lead to depression, and that reducing the time spent sitting down by half an hour a day already reduces the risk of diabetes. The database and the biobank got started thanks to a large investment from the European Regional Development Fund, complemented by grants from the provincial authorities, the university and the hospital. “The infrastructure for cohort studies is usually funded by those kinds of parties, not so much by organisations like the Dutch Diabetes Fund or the Dutch Heart Foundation, who are more interested in the scientific projects.” At the time of the interview, it was not yet fully clear how the completion of phase 2 is to be funded, but CARIM is determined to complete the study and maintain the database.

A NEW BEGINNING

The new location, at the hospital, is less stylish than the previous one. “But none of the participants have complained about that. They often already know their way around the hospital, making it easier for them to participate. Some of them even claim they’ve never been at the other site. Apparently, it didn’t make much of an impression on them. As for me, I’d rather have a nice team than a fancy room, and that probably also goes for the participants.” Whereas at the previous location, there was always a doctor present, in case someone became unwell or had other complications, the hospital is of course literally swarming with doctors. “Here you could theoretically also bring someone in for measurements who is in a hospital bed, which would not have been possible at the other site, nor at a university lab. Since we moved here, the number of requests from researchers for our data as well as for the use of our infrastructure has already risen. In short: this is an excellent place for us strategically. I hope that in five years’ time we’ll be able to say this was a good move for The Maastricht Study and for CARIM.”

ONE OF THE FINDINGS OF THE STUDY SO FAR IS THAT A THIRD OF ADULTS IN LIMBURG HAVE DIABETES OR PRE-DIABETES

INTERVIEW

MICHAEL JACOBS

“Suddenly I was the patient”

The surgeon who leaves the operating theatre downhearted after hours of surgery, as they have to tell the patient’s loved ones that he or she has unfortunately not made it. In his career, vascular surgeon Michael Jacobs has had to assume this role, known to most people only from films and TV series, more often than he would have liked. He had literally never thought that he himself would ever be allocated the role of patient. “I thought: I’m in the wrong movie. I’ve learned so much from that experience.” As he turns 67, he reminisces about the ‘four lives’ he has had. And about the fifth, which is about to start.

What he often hears around him is “Go and enjoy your retirement while you still can.” But if there is anything that emerges during an interview with vascular surgeon Prof. Michael Jacobs, is that to him, enjoyment equals getting things done. The list of things he has managed to achieve is impressive. And yet he does not refer to himself as ambitious. “Active”, he laughs.

A DECENT CAR

At the time he graduated from secondary school, university medical education was just starting in Maastricht. The pioneering spirit appealed to him, as did the teaching system used there. “I wanted to learn a hands-on trade, help people, not sit behind a desk in an office all day.” Surgery was the discipline he felt most attracted to, and he managed to secure a traineeship with the famous Prof. Greep, who trained students at Maastricht and was head of the Department of Surgery. “To be admitted to this illustrious company, you had to excel in something. And you had to have a decent car.

I WANTED TO LEARN A HANDS-ON TRADE, HELP PEOPLE, NOT SIT BEHIND A DESK IN AN OFFICE ALL DAY

It was a great time, when budgets for social activities were much more generous than now. And so I would find myself once again in evening dress at some smart venue, as Prof. Greep was celebrating the fact that he had got his PhD 25 years ago. Only he could come up with something like that.”

For his further training in complex cardiovascular surgery, Michael then had the opportunity to work in Houston in the US, where Prof. Cooley led what was a kind of paradise for complex surgery. “There were 10 operating theatres in one centre, where fifty open-heart surgeries were being performed each day. I easily worked a hundred hours a week; that means your learning curve is really steep. It was great.” His time working as a surgeon, for a total of 40 years, is what Michael calls his first life.

SECOND LIFE

His second life began in 1997, when he organised ‘his’ international conference for surgeons: the European Vascular Course (EVC), for the first time. “At the time there were already too many ‘ordinary’ conferences, but not enough ‘hands-on’ training opportunities for surgeons. We started the EVC in Marseille, followed by a few times in Amsterdam, and for the last 15 years we’ve been at the MECC exhibition and conference centre in Maastricht.” For the three-day event, two thousand surgeons from all over the world come to Maastricht. Three hundred workshops are held in 48 rooms. Participants are taken from and to various airports by coach, hotel rooms are arranged. “It’s a huge logistic operation. Fortunately, I have an excellent organising agency for the conference, but I’ve also learned that if you don’t monitor things meticulously, errors will creep in. I can hardly put into words the level of detail this involves. From checking whether people actually arrive on the day they’ve indicated, to ensuring that no unnecessary hotel rooms are

booked, and down to the frozen butter we once had with the 'luxury rolls'. Nowadays I go and sample the goods at the catering firm beforehand. It's just: check, check and double-check."

For someone who once said he was happiest in the operating rooms, you may wonder why he would want to add this source of stress. "At the OR, I perform operations at the most complex level imaginable, and you can't be disturbed or have meetings there. I'm absolutely allergic to the endless rounds of meetings so common in the Netherlands. I want to *do* things and see results. So when at the very end of the EVC I'm standing around at the coaches that are taking everybody home, talking to the young doctors who are so happy about everything they've learned, I enjoy that more than just operating for five days."

MAASTRICHT CHALLENGE

It was in this same entrepreneurial spirit that the challenge of founding a cardiovascular centre (HVC) at the Maastricht hospital appealed to him. But that was not the reason why he returned to Maastricht from Amsterdam in the year 2000. "I was having a great time there as a professor and head of the Department of Vascular Surgery, but the temptation of stepping into Professor Greep's shoes was great. In addition, I was put in charge not only of vascular surgery, but of all surgery, so including traumatology and paediatric surgery; I would be leading a larger group, and I liked a challenge." One year after his return to Maastricht, he was invited to found the HVC, which would represent a one-stop approach for patients with any kind of cardiovascular disease. Until that time, a patient who had to be operated upon or undergo PTCA had to visit six different hospital departments, meaning it would take them four months to get an open-heart operation. We really had to come up with a different system". After some years of lobbying and attacking some hallowed institutions, HVC got going in 2012. Thanks, among other things, to the cooperation with CARIM, the HVC is now solidly based.

TV PROGRAMME ON SURGEONS' WORK

It is this kind of non-surgical work in the hospital environment that Michael calls his third life. In this life, he was once the first PhD candidate to defend his thesis at Maastricht University, and in 1995 he was the first professor to have been trained at Maastricht. But another element of his third life was his many years of work for a Dutch TV programme on the work of surgeons ('*Chirurgenwerk*'). Or leading the Department of Vascular Surgery at the Aachen hospital, just across the German border. For nineteen years he worked there as a surgeon and head of the department, whereas it was originally intended as a two-year stint. "Within my personal mindset, which is to always want more and bigger, it was fantastic to be head of department in two countries at once. At Aachen we created the field of complex aortic surgery from scratch, and turned it into the

THANKS, AMONG OTHER THINGS, TO THE COOPERATION WITH CARIM, THE HVC IS NOW SOLIDLY BASED

largest in Germany in five years' time. Mission completed. But at the same time, I'd never recommend anyone to combine two jobs in two countries with two different cultures like that. Since you're 'only' present in both places for half the time, you often get critical questions from your colleagues. You work your guts out and they still say 'I wish you were here a bit more often'."

DINOSAUR

At Aachen, Michael also trained a number of surgeons in complex aortic surgery, as one of the few remaining masters of this art in Europe. In about 10 hours, he and his team are able to replace a patient's entire aorta. For some, often young, patients, this is their only chance of survival. And even if the operation has been carried out perfectly, without complications, 10-20% of the patients still die. "What keeps you going is the thought that without the operation, these patients would almost certainly also have died. You have no other choice. But this operation is different each time and it means you have to switch between scenarios all the time. That requires a learning curve of some ten years." For a long time, it looked like Michael would not be able to pass on the torch to a successor. He used to call himself a dying species, a dinosaur. "As soon as I had trained some surgeons, they became head of department somewhere else, and that was the end of it. Now at the last moment, there is this younger colleague at Maastricht, Elham Bidar, who is actually interested in continuing this. Apart from the long learning curve you have to go through, you have to be able to deal with the fact that young patients sometimes die, despite your best efforts." He remembers all these patients even better than those who did make it. "The first questions running through your head when someone dies like that, which haunt you even in bed, are: what could, or should, I have done differently? Did I miss something? If you go over this again in your mind, which is a pretty quick process after

I'VE LEARNED A LOT FROM THE EXPERIENCE, ABOUT HOW TO COMMUNICATE WITH PATIENTS

you've done a thousand operations, and you conclude: we did nothing wrong, this was just a matter of a very complex patient, then I can live with it. I've learned a lot from them."

FOURTH LIFE: FAMILY

His fourth life is what matters most to him: his family and friends. He has three children from his first marriage, and an 18-year-old son from his second. "My eldest daughter has a son who's the same age. My grandson and my son get along very well, which is very special. I've invested as much time in the children as I could during my career, but of course it's never enough." Now that his fifth life, his retirement, is imminent, Michael will have to find a new balance. At any rate, he will continue to do the aortic surgery at Aachen for some time, and he is going to hold on to the EVC in the coming years. And then there are a number of interesting projects abroad, which means he might be "working nine days a week" if he is not careful. A nice easy-going holiday in Europe sounds like a good idea, as does not being fettered to his agenda all the time. But going golfing every day, or sitting at home? No.

IN THE WRONG MOVIE

"The people around me are saying: you've given everything you had for forty years, for God's sake go and enjoy the years you've got left! And I definitely intend to do that. Because seven years ago I got to experience how vulnerable I too turn out to be." It was during the EVC that he felt a massive headache coming on, which turned out to be caused by a tumour in his head the size of a ping-pong ball. "I've had radiotherapy and all that misery. I would be sitting in the waiting room with my wife and thinking: I'm in the wrong movie. Suddenly, I was the patient. And I still am, as last September I had to be operated on again as the tumour had grown back. I have to have a scan every three months, and I get very nervous in the week before that." Although he realises that it is a "completely naive thing to say", until this happened at the age of sixty, he had never thought that he could get a nasty cancer. "I was immortal. As a surgeon, nothing would ever happen to me. Ever since then, '*carpe diem*' is what's etched onto my brain. And I've learned a lot from the experience, about how to communicate with patients. I mainly saw very many good, inspiring colleagues, but also a few who could still learn a thing or two. What I've realised most is that I need to take even more time for breaking bad news to patients. Have they understood the message correctly, or has all the information evaporated due to their nervousness? I've had to face the facts myself."

On 26 April 2024, Michael made his farewell speech as professor at Maastricht University, and on this occasion, he reminisced about his four lives. The speech was entitled "What a challenging journey". "Turning the four paths into a liveable concept, that was the challenge, and I think I've managed that. At least it wasn't a boring journey."

FACES

BLOOD P1 BLOOD COAGULATION, VENOUS THROMBOSIS & BLEEDING


AARON ISAACS


ALMA MINGELS


AMAURY MONARD


ARINA TEN CATE-HOEK


BAS VAN BUSSEL


CONSTANCE BAATEN


DENNIS SUIJLEN


ELISABETTA CASTOLDI


ELKE MAGDELEYNS


ERIK BECKERS


FATMA KARAPINAR


FRANK VAN ROSMALEN


GEERT-JAN KUIPER


GERRY NICOLAES


HANS IPPEL


HEIDI NOELS


HENRI SPRONK


HUGO TEN CATE


INGRID DIJKGRAAF


IRENE KEULARTS


IWAN VAN DER HORST


JAN-WILLEM SELS


JUDITH COSEMANS


JUR TEN BERG


KANIN WICHAPONG


KRISTIEN WINCKERS


MAGDI NAGY


MARIJKE KUIJPERS


MONIKA STOLL


OTTO BEKERS


PAOLA VAN DER MEIJDEN


RENÉ VAN OERLE


RENSKE OLIE


ROB DRIESSEN


RORY KOENEN


SIMONE WIELDERS


STELLA THOMASSEN


STEVEN MEEX


STIJN AGTEN


THIJS VAN HERPT

TILMAN HACKENG

YVONNE HENSKENS

FACES

BLOOD P2 ATHEROSCLEROSIS, ARTERIAL THROMBOSIS & STROKE


ANDY BAKER


CASPER MIHL


CHRISTIAN WEBER


CLAIRY DINJENS


DIETBERT NEUMANN


ELINE KOOI


EMIEL VAN DER VORST


ERIK BIESSEN


FELIX MOTTAGHY


GREGORIO FAZZI


JACK CLEUTJENS


JACQUES DEBETS


JOACHIM JANKOWSKI


JOACHIM WILDBERGER


JOS BROERS


JUDITH SLUIMER


LIEVE TEMMERMAN


MARC VAN ZANDVOORT


MARION GIJBELS


MARJO DONNERS


MAT ROUSCH


PIETER GOOSSENS


REMCO MEGENS


ROB HOLTACKERS


ROBERT VAN OOSTENBRUGGE


SÉBASTIEN FOULQUIER


SIMON SCHALLA


SYLVIA HEENEMAN


WERNER MESS


WIM VAN ZWAM

FACES

VESSELS P3 VASCULAR COMPLICATIONS OF DIABETES & HYPERTENSION


AMÉE BUZIAU


ANNEMARIEK DRIESSEN


BASTIAAN DE GALAN


BOY HOUBEN


BRAM KROON


CARLA VAN DER KALLEN


CASPER SCHALKWIJK


COEN STEHOUWER


ELLEN FRANKFORT


JEAN SCHEIJEN


JULIE STAALS


KRISTIAAN WOUTERS


MARC HEMMELDER


MARGEE THEUNISSEN


MARLEEN VAN GREEVENBROEK


MARTIJN BROUWERS


MIRANDA SCHRAM


PAUL SCHIFFERS


PETRA NIESSEN


PHILIPPE VANGRIEKEN


RONALD HENRY


SIMONE EUSSEN


THOMAS UNGER


VICKY VERMEULEN


YVETTE DERKS

FACES

VESSELS P4 REGENERATIVE & RECONSTRUCTIVE CARDIOVASCULAR MEDICINE


ARMAND JAMINON


BAREND MEES


BART MAESEN


CECILE MAASSEN


CENGIZ AKBULUT


CHRIS REUTELINGSPERGER


DANIËL MOLIN


ED ERINGA


ELHAM BIDAR


ELISA D'ALESSANDRO


GEERT WILLEM SCHURINK


JOS MAESSEN


LEON SCHURGERS


LISETTE UNGETHUM


MAARTEN SNOEIJS


MAARTEN VAN DINTHER


MARK POST


MICHAEL JACOBS


NIKO DECKERS


NYNKE VAN DEN AKKER


PETRA LUX


PEYMAN SARDARI NIA


PIETER VAN PAASSEN


ROBERTO LORUSSO


SANDRO GELSOMINO


SUZANNE KATS


SYLVIA MARIANI

FACES

HEART P5 STRUCTURAL HEART FAILURE


ATHINA VIDAKI


BEN JANSSEN


CAMILLA SORAGNI


CHRISTIAN KNACKSTEDT


ELLEN WELTJENS


GUIDO HAENEN


HANS-PETER BRUNNER-LA ROCCA


JOB VERDONSCHOT


LEON DE WINDT


LIZ JONES


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MARTINA CALORE


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MICHIEL HENKENS


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PAULA DA COSTA MARTINS


PETER LEENDERS


RICK VAN LEEUWEN


SÉBASTIEN FOULQUIER

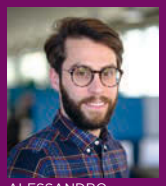

SERVÉ OLIESLAGERS


STEPHANE HEYMANS


WOUTER VERHESEN

FACES

HEART P6 COMPLEX ARRHYTHMIAS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AURORE LYON


BART SPRONCK


BASTIAAN BOUKENS


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CHAHINDA GHOSSEIN-DOHA


CHANTAL MUNTS


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FRANS VAN NIEUWENHOVEN


FRITS PRINZEN


GEERTJE SWENNEN


HARRY CRIJNS


JOOST LUMENS


JORDI HEIJMAN


JUSTIN LUERMANS


KEVIN VERNOOY


KOEN REESINK


MARC VAN BILSEN


MATTHIJS CLUITMANS


NICK VAN OSTA


PAUL VOLDERS


RACHEL TER BEKKE


ROEL SPÄTJENS


ROEL MEIBURG


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ULI SCHOTTEN


VANESSA VAN EMPEL


WOUTER HUBERTS

COLOPHON

EDITOR
Tara de Koster, CARIM

IN COOPERATION WITH
CARIM Office
CARIM staff members

INTERVIEWS
Femke Kools, FemKools
Jan Klerkx, Bèta Vertalingen

PHOTOGRAPHY
Joey Roberts, Maastricht
Sandrine Seyen
Johan Latupeirissa

MEDIA & STRATEGY
Muis Mücher, Maastricht

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Drukkerij Hendrix

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CARDIOVASCULAR RESEARCH INSTITUTE MAASTRICHT
Maastricht University Medical Centre+
Universiteitssingel 50, 6229 ER Maastricht
P.O. Box 616, 6200 MD Maastricht, the Netherlands

TELEPHONE
+31 (0)43 3881766

E-MAIL
carim-office@maastrichtuniversity.nl

WEBSITE
www.carimmaastricht.nl