CARIM ANNUAL REPORT 2021

SCHOOL FOR CARDIOVASCULAR DISEASES

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CONTENTS

PREFACE

PICK UP THE PIECES

With pride and gratitude I present to you our CARIM Annual Report 2021. It has been a year in which we tried to slowly slip back into regular business, and to find back the better side of life. Blood is thicker than water, and everywhere within our Institute research activities sprouted again as measures were lifted, and fed by enthusiasm from our young scientists, happy to be unleashed again in the arena of science and society.

I had mentioned before, if only we'd learn our lessons from the previous years, but apparently we are only human, and too many still try to make the world turn round by money and greed, while good and carefulness can make so much more difference. In "Where have all the flowers gone?", it was already questioned in the sixties: "When will we ever learn?". Well, we still do not, and now we're moving back from viral into human turmoil.

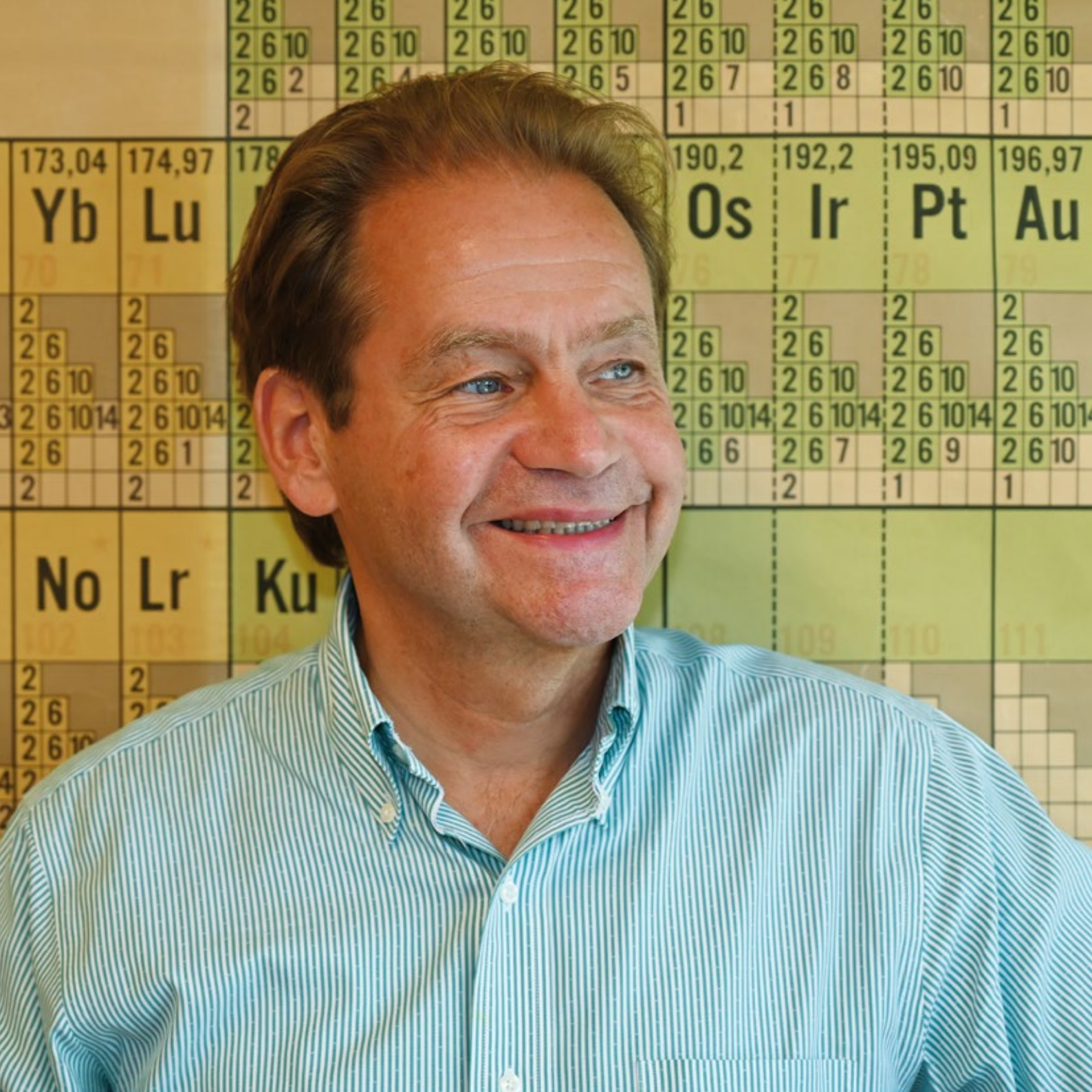
Humanity is heterogeneous, and most of us do good, from a humble perspective without self-regard, and perhaps it is true that most of these fellow human beings are among the less heard, the less demanding, the less provocative. But not so the greedy and the relentless, who are shamelessly pursuing their goals. Scientist are human as well, and also here we can observe similar behaviour. Between the extremes of scientists *pur sang* and career scientists using discovery to merely climb the academic and societal ladder, all flavours of behaviour are present, and hail to those that are curiosity driven, who act and lead by example. The ones that coach, and inspire, the ones that step aside and even back, to let their pupils flourish, and let them develop their own scientific identity. We have now learned and implemented that the academic ladder is in fact an academic mattress, soft, with many rewarding team science positions that are more gratifying and equal, and with less clear "top positions". The structure allows better interaction and mutual motivation and support, and has created a more healthy research infrastructure.

But now we're there, and we have to pick up the pieces…

After years of redefining science professionals, what to do and especially what not to do, it is now time to return to what scientists should be all about: discover, publish, acquire grants, build groups, coach PhD candidates and teams by fierce motivation and gentle coaching. We lucked out with our academic institute, our intellectual playground, at which we can explore chemistry, physics, biology and medicine to stimulate and satisfy our curiosity. There is actually no better job in the world. Be flexible, let science lead the way, and don't let a project description force you to follow that path, allow yourself and your students to take a left or right at the first scientific intersection of unexpected findings.
It's a chance to diverge from your tutor, establish your niche, and expand your teams research portfolio. Serendipity has brought us far.

Our current annual report is an up-to-date display of team science efforts within CARIM. It shows once more that CARIM is an inspiring cradle to young talent, who pioneer on high impact science and societal engagement. Our CARIM community connects arts and sciences, lab and clinic, ambition and reflection. We feel that we exemplify the academic institute of today without taboos, silence of speech or suppression of opinion. We are CARIM.

CARIM rides the wave of change, and by tackling technological challenges at the forefront of science, we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now enter a decade in which the patient serves as a lab model to prevent and cure disease. The ability to establish digital copies of patients hearts to predict outcome of intervention through the digital twin approach, the power of analysing and correlating patient data with geographical and social-economic impact on health in our region through the Maastricht Study, and the magic of creating patients tissue in the lab to study pathology and therapy through iPSC technology, make us one of the first to actively shift from animals to humans as *ex vivo* and *in vitro* models. In addition, this allows CARIM to limit animal experimenting to the most necessary, but we should realise that we can never do without.

CARIMs Executive Board has welcomed two PRIORI members by draw, and young staff members of CARIM are well represented in the Dutch Cardiovascular Alliance to sketch our future national cardiovascular research agenda. We keep on enriching our bachelor and master students, pre-PhD, PhD candidates and postdocs through our unique HS-BAFTA programme, offering time outs to engage in science, and to go abroad for scientific and cultural exchange, crucial to healthy development of independent researchers.

CARIM becomes more active in entrepreneurial activities, and has efficiently aligned with Brightlands Maastricht Health Campus to establish IP and spin off activities, offering broad and alternative opportunities for CARIM researchers to expand or change their positions.

All of these topics lay in front of you, in our current annual report that is packed with division highlights, opinions, new personal grants and contracts, arts and sciences, and all awards and prizes bestowed upon our fellow CARIM employees in this exceptional year.

This is CARIM 2021.

I hope you enjoy your reading.

Professor Tilman Hackeng
Scientific Director CARIM
School for Cardiovascular Diseases

PROFILE

01

PROFILE

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

CARIM is built around three research divisions, 'Blood', 'Vessels' and 'Heart', comprising six programmes: 1. Blood coagulation, venous thrombosis & bleeding; 2. Atherosclerosis, arterial thrombosis & stroke; 3. Vascular complications of diabetes & hypertension; 4. Regenerative & reconstructive cardiovascular medicine; 5. Structural heart failure and 6. Complex arrhythmias. These six programmes together host 20 Principal Investigator (PI) groups, which represent independent research, infrastructural and financial units within CARIM. CARIM addresses key scientific questions through optimal combinations of CARIM programmes, PIs, researchers, and infrastructure in an optimal team science setting combining track record, expertise, and innovative content and to disseminate results to scientific communities and to society as a whole.

All three divisions involve basic as well as clinical programmes, and are led according to a shared governance principle, executed by the division leader together with basic and clinical scientists from the divisions. This shared governance system enables shared responsibility for the scientific progress of programmes, for linking activities and seeking collaborations between PIs and divisions and for mentoring of PhD candidates, postdocs and talent 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, stiff ambitions, good technological facilities and a critical learning environment. CARIM is one of the six research schools and two 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 school by the Royal Netherlands Academy of Arts and Sciences (KNAW) and recognised as an international training site for Early Stage Researchers by the European Commission. CARIM researchers have been very active in EU networking activities and the establishment of (inter)national alliances. In total, CARIM is currently involved in many European projects including ten ITN programmes with a total number of more than 30 Early Stage Researchers allocated to CARIM.

KEY FIGURES 2021

ANNUAL BUDGET: **20.9** M€

NEW CONTRACTS AND GRANTS: **6.0** M€

RESEARCHERS: **163.8** FTE (101 INTERNAL PHDS)

TECHNICAL AND SUPPORTING STAFF: **51.0** FTE

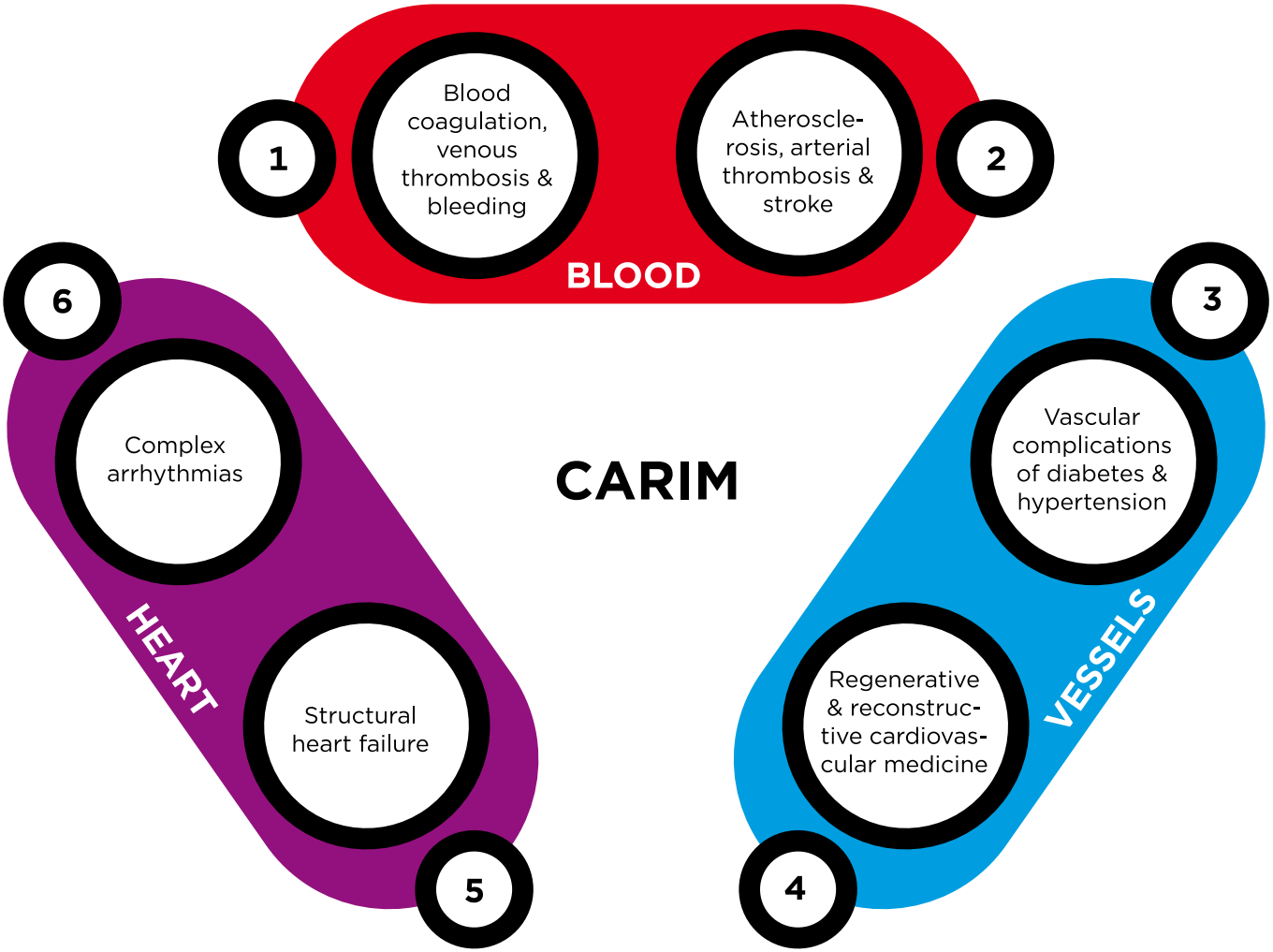
DEPARTMENTS/DISCIPLINES: **17**

SCIENTIFIC ARTICLES: **1077** (SCI/SSCI: 883)

PHD THESES: **56**

in collaboration with industry, sharing its expertise but maintaining its independence as reflected by the right to independently publish. Ongoing collaborations with industry include, among others, Medtronic, Bayer, Roche, Abbot, Siemens and Philips. Furthermore, CARIM researchers are involved in other Public Private collaborations in (inter) national networks such as NHF CVON, Horizon 2020, 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).


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

INTERVIEW

JUDITH SLUIMER, ROGIER VELTROP AND CHAHINDA GHOSSEIN-DOHA

When I'm grown up, I'll be: a leader!

None of the three have clearly defined plans for their future role as leaders in the cardiovascular world. Although Rogier Veltrop has to admit that he is thinking every day about where he wants to go from here and thus what he spends his time on. Chahinda Ghossein-Doha, the physician of the three, could even imagine a role in politics for herself.
Judith Sluimer may have already mastered the political aspect of science more completely than she realises herself. Together, they have been selected to take part, on behalf of CARIM, in the 'Leadership Programme' of the Dutch Cardiovascular Alliance (DCVA).

Why did you want to take part in this programme?

Judith Sluimer: "Within the Medical Faculty I've already taken part in their 'top talent programme', which involves learning leadership skills, but there's always new things you can learn in that area, from other people. My main motivation was to expand my network in the Netherlands; coming into contact with various people, thereby creating more opportunities for multidisciplinary research. My network in Europe and the US is already strong. In the Netherlands, it's easier for researchers living in the urbanised west of the country to find each other, simply because they're relatively nearby. That's how it works, really. The programme enabled me to start collaborating with Kak Khee Yeung, a vascular surgeon from the Amsterdam Academic Medical Centre, who manages a wonderful biobank, which I didn't know about. Next month she will send samples to Maastricht, so we can use them for research."

Chahinda Ghossein-Doha: "That's precisely how effective collaboration comes about! Not from a vague suggestion of 'We should work together sometime'. In this programme you show your vulnerable side, making it easier build up a bond, and that's how it happens. On the one hand, I want to take part in order to further develop as a researcher, develop my profile. You realise that you need more leadership skills to be able to feel content with your own role, which for me means that it's of use to others. On the other hand, DCVA has a good reputation as regards developing towards the future, so you want to be part of that. And I was very much attracted by the fact that they work in projects, which is good for your CV as well as your professional development. And it's also instructive just to see what they focus on in a selection process."

Sluimer: "Last year I'd submitted a motivation letter, but I wasn't selected for an introductory interview, as there were already enough candidates like me, ha ha! Of course, Rogier has a unique selling point in that respect."

Rogier Veltrop: "Mind you, I wasn't selected either last year. What Judith is referring to is my heart transplant in 2015, which means I'm not only a researcher but also an experiential expert. That has made me highly motivated to want to speed up my career. My hereditary heart condition meant that my previous scientific career was cut short, so I've lost a lot of time climbing up the research ladder. I'll be completing my PhD thesis shortly, and then I want to build my own research group as soon as possible. That's another

I THINK IT'S VERY IMPORTANT TO REALISE THAT YOU CAN'T DO EVERYTHING YOURSELF

thing this programme is important for: to show that you've done this, with these people, at this level, and so one day hopefully to be able to enter one of the talent classes in the Faculty."

Are you currently in a leadership role?

Sluimer: "I'm leading a small group of researchers and technicians and chairing the "U(H)D committee, that advises the FHML dean on assistant and associate professorship promotions."

Veltrop: "I'll still have to build that up. Judith has staff working with her, while I only have three students in my laminopathy group, plus a technician who supports me with a lot of enthusiasm."

Sluimer: "Still, you're a leader at every level, is what I've learnt in this programme, whether the people working with you are paid or not. It's just that students stay for a shorter while than staff, which is sometimes difficult. But then, if the collaboration isn't very smooth, they're also gone more quickly."

Ghossein-Doha: I'm supervising a PhD student and technicians in the Netherlands, Belgium and Italy, and I'm currently vice-president of the international study group on maternal haemodynamics, where I'm in charge of organising this year's conference in June. Besides, I am chair of the Queen of Hearts Foundation"

And do you know in what context you hope to be doing this later, "when you're grown up"?

Ghossein-Doha: "I hope to be in a position where I can exert some influence on healthcare improvement. That could be from a position in science, or perhaps from a political position. That's another context in which, as a physician, you can offer valuable contributions to the policy process, as you've been at the coalface of healthcare. I think there's a role there for doctors."

Sluimer: "I do have certain ambitions, but currently I'm enjoying research a lot. Supervising PhD students is still quite a challenge to me, dealing with people with very different characters. I think I currently find that more interesting than managing a large organisational structure. But I can't exclude the possibility that if such an opportunity should present itself to me in the future, I might go for it."

Veltrop: "I'm too much preoccupied with my future, I'm aware of that. There's not a day when I don't think about where I want to go from here and what steps I should take. That's not just because of the time I've lost, but also because I know I basically won't make it to my retirement. Thanks to improved medication, donor hearts are lasting ever longer, but if I do make it to my retirement, I'll be among the top ten people who have survived longest with a donor heart. That's why I want to progress rapidly, so I don't see myself in postdoc positions for eight years."

What would you still like to learn?

Veltrop: "In my previous research life, in the US, a Nobel laureate would come along each month to give a talk, and their message was always: make sure you enjoy your work. And I do enjoy it every day, but that alone is not enough to be successful. I think it's important to stay true to yourself, but at the same time I'd like to develop more political skills. That may seem contradictory, but I think it's mostly a matter of how you formulate things. When I'm at a reception with

Judith, I'll use different words than when we're in a board meeting. I still want to develop those skills further. And learn to be patient; that's one of my weaker points."

Sluimer: "I can be very direct with people, which can be awkward at times. Sometimes you just have to think strategically and prepare meetings thoroughly. So think of a goal you want to achieve, instead of reacting spontaneously, although an off-the-cuff reaction can also get a laugh sometimes."

Veltrop: "That's exactly what I mean. If I can no longer make jokes, that takes the fun out of work for me. But I also understand that it may sometimes be less appropriate."

Sluimer: "Humour is actually very useful sometime, to take the sting out of things. I hope that if we're ever in the board room together, we can still crack jokes."

Ghossein-Doha: "The programme also helps you discover your own character. For instance, I found out that, according to a particular theory of personality, I attach great value to collaborating with people, but if you actually want to get ahead in your career, it's apparently also important to understand the politics behind it. So then I thought: is that really what I want? That's when you realise that it doesn't have to be about back-room politics. You can do it your own way and stay in touch with yourself. Another thing I would like to learn to do better is letting things go. When something isn't working, a discussion isn't running smoothly or you're not getting along well with someone, I can worry about that a lot. Whereas: not everything will always go the way you like it, and you can't agree with everybody all the time."

At the same time you're also working on a practical project with a team. What is that about?

Ghossein-Doha: "I'm working together with a cardiologist from Groningen and a thoracic radiologist in Rotterdam on a project entitled 'valuable cardiovascular research'. It ties in with the current national debate about other ways to acknowledge and value researchers, and how that applies to the cardiovascular research field in the Netherlands. What are the main items that should receive more attention? We're currently thinking about more team-based research. Because personal grant applications, for instance for NWO's Incentive Grants, are full of the word 'I', and other quality checks are also highly individual, whereas if you then become a professor, you're expected to lead multidisciplinary consortia. That's why we're investigating, together with the Heart Foundation and ZonMW (the Netherland's Organisation for Health Research and Development), how you can encourage team-based research among scientists in their mid-career stage. We're working on a white paper which is to be published by the end of the year, as a statement on our vision."

Veltrop: "Judith and I are working on the Heart Tissue Bank. That's a nationwide initiative which aims to make donor hearts available for scientific research. How can hospitals and universities cooperate in such a national biobank, and are they willing to do so? We're facing many challenges there."

Sluimer: The aim of our project is to produce an advisory report about ways to obtain more hearts for this Heart Tissue Bank. So far, we've identified the stakeholders, conducted interviews about their interests and constraints, and we'll be looking to see if we can write a grant application to raise more funding."

What type of leader would you like to become eventually?

Sluimer: "I find the guest speakers who are in higher management jobs very interesting in that respect. The other day I heard Marja van Dieijen-Visser, the former chair of the Board of Directors of Maastricht UMC+. She's the one who taught me that you're a leader at every level. I thought she was unpretentious, authentic and fair, even though she's had to fight very hard, especially against men who didn't believe in her or who were after her job."

Veltrop: "She was up against a lot of obstruction, with some people even ignoring her when she entered the room, but it didn't make her vindictive. She just did her job, and did it well. Another guest speaker was Jeroen Geurts, the Rector Magnificus of VU Amsterdam."

Ghossein-Doha: "That was fantastic. Rogier and I interviewed him, using the format of the Dutch TV programme College Tour. The participating audience had submitted questions, which led to a very lively discussion. I was impressed by his enthusiasm and youthfulness. It was great to see that you can enjoy and combine so many different things and be so lively, even in his position. The fact that that's possible. I liked that, because that's how I am too."

Sluimer: "Of course there are different styles of leadership, and what you take from it mostly is how *you'*d like to be managed and how you hope to do it yourself one day. Marja and Jeroen appealed to me because they tried to remain authentic, being genuinely interested in the people around them. Getting the best out of your team, that's what I attempt to do too, with variable degrees of success. But that's the type of leader I hope to be and to become."

Ghossein: "If you manage to get to the top and find you've not lost the people around you, it means you've done well, I think. I think it's very important to realise that you can't do everything yourself. To accept that and be aware that you have colleagues who are very good at certain things, recognising that and leave it to them but also give them their due. That's the way to progress as a team."

YOU'RE A LEADER AT EVERY LEVEL

INTERVIEW
MICHIEL HENKENS

"We are the bridge between donors and researchers"

Cycling to Paris to raise sponsor money, giving interviews and presentations to promote name recognition, consulting with researchers, and attending the first heart donations in Amsterdam; these are just a few of the activities of the Netherlands Heart Tissue Bank's coordinator. Michiel Henkens was nominated by CARIM as a candidate for this post in 2021, and he got it. Although even he must admit that there are 'only' 24 hours in a day, he does his best to use them as efficiently as he can.

During this interview about the Netherlands Heart Tissue Bank (part of the Netherlands Heart Institute, NLHI), he frequently mentions the Netherlands Brain Bank. The Heart Tissue Bank, founded in 2020, makes use of many of the facilities of the Brain Bank, which started in 1985. "The Amsterdam Medical Centre has an autopsy team on standby 24/7 for the Brain Bank, and this team also performs the autopsies for the Heart Tissue Bank," explains Henkens. "So far, it's been too expensive to establish such a service at multiple sites in the Netherlands, and it's also very important to have an expert team at the ready to carry out the related procedures." This means that the coordinator has travelled up to Amsterdam several times to attend the first heart donations for the Heart Tissue Bank. "I think it's important for me to attend these procedures myself, if possible, not only in order to implement improvements but also to get to know all the staff involved."

PHD RESEARCH PROJECT

At the time of the interview, Henkens has almost completed his PhD thesis, after which he will start his pathologist training in Maastricht in the summer. After having received

degrees in health sciences and medicine (with distinction) at Maastricht University, his long-held ambition to go into research was realised when he entered a PhD programme at the cardiology department, a position that was offered to him on the basis of a research internship he did. His PhD project focused on improving the early detection and risk stratification of cardiomyopathies (heart muscle diseases) and heart failure. One of the discoveries he made during his research was an ECG characteristic that can predict life-threatening arrhythmias in patients with heart failure due to dilated cardiomyopathy.

DATABASE ON CARDIOLOGY PATIENTS

The reason he was nominated for the post of Heart Tissue Bank coordinator by CARIM was probably also partly to be found in his PhD research. Together with other PhD candidates and supervisors, he set up a cardiology-wide database for all patients who present with actual or suspected cardiomyopathies or heart failure, or who are referred for the screening for these conditions. “One of the aspects we gave a lot of attention to when setting up this large scale registry was to optimise the way in which data that are already being collected for routine clinical care can be made easily available to researchers. In addition, we put a lot of effort into automating these processes in order to leave the researchers more time to do their actual research.” And time is scarce if you are in training to become a specialist and are also coordinating the Heart Tissue Bank. “So far, research has been the main theme in my career; it’s my passion, so I intend to go on doing this forever. A registry like the Maastricht Cardiomyopathy Registry (mCMP Registry) helps to make that possible.”

PROMOTING NAME RECOGNITION

In his work as a coordinator, he has already realised a comparable logistic improvement. Like his colleagues at NLHI, he only has a small proportion of his working week available for the Heart Tissue Bank, so he wants to do the work as efficiently as possible. “Keeping the Heart Tissue Bank going involves a lot of logistics. Things like registering donors, but also all of the actions that need to be taken when a donor dies, or the actions involved in making tissues available to researchers. In the past year, we’ve taken a critical look at the entire logistics of the Heart Tissue Bank, just as we did with the mCMP Registry, in order to automate as much of it as possible. That leaves more time to spend on other activities.” Such activities include promoting name recognition for the organisation. Henkens expects that by the summer of 2023, 15 organ donations will have been carried out. To achieve this, it is important that as many people as possible are aware that they can register as a donor with the Heart Tissue Bank, including healthy people. “Any adult Dutch person can currently register as a potential donor for the Heart Tissue Bank. The Heart Tissue Bank offers a unique opportunity to compare tissues from persons with heart conditions and different stages of the disease with those of persons without such conditions. This makes it possible for researchers to get a better understanding of not only the end-stage of heart diseases, but especially the earlier stages as well.”

PLANS FOR THE FUTURE

The primary aim is to boost scientific progress. “We are there for the researchers, so it’s with them that I have many discussions. For instance, to gauge their interest in the type of tissue we are collecting and to see if anything needs to be, and can be, added to our tissue-collection protocol for them. We are the bridge between donors and

THE MAIN THING FOR ME IS TO MAINTAIN THE PASSION I CURRENTLY HAVE FOR MY WORK

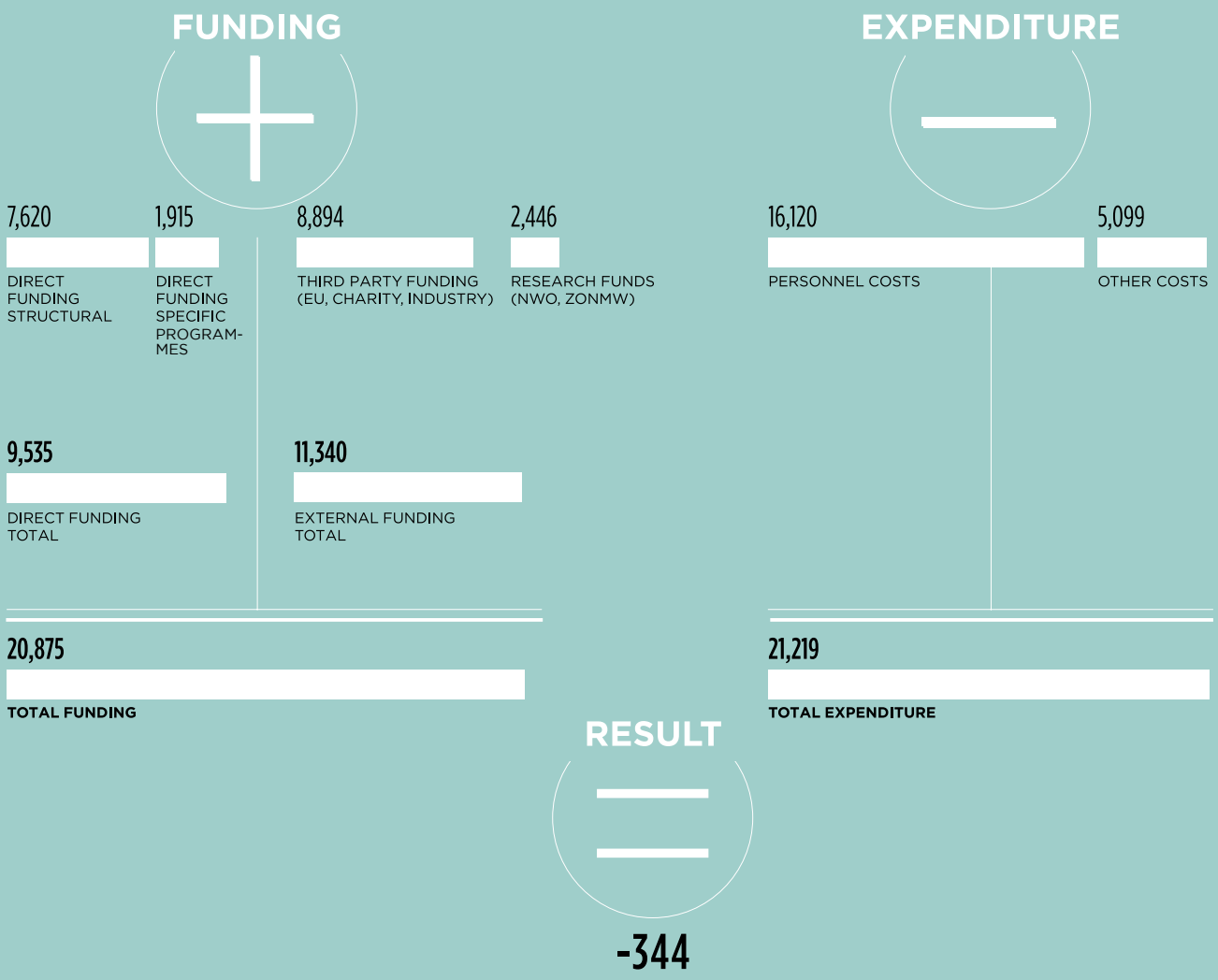
researchers, so we try to relieve the researchers of work that they can't do themselves due to lack of time, money, staff or expertise. In the end, we want to become as well-known as the Brain Bank, where they sometimes perform several brain donations a week, which have made many research projects possible all over the world since 1985. So we're very grateful to the Brain Bank for their cooperation and for the opportunities they provide us with."

His non-profit organisation needs fund-raising to keep the costs for researchers as low as possible. To this end, the coordinator cycled all the way to Paris last May, together with the 'Team Heart Tissue Bank' as part of the Cycle Paris event: 550 kilometres in four days. "That was also useful to get rid of the extra pounds I put on during the Covid lockdown," he smiles. And on top of all this, he recently bought his first house together with his girlfriend, in the town of Weert, which they are currently completely renovating. "I do it all with a lot of passion and pleasure, so that helps," he says. "I'm ambitious, but I don't plan my future in every detail. In about five years from now, I want to be a pathologist, and by then I hope to have set up, together with my team, a successful Heart Tissue Bank which already has supported many researchers. What I'll do after that is something I'll think about when I get there. The main thing for me is to maintain the passion I currently have for my work."

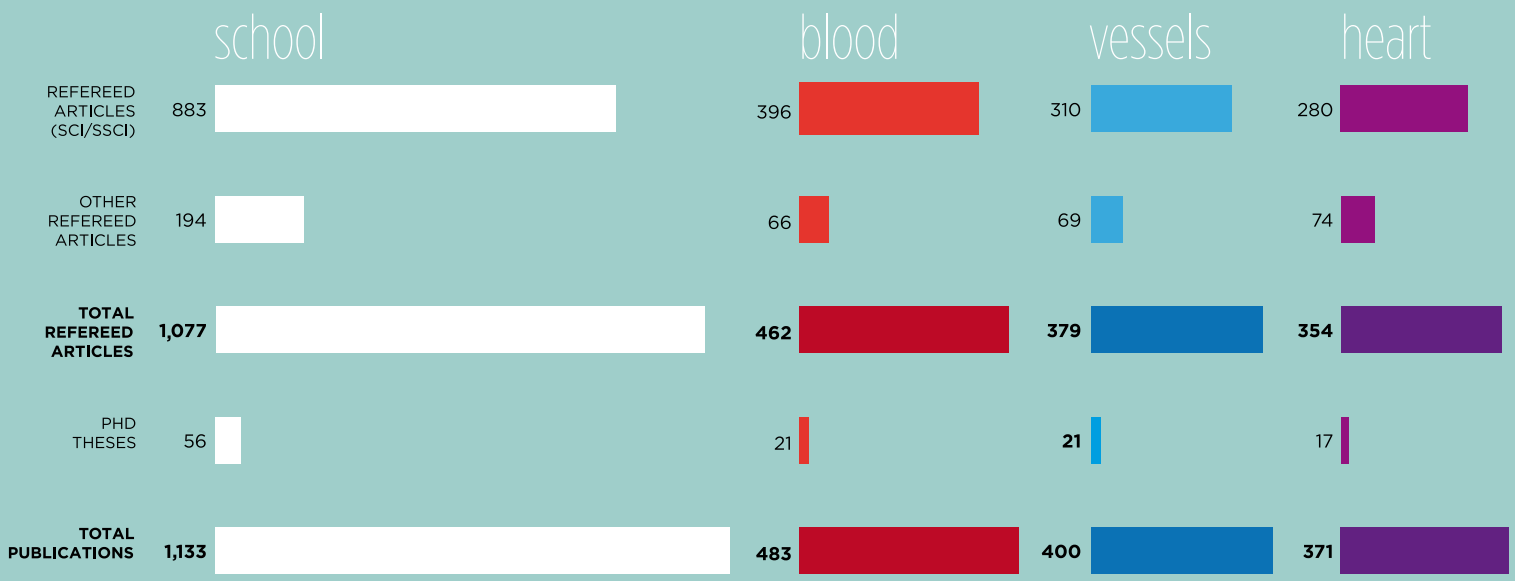
FACTS AND FIGURES

02

FUNDING AND EXPENDITURE (K€) AT SCHOOL LEVEL 2021



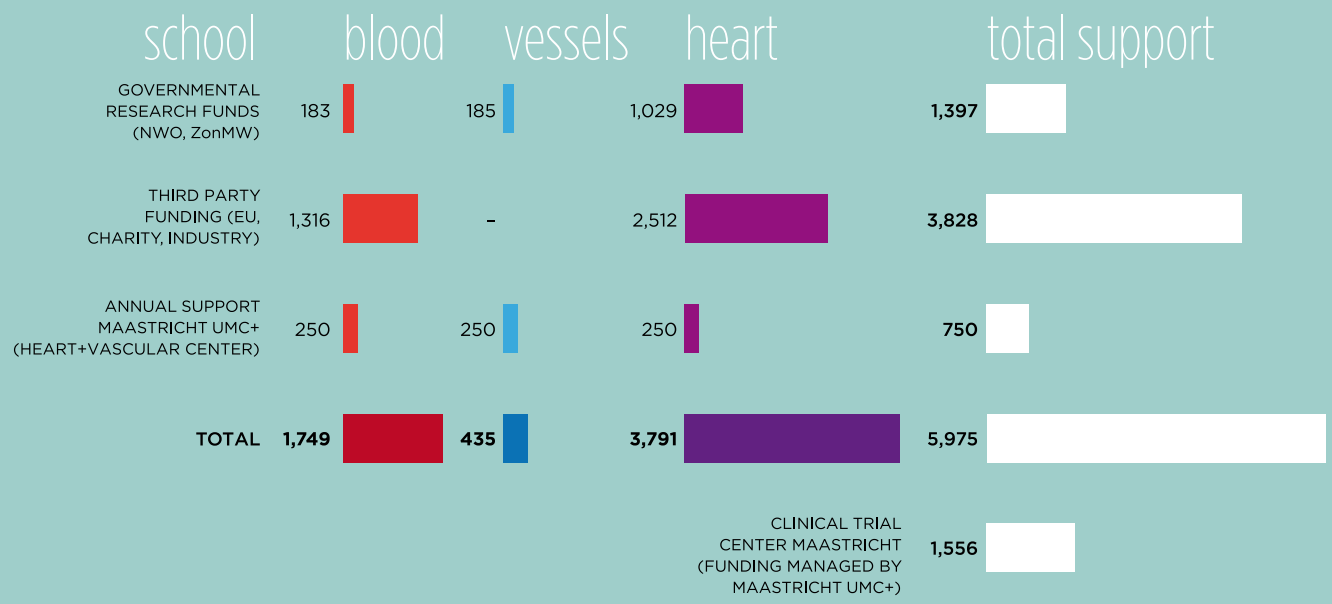
RESEARCH OUTPUT IN 2021



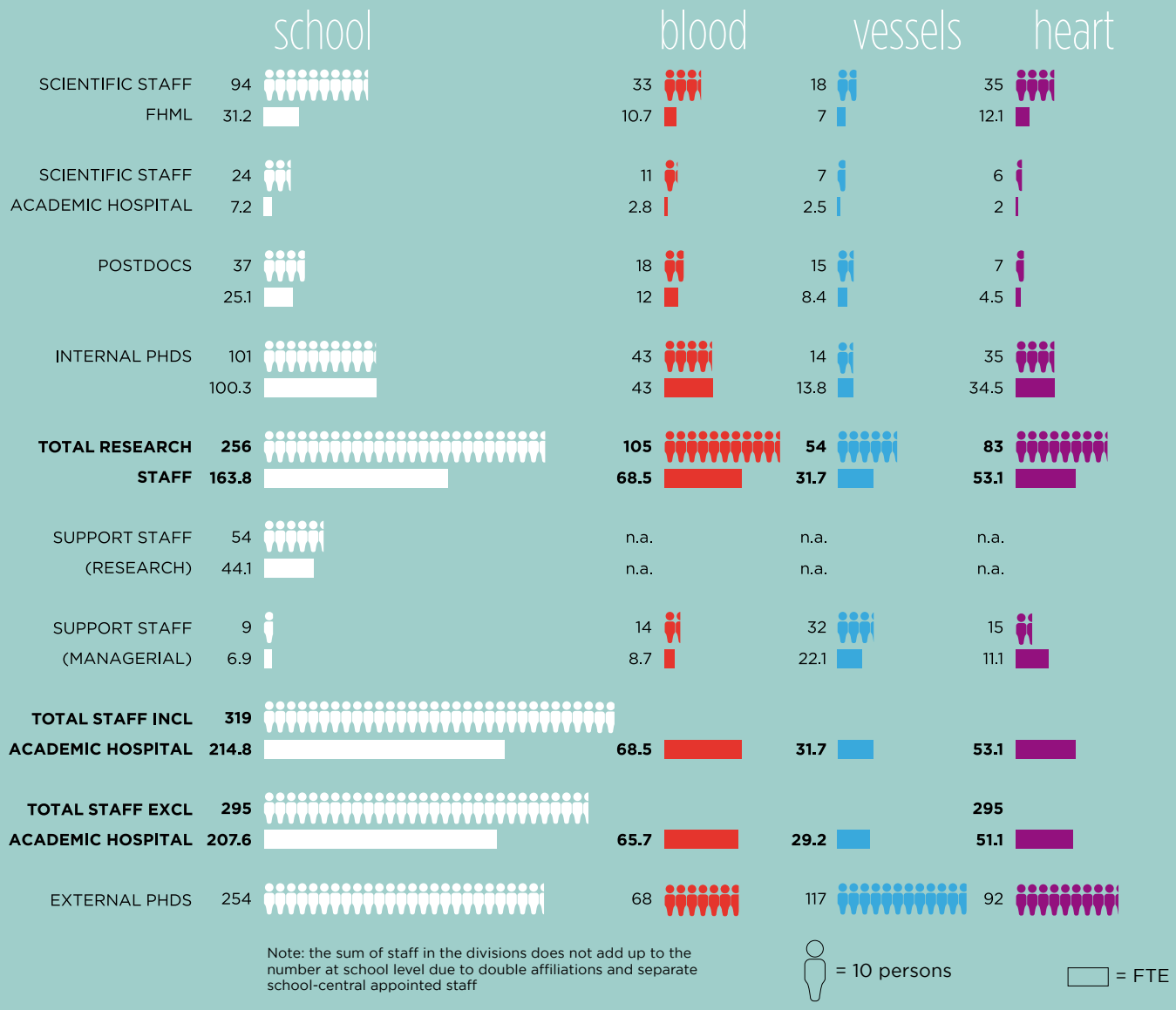
ACADEMIC STAFF **31.2** FTE
RATIO REFEREED ARTICLES PER FTE ACADEMIC STAFF **28**

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

NEW CONTRACTS AND GRANTS (K€) IN 2021



SUMMARY OF SCIENTIFIC AND TECHNICAL STAFF CARIM AT THE END OF 2021



HIGHLIGHT
DIVISION BLOOD

CHRIS REUTELINGSPERGER

Annexin A5, a tale of a scientific journey

In 2010, the CARIM Annual Report featured the 'CARIM Molecule of the Year: Annexin A5' with a short narrative about its discovery and the scientific road towards understanding its significance in health and disease. The story highlighted aspects of its resolved structure and elucidated biological activities, and concluded with the paragraph "Where the road will lead us to remains to be seen. However, if applying the rules of the method called science the road will very likely provide unexpected and exciting points for dazzling sightseeing, no matter what the name of annexin A5 then will be." Twelve years later I admit that we are still lacking a clear picture of its physiological and pathophysiological functions, despite the numerous details that have been generated by scientific research. In some sense there is still a paucity, but this could be only an apparent paucity, because our scientific mind is confined by an innate mechanism that construes comprehension from thoughts that are compartmentalised and that are logically connected. In other words, we see the overall picture only if we recognise relationships between details, irrespective of the quantity of details.

Annexin A5 (anxA5), a 35 kDa protein, acts as a strong anticoagulant by binding the phosphatidylserine (PS) of biological membranes in a Ca^{2+} ion dependent manner. AnxA5's anticoagulant activity became apparent during my PhD project, which explored the procoagulant structures of vascular tissue. This led to its discovery and description of its structure and anticoagulant mechanism. The discovery instigated the filing of a patent (US5066787A) claiming the use of anxA5 for the treatment of patients at risk of developing thrombosis. The patent secured financial resources to continue the research. The scientific road towards understanding its significance for the human organism in general and for haemostasis and thrombosis in particular, turned out to be tough, and has not yet resulted in a clear picture of its *in vivo* relevance. The most puzzling finding was that a genetic knockout had no noticeable effects on the physiology of the developing and adult mouse. The explanation for this was, and still is, sought in the phenomenon of redundancy.

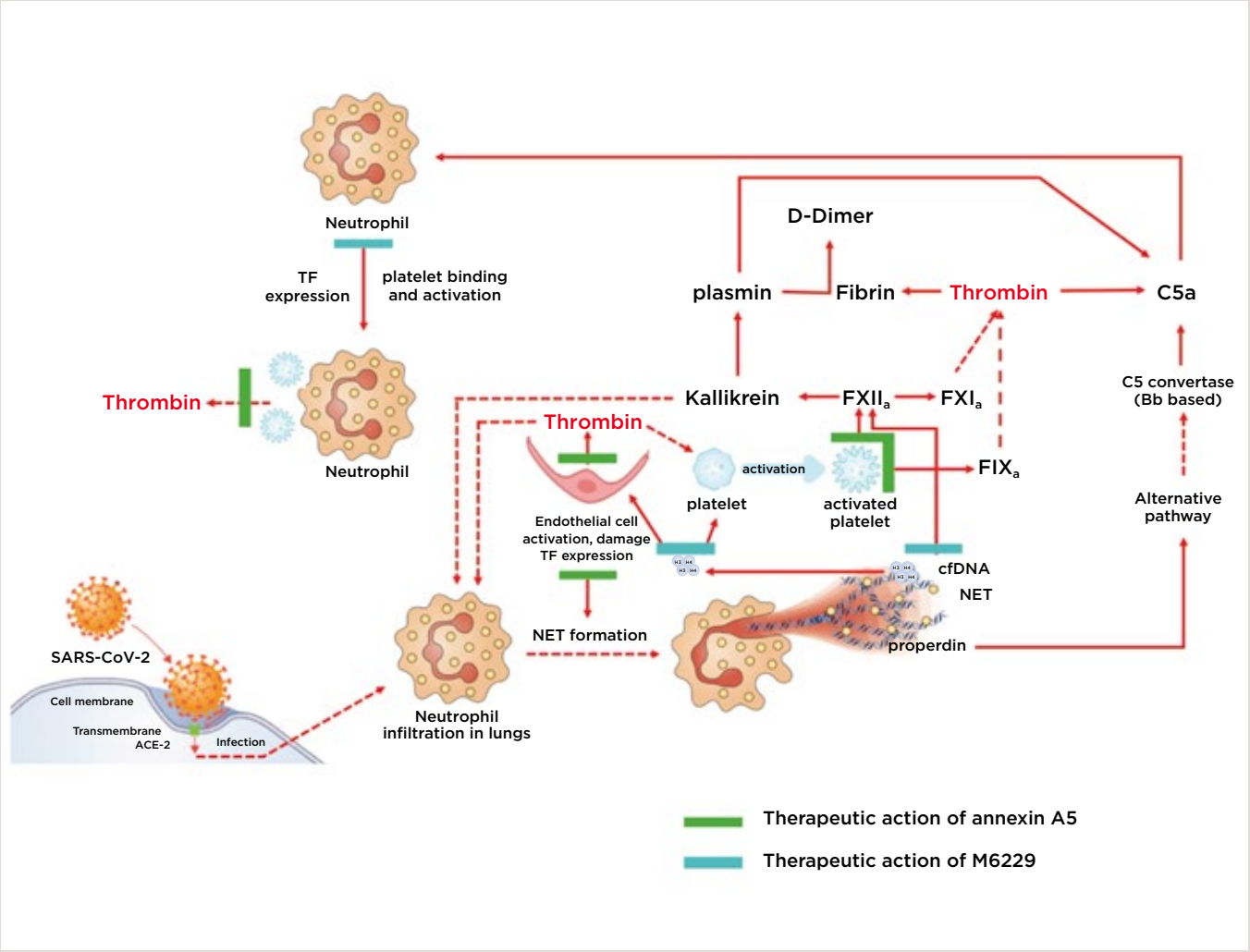
Understanding became even more complicated by a multitude of distinctive biological activities reported for anxA5. These include inhibiting phospholipase A_2 activity, regulating pyruvate kinase M2 activity, regulating integrin avβ5 expression, regulating protein kinase Cα and θ activity, inhibiting LPS activation of TLR4/MD2, stabilising and repairing membrane defects, inhibiting cell death, acting as immune checkpoint inhibitor, and facilitating cell entry by viruses. The various activities are, moreover, differentially compartmentalised *in vivo*. Some occur intracellularly and some extracellularly. AnxA5 has been detected in blood plasma, cerebrospinal fluid and seminal plasma, suggesting that it is secreted by cells. The absence of a signal sequence in anxA5 excludes secretion following the classic secretory pathway and points towards unconventional protein secretion (UPS). AnxA5 secretion through UPS has been hypothesised and may involve one of the exosomal secretory pathways. Molecular mechanisms of anxA5 UPS and their regulation have not been investigated in detail so far and it is therefore still unclear whether extracellular anxA5 results from a controlled process or from an accidental process such as cell injury.

This crowded and puzzling background of biological activities offers a rich arsenal of applications of anxA5 for *in vitro* and *in vivo* research as well as for diagnosis and therapy in the clinic. At the core of these applications are its properties of binding PS with high affinity and building a two-dimensional lattice on the phospholipid surface. Also, the robustness of its structure-function relationship, allowing covalent coupling of a variety of compounds to anxA5 without affecting its PS binding, has been fundamental to the success of anxA5 as an applicative molecule. Applications include the detection of stressed and dying cells, activated platelets and aged erythrocytes. Clinical studies have been designed and performed to assess the feasibility of locating and measuring cell death in patients, using anxA5-Tc^{99m} and single photon emitting computed tomography (SPECT). These studies gave promising results but were discontinued before reaching market authorisation for anxA5-Tc^{99m}, for reasons other than scientific ones.

The COVID-19 pandemic came upon us unexpectedly, and not only had disastrous effects on individuals and society but also brought opportunities for science to learn more about the immunology of the human body. In a concerted action by the Department of Biochemistry (CARIM), the Immunology group of Pieter van Paassen (CARIM, Maastricht UMC+) the Clinical Haemostasis and Thrombosis group of Henri Spronk and Hugo ten Cate (CARIM, Maastricht UMC+) and the intensive care unit of Maastricht UMC+ (Marcel van de Poll and Iwan van der Horst), we designed and implemented the COVAH study (METC 2020-1315).

FIGURE 1 Hypothesis of the triangular relationship between innate immunity, the complement system and the coagulation system driving the immunothrombotic response to SARS-CoV2 infection. The coloured rectangles indicate the potential target sites for the therapeutic action of anxA5 and M6229. We hypothesise that the immunothrombotic triangle is also activated during the acute phases of ANCA-associated vasculitis and of TMA in SLE and APS. NET - neutrophil extracellular trap; cfDNA - cell free DNA; H3 and H4 - extracellular histones 3 and 4; TF - tissue factor; FIXa, FXIa and FXII - activated coagulation factors IX, XI and XII.

HIGHLIGHT


Neutrophil
TF expression
platelet binding and activation
D-Dimer
plasmin
Fibrin
Thrombin
C5a
Thrombin
Neutrophil
Kallikrein
FXII$_a$
FXI$_a$
C5 convertase (Bb based)
Thrombin
activation
FIX$_a$
platelet
activated platelet
Alternative pathway
Endothelial cell activation, damage TF expression
cfDNA
NET
properdin
NET formation
SARS-CoV-2
Cell membrane
Transmembrane ACE-2
Infection
Neutrophil infiltration in lungs
Therapeutic action of annexin A5
Therapeutic action of M6229

HIGHLIGHT

The study explored the triangular relationship between the innate immunity, the complement system and the coagulation system as a driver of COVID-19 pathogenesis and in particular as a driver of immunothrombosis in these patients. We focused on circulating biomarkers of neutrophil extracellular trap (NET) formation (extracellular histone H3), complement activation (C5a), activated coagulation (complexes of activated coagulation factors and their natural inhibitors) and dampening of inflammation (annexin A1). The study results (DOI: 10.1161/CIRCULATIONAHA.120.050656) were consolidated in the hypothesis that the triangular relationship involves amplifying loops which, if not counteracted effectively, transform the defence into a fulminant immunothrombotic response (Figure). Based on this hypothesis we inferred that individuals who develop COVID-19 after SARS-CoV2 infection have insufficient capacity to suppress the amplifying loops between the three defence systems. Hence, the molecular basis for the amplifying loops provides potential targets for therapeutic intervention. Interestingly, recent papers on COVID-19 report PS-expressing membranes as catalytic surfaces to the amplifying loops. Moreover, COVID-19 patients with acute pulmonary embolisms have circulating extracellular vesicles expressing PS. These vesicles trigger NET formation via activation of endothelial cells. This process is strongly inhibited by anxA5 (DOI: 10.1111/bjh.18019).

The role of PS in the progression of COVID-19, combined with the availability of clinical grade GMP human recombinant anxA5, has triggered the design of a clinical trial at Maastricht UMC+ to assess the therapeutic potential of intravenously administered anxA5 in COVID-19 patients. Although the study (EudraCT 2021-002200-12) has been approved, no patients have been included yet because of the (fortunately) subsiding coronavirus pandemic.

Together with Pieter van Paassen, we have identified other indications with an underlying immunothrombotic triangle that could benefit from treatment with anxA5. These include anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis and thrombotic microangiopathy (TMA) in systemic lupus erythematosus (SLE) and anti-phospholipid syndrome (APS). Designs of clinical trials to test the efficacy of anxA5 for these indications are underway.

The ‘anxA5 and cell death’ journey came upon an unforeseen crossroad, leading to the exploration of the cell-death-inhibiting properties of heparin. Together with Gerry Nicolaes (CARIM, Biochemistry) we discovered that heparins with low anticoagulant activity efficiently neutralise the cytotoxic activity of extracellular histones that are released by NET formation and cell death. Extracellular histones appear to constitute another branch of the molecular basis of the amplifying loops of the immunothrombotic triangle (Figure) in COVID-19 (DOI: 10.3389/fcimb.2021.694186) and in sepsis (DOI: 10.1182/blood-2013-07-514984). The therapeutic application of low-anticoagulant heparin was patented by UM/Maastricht UMC+ (US9,155,756) and licensed to Matisse Pharmaceuticals for clinical development. Currently, a phase 1/2a clinical trial is investigating the low-anticoagulant heparin M6229 in patients with sepsis at the intensive care unit (trial identifier NCT05208112).

Decades of research have not delivered a comprehensible picture of the physiological and pathophysiological significance of endogenous anxA5. Multidisciplinary

research with anxA5, however, has contributed to our understanding of the biology of vascular disease and has created therapeutic opportunities to combat acute episodes of vascular disease that are characterised by fulminant inflammation and an immunothrombotic response.

The scientific journey with anxA5, which has not ended yet, also exemplifies the synergies between the apparently conflicting entities of scientific research at universities and intellectual property. Finally, this tale should not end without mentioning that the journey would not have encountered the many exciting “points for dazzling sightseeing” without the excellent support of Cecile Maassen, Niko Deckers, Lisette Ungethüm, Petra Lux and Leon Schurgers (CARIM, Biochemistry).

INTERVIEW

ARTS & SCIENCES

EHSAN NATOUR

Arts & Sciences

Halfway through the interview, Ehsan Natour says: “I am a poetic person, as I’m Arabic. In this project, that helps.” The Maastricht heart surgeon does indeed tend to use language that is rich in images, sometimes digressing, but without losing sight of his main message. As he succinctly puts it: “It’s a matter of awareness, acknowledgement, recognition, the low point and the resilience.” His mission is to support people whose life has been ‘put on hold’ by a traumatic event, to help them recover more rapidly. Art is an invaluable tool in this process.

"ART DESCRIBES WHAT YOU CAN'T EXPRESS IN WORDS"

Whereas doctors often have little time available for an interview, Ehsan Natour has set aside an hour and a half of his time. This is partly because at the time of the interview he is working reduced hours due to long Covid. He sometimes pauses to catch his breath. On the other hand, his story shows that he always likes to make time for people. It makes you wonder what his outpatient consultations look like, while at the same time you think: a doctor who takes enough time for you, that's worth waiting for.

Life stands still

In 2019, Natour founded the '*Stichting Stilgezet*' (standstill foundation), after having carried the idea around with him for years. He saw how the lives of patients are almost literally put on hold when they have to undergo open-heart surgery. "Which, by the way, is also true after a serious accident, or other diseases like cancer, COVID-19 or some huge financial crisis or pandemic. Hospitals don't pay enough attention to this. By devoting attention to people's anxieties and worries, the foundation tries to give them a helping hand, so that they recover more quickly." It is important to note that recovering does not mean "going back to who they were". "After a crisis, people want to return to their former situation as quickly as possible. But that old situation will never come back again. You're moving towards a 'new normal', which involves accepting your limitations. That's very important." To illustrate this, he shows the 'crisis curve', which in his view applies to any traumatic experience. It goes from the first minor symptoms, which you try to argue away, to the lowest point (for instance the open-heart surgery, in which you are vulnerable and completely dependent on others) and then the way back up, out of the low point. "Everyone will go through such a curve at some stage in their life. Prepare yourself, is what I say, by regularly asking yourself how you're really doing. That will help you get out of such a crisis in a better state."

Attention to emotions

This is why the foundation is not aiming solely at patients and their loved ones, but at anyone with a conscious attitude in life. Patients share their experiences on its website. In addition, there are all kinds of projects, often artistic in nature, which give attention to people's emotions. "Doctors don't learn enough about this in their medical training, really talking with patients and listening to their concerns and anxieties. There isn't enough time for that in everyday practice either. Patients have little contact with the doctors in charge of their case, and the nursing staff is too busy. That does little to boost their confidence, and hence their recovery process." During his medical training in Kiel (Germany), where the Palestinian moved from Israel at age nineteen, he worked as a nursing assistant at a hospital for six years. "After the physicians had done their ward round, we used to take the time to explain what exactly the doctor had said. That's of course not really how it ought to be." Natour already felt at the time that he did not want to specialise in general internal medicine but become a surgeon, although a surgeon who is interested in the person behind the patient.

YOU'RE MOVING TOWARDS A 'NEW NORMAL', WHICH INVOLVES ACCEPTING YOUR LIMITATIONS THAT'S VERY IMPORTANT

Musical heart

Before coming to Maastricht in 2016, he had worked in Groningen for eight years, where he was already inspired by the idea of the heart as a musical instrument. He is currently preparing a musical composition inspired by this idea. "Music is a universal language, which alters your heartbeat and breathing. Your hormone levels also respond to it, making you feel more at ease. This is why music therapy is also effective for psychiatric patients and people with dementia. But by now we also know from research that music can reduce pain perception. In short, music strengthens communications between people, as it describes things we can't express in words." The same is of course true for other forms of art, which is why Servé Hermans of the local theatre company Toneelgroep Maastricht is working on a theatre show with music, based on interviews with patients. Natour hopes that it will premiere at the local Cultura Nova festival in 2022. His own book, which he wrote about his experiences in care practice, came out in early 2022. It is entitled Wenn das Leben stillsteht, and is now also published in Dutch and in English. A podcast and a volume of poetry are also in the making, and he is also thinking about meetings where patients and loved ones can listen to each other's stories, in order to make them feel more listened to and connected.

Research

And finally, of course, there is the scientific research. His crisis curve can be roughly divided into four phases, "Think of Vivaldi's Four Seasons!", and Natour would like to investigate, for each phase, patients' experiences with the various care parties involved in their life. "Cardiologists, psychologists, rehabilitation physicians, nurses and above all their loved ones; each of those play a major role in a different phase. This study will have to help us to better understand the emotional and social aspects of major medical procedures, and to offer individual patients a tailored therapy. As we know that personalised support leads to more rapid rehabilitation and hence reintegration."

Sponsors and ambassadors are crucial to all these activities of the '*Stichting Stilgezet*'. More information is available at www.stilgezet.nl

INTERVIEW

STELLA THOMASSEN

Finding the gold in the darkest hours

For the last 33 years, Stella Thomassen has been a great connector of people at the Department of Biochemistry, and has been a familiar, inspiring presence for many. Sufficient reason to grant her the 2021 CARIM Commitment Award. “But I don’t want to end my career in the lab,” she says firmly, even though she has the most original lab in Maastricht.

“Have you got Albert Einstein for me?” is what you can sometimes hear at Stella Thomassen’s lab. The pipettes are each named after a famous scientist. The three thrombinoscopes standing side by side are called ‘Earth’, ‘Wind’ and ‘Fire’. The two spectrophotometers are known as a married couple, Franz and Sissy. Around the entire room, high up along the walls, there is a long shelf carrying hundreds of different empty beer bottles. “We’ve tasted them all,” says Stella proudly, “after five o’clock. Sometimes people bring in empty bottles, as they think we collect them, but that’s not how it works.”

At a corner of the shelf stand empty wine bottles, each carrying the name of a PhD candidate and a date. “Whenever one of the PhD candidates had an article published, that had to be celebrated, and we would keep one of the bottles here. I think that’s important: work hard, play hard. A PhD programme is serious and stressful enough as it is.” She is also famous for her bitterballen, the famous Dutch savoury meat snacks, which she used to deep-fry in a fume cupboard. “And I make the world’s best Bicky burgers.” The Acknowledgements sections in the PhD theses invariably thank her for the cheerful parties at the department. “But I also work very hard!” When asked what she is most proud of, however, she says: “I think I managed to retain many people

for science, by creating a pleasant atmosphere. It's up to you to get something going."

BIG SURPRISE

It came as a big surprise to her that her efforts were rewarded with the CARIM Commitment Award in 2021. As a research assistant, being celebrated like this is something she has not seen very often. In fact, a few years earlier she had told her colleagues in a Christman speech about the moment when a professor for whom she had worked so hard for decades forgot to mention her in the word of thanks in his farewell speech. "For a moment, I thought of quitting my job." After they had made up, she used the experience to invest in her own development, as a result of which she now looks back on the incident as 'a great gift'.

For the past seven years she has also been working as a mentor to students in the first three years of their Bachelor programme. "I love doing that: watching them grow, professionally and personally. I've really become more of a people person, and perhaps I'd like to do more of that kind of stuff in the future: mentoring or PhD coaching." In November 2020 she also got her UTQ (university teaching qualification) certificate.

GOING FOR A PHD

Working in a lab has become rather routine for her. "I've been in my maximum salary bracket for years. So Tilman (Hackeng, ed.) is encouraging me to go for a PhD, since I've now had three first-author papers published during the last five years, based on my independent research into mechanisms of natural anticoagulation. Hopefully, having a PhD degree to my name will give me more opportunities for further growth. I only hope I have enough energy for that."

There is a reason why her energy is limited. In December 2020 Stella was diagnosed with a very aggressive form of breast cancer. Fortunately, it was discovered in time, and she will have completed the entire treatment programme in September 2022. At the time of the interview, she is working half-time. "I feel nowhere near as physically fit as I used to, and I have trouble focussing. My hairdo is another thing I still have to get used to. I always used to wear my hair very long. My father used to say: 'If I find you've been up to no good, I'm going to cut off your hair.' So it was awful to lose my hair with the chemotherapy." Stella has learned many things during the past year, and one thing she still hopes to do sometime is hold a TED talk about her experience with cancer. "The title would be 'Finding the gold in the darkest hour of your life.'"

WORKING ON AMBITIONS

Time was when such a presentation would have been unimaginable for her, because of her fear of speaking in public. That was another thing she overcame, by joining the Toastmasters club and the PechaKucha storytelling platform. This enabled her to hold her memorable Christmas speech. She entered the room with her hands raised in the air, while the song 'Life will never be the same' blared from the speakers and everybody copied her 'victory gesture'. "It's bizarre that it was only then, through my disease, that I actually realised that life would never be the same again."

The main message in her speech to the support and management staff was: keep on developing! An essential part of this are the periodical performance interviews with managers. "That's where you can express your ambitions. Not all support staff members have the ambition to further their career, but those who do will have to draw attention to it themselves." How far she herself has come in that

THE MAIN MESSAGE IN HER SPEECH TO THE SUPPORT AND MANAGEMENT STAFF WAS: KEEP ON DEVELOPING!

respect is clear from the fact that when she turned 21, her mother arranged a work placement for her daughter at the Biochemistry lab of what was then called *Rijksuniversiteit Limburg*. “I was at college in Turnhout (Belgium), and had to find an internship. My mother was afraid that I would go “all the way to Antwerp”, and so she cycled to Maastricht to arrange things. In those days, it was not at all obvious for a Belgian student to do their internship in the Netherlands. And the pleasant atmosphere and people then made me stay on.”

CONTRACEPTIVE PILL

She retains many good memories of the many scientific studies she was involved in, mostly studies into the risk of thrombosis for women using third-generation oral contraceptives. The staff had developed its own test for measuring the hereditary factor V Leiden mutation, and to validate the test, many of the lab colleagues, including Stella and one PhD candidate’s girlfriend, had blood samples taken. It turned out that the elevated risk of thrombosis they both had was not caused by this factor V mutation, but that both were using a third-generation pill. “The manufacturer Organon of course criticised our findings, so there was a bit of nervous tension for a while. But a randomised crossover study in collaboration with the Amsterdam Academic Medical Centre enabled us to prove that the pill was indeed the cause. If you also have factor V Leiden, that will further increase the probability of thrombosis, with all the attendant risks. When people think about thrombosis, they think of elderly people, but they’re not the only group at risk.” This is where the thrombosis lobbyist in Stella emerges. Since 2014, 13 October has been named World Thrombosis Day, and on that day Stella and her colleagues go campaigning, at the hospital or in town, to familiarise the wider public with this serious disease and its risks. “When I heard that I thought: Yes! At last a special day for our cause.”

It’s hard to imagine a Biochemistry lab without Stella, and at the very least it will be somewhat quieter. But she thinks it might happen when the lab moves to a different floor shortly. “I’ve always said: if my bottles move, I have to move on. But first I will organise a Bicky burger party after the lab has been cleared out. But perhaps you’d better not write that down...

GRANTS, PRIZES AND HIGHLIGHTS

03

SCIENTIFIC HIGHLIGHTS

In 2021, the successful work of our researchers was reflected in 1,077 scientific publications in peer refereed journals of which 883 Science Citation Index (SCI) articles excluding abstracts and letters to the editor. 56 PhD candidates successfully defended their theses, 1.4 million Euros of funding were received in competition from national science foundations and 3.8 million Euros funding from third money parties, charities, EU framework programmes and industry.

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RESEARCH GRANTS AWARDED TO INDIVIDUALS

NHS DR E DEKKER PROGRAMME

Within the framework of the Dr E. Dekker programme of the Dutch Heart Foundation, **Uyen Nguyen** (Dept. of Cardiology) and **Martijn Hoes** (Dept. of Genetics & Cell Biology) both received a grant. Uyen received a Clinical Scientist grant of € 245,000 for her project 'Predicting and preventing arrhythmias in heart failure'. Patients with heart failure in which the ventricles do not contract at the same time due to a conduction disturbance are usually given a special pacemaker. This pacemaker delivers an electrical impulse to both ventricles simultaneously. However, patients who receive this treatment sometimes also experience cardiac dysrhythmia, which can lead to a cardiac arrest. Doctors do not know in advance in which people this can happen and to what extent there is a relationship between these cardiac dysrhythmias and the pacemaker therapy.

To better understand the occurrence of life-threatening cardiac arrhythmias, it is important to properly map the heart's current impulses during the recovery phase. Uyen will therefore examine these patients before and after the implantation of such a pacemaker with a comprehensive cardiac ultrasound that consists of a kind of 'vest' of 200 electrodes. In this way she can analyse how the current stimuli and the electrical recovery on the heart are influenced by the pacemaker and to what extent they change in patients with cardiac arrhythmia. She is also using computer models to investigate where in the heart the pacemaker leads to the most favorable current-pulse conduction in certain patients. With her research she hopes to be able to predict and prevent arrhythmia in these patients. See pages 62-65 for a full interview with Uyen.

Martijn received a Postdoc grant of € 270,000 for his project 'Unravelling the pathogenesis of peripartum cardiomyopathy'. This grant allows Martijn to study why some women develop peripartum cardiomyopathy during or immediately after pregnancy. It is currently unknown what causes this form of severe heart failure or how it should be treated. Martijn will make small pieces of cardiac tissue from pluripotent stem cells to investigate which molecular mechanisms are impaired in tissues from patients compared to healthy familial control tissues. That way, specific aspects of the disease can be studied without the need for patients to undergo invasive procedures. Previously, Martijn demonstrated that cellular metabolism may be impaired in these patients and he believes that pregnancy hormones

play a key role in the pathophysiology on peripartum cardiomyopathy. Therefore, he plans to combine serum from pregnant women with the generated cardiac tissues to induce pathological effects in patient-derived tissues.

NWO TALENT PROGRAMME

Stepan Denisov (Dept. of Biochemistry) has received a Rubicon grant from NWO for his research on ticks and loss of balance. The Rubicon programme allows recently graduated scientists to gain experience at a foreign top institute. This is an important step up in a scientific career. Stepan will use his grant for a two-year stay at the University of Oxford, UK where he will conduct research on ticks. Ticks may be unpleasant parasites, but we can learn quite a few tricks from them, particularly on how to intervene in our immune system. In this project, Denisov will try to modify tick proteins for the treatment of life-threatening hyperinflammation. Each year, NWO awards the Rubicon grant to 60 young researchers.

DUTCH DIABETES RESEARCH FOUNDATION

Two CARIM researchers have received a grant of € 275,000 for scientific research from the Dutch Diabetes Research Foundation.

Dr **Thomas van Sloten** (Dept. of Internal Medicine) receives the grant for his project 'A microvascular imaging approach to understand brain diseases in type 2 diabetes'. Stroke, dementia and depression are devastating diseases that are two times more common in individuals with type 2 diabetes. To identify improved prevention therapies, Thomas and his team will use advanced imaging techniques to investigate the role of microvascular dysfunction in the etiology of diabetes-related stroke, dementia and depression. Data of the Maastricht Study will be used. In 2019, Thomas already received a Veni grant and a clinical-scientist Dekker grant of the Dutch Heart Foundation for his research.

Philippe Vangrieken (Dept. of Internal Medicine) received the grant for his project 'Methylglyoxal as a mediator of insulin resistance: novel mechanism and unique target'. The accumulation of methylglyoxal and microvascular complications may be a key driver in the development of T2DM. There is ample evidence for an association between methylglyoxal and insulin resistance and thus a role of methylglyoxal in the development of diabetes and its associated microvascular complications. This project aims to unravel how methylglyoxal levels cause insulin resistance and to evaluate whether the methylglyoxal-quenching compound hesperidin prevents the development of insulin resistance and subsequent T2DM. Prior to the current grant, Philippe already received a personal NWO grant, which was on the development of microvascular complications during pregnancy.

DUTCH THROMBOSIS FOUNDATION

The Dutch Thrombosis Foundation has funded the projects of two CARIM researchers. Prof. **Leon Schurgers** (Dept. of Biochemistry) received a grant of € 250,000 for his project 'Virchow's triad: *in vitro* use of iPSCs creating Virchow's organoid to study all three pillars of the triangle'. To understand thrombosis 100%, we need to look at all three causes at the same time. According to Virchow's triad, they are: delayed blood flow, changes in the vessel wall and changes in the composition of the blood. At present, thrombosis is measured in a tube of blood. With the development of 'Virchow's Organoid', we can also analyse the two other components that contribute to thrombosis. By looking at all three components, it will be possible to safely tailor anticoagulants to a patient's needs. Moreover, this method opens the door to the development of new, better anticoagulants.

Dr **Rory Koenen** (Dept. of Biochemistry) received a grant of € 250,000 for his project 'The interplay of blood coagulation and inflammation: unraveling the modulation of tissue factor pathway inhibitor activity by neutrophil enzymes'. It is known that certain (inflammatory) reactions of the body, such as atrial fibrillation or coronary infection, increase the risk of thrombosis. Neutrophils, a type of white blood cell, play a crucial role in thrombosis as an inflammatory response by forming so-called 'neutrophil extracellular traps' (NETs). Inactivation of a specific enzyme can combat thrombosis in these cases. This may be a lead-in point for new anticoagulation methods without the additional risk of bleeding.

OTHER AWARDS, PRIZES AND GRANTS

Dr **Justin Luermans** (Dept. of Cardiology) was awarded a grant of € 800,000 within the programme 'Efficiency Studies' of ZonMw for his project 'Permanent left ventricular septal pacing versus right ventricular pacing in patients with advanced atrioventricular block: a multicenter randomized trial'. In this study, the research group will compare cardiac left ventricular septal stimulation with traditional right ventricular stimulation in 470 patients who need a pacemaker because of bradycardia. The aim is to see whether pacing the left ventricular septum of the heart in pacemaker patients preserves heart contractile function and leads to less heart failure than traditional right ventricular stimulation.

The RECOVAC consortium, in which Prof. **Marc Hemmelder** (Dept. of Internal Medicine) participates, has received a grant of € 3.3 mln from ZonMw (*COVID-19 Urgente Onderzoeksvragen Traject Vaccinstudies*) to study the effect of COVID-19 vaccination in patients with chronic renal failure. The RECOVAC consortium is a Dutch partnership of the Nephrology Departments of all university medical centers, Santeon, Nefrovisie, the Dutch Transplantation Foundation and the Dutch Kidney Patients Association. They are working together in this project to investigate how the immune system of kidney patients responds to vaccination, how effective the vaccine is in the long term and what the side effects are. At CARIM, the study on antibody response after vaccination and national registry study will be performed by PhD candidate Pim Bouwmans.

Dr **Dlzar Kheder,** (Zakho University-Iraq and Pavia University-Italy) was awarded a Marie Curie personal fellowship career restart grant (€ 187,000) and joined the group of Prof. Judith Sluimer in the Department of Pathology in June 2021 for two years. Altogether, he will combine the host's techniques, including single cell sequencing and a fibroblast functionality screening platform, with his skills in vascular contractility analysis. By integration of these techniques, he will identify key fibroblast players promoting or preventing vascular ageing and dysfunction.

The DEFENCE study, in which Dr **Chahinda Ghossein-Doha** (Dept. of Cardiology) is work package leader, has received over € 800,000 funding from ZonMw. Over 500 patients will be prospectively included once they get infected with SARS-Cov-2. Follow-up during admission and until six months post discharge with a comprehensive cardiovascular evaluation including cardiac MRI will enhance our understanding of myocardial involvement in the disease course. This study will provide insight in the incidence of myocardial damage during COVID-19 infection. Moreover, it provides a clinical intervention strategy to decide which patients should be admitted to cardiac follow up. This will enable validation and optimisation of the clinical care pathway for potential future pandemics and will identify those patients at high-risk for developing cardiovascular complications that need routine cardiac follow-up. Prevention of myocardial damage and its consequences has been identified as one of the top 10 knowledge gaps in the current COVID-19 pandemic by the Federation of Medical Specialists (FMS) and included in the multidisciplinary knowledge agenda. The two-year project is part of ZonMw's COVID-19 programme and is a collaboration between the Dutch Cardiovascular Alliance, UMC Utrecht, Amsterdam MC, UMC Groningen, EuroQol and Maastricht UMC+.

Cardiac resynchronisation therapy is an established treatment option for patients with heart failure and disturbances in the electrical conduction of the heart. It consists of a pacemaker and electrodes in the left and right ventricle. Appropriate timing of stimulation of these electrodes coordinates the electrical activation thereby improving cardiac pump function. Abbott developed an algorithm (SyncAV) that allows for automated and ambulatory optimal synchronization aiming at fusion of the activation wave fronts coming from the pacing electrodes as well as intrinsic conduction. The group of Prof. **Frits Prinzen** (Dept. of Physiology) is the ECG corelab of the 1,500 patient randomised controlled trial that investigates the long-term benefit of the use of SyncAV as compared with conventional single manual optimisation. Besides supporting the benefit of SyncAV, the ECG data may also help to further improve the algorithm.

REHAB+, in which Prof. **Arnoud van 't Hof** (Dept. of Cardiology) is involved, is a novel, home-based, mobile cardiac rehabilitation programme that has been co-created with patients, cardiologists, and rehabilitation centres. It offers an optimised digital platform and regular interaction of patients with healthcare professionals to ensure a proper educational environment to establish lifestyle changes and reduce their long-term cardiovascular risk profile. REHAB+ has been awarded an Education grant by the European Institute of Innovation and Technology (EIT) Health to promote healthcare innovation. The REHAB+ study will assess whether mobile tele-monitoring guided cardiac rehabilitation (the REHAB+ programme) result in better sustained and improved effects on physical, mental, and social outcomes in post-myocardial infarction patients, as compared to patients who follow the traditional centre-based cardiac rehabilitation programme. This prospective

observational study is currently enrolling patients in four hospitals located in Spain and the Netherlands, and results are expected in 2023.

Sophie van de Walle was awarded the Harry Crijns Research Grant during the annual CARIM Symposium. Her goal is to move from a curative to a preventative approach for heart disease: the LANDMARC study. The Harry Crijns Research Grant is installed by the *Hart en vaat onderzoekfonds Limburg,* part of the Health Foundation Limburg, and sponsored by Bayer, Amgen and Sanofi. The grant of € 25,000 is periodically awarded to young scientists who are engaged in clinical cardiovascular research and thereby contribute to the realisation of the objectives of the foundation.

Rogier Veltrop, funded by the MSCA-ITN CaReSyAn network, won the Avento Grant 2021 worth € 30,000 to continue his innovative work on iPSC-derived cardiomyocytes in the field of mechanotransduction and signaling pathways. Rogier also received a CytoSMART Research Grant. The CytoSMART Research Grant is an initiative to help motivated students and researchers improve their project's quality. The grant offers a CytoSMART live-cell imaging device that can be used for research purposes for a specified period of time. These devices are suitable for monitoring cell cultures in any research topic that could benefit from live-cell imaging.

Furthermore, the following prizes were awarded to our PhD candidates:

- Kim Maasen: Young Investigator Award during the 38th International Symposium on Diabetes and Nutrition (DNSG 2021)
- Anne Raafs: 'Best oral presentation' during the NVVC (Nederlandse Vereniging voor Cardiologie)

- Armand Linkens: the best Short Presentation Award at the 14th congress of the International Maillard Reaction Society (IMARS14)
- Titus Lemmens: Scientific Excellence posterprize ECTH 2021 Ghent
- Anouk Gentier: *'Prix d'Honneur de la Jeunesse'* during the ECTH Ghent
- Mohammed Ghossein: Pélerìn Pitch Prize 2021
- Elias Wieland: ERASMUS+ staff mobility grant, CARIM grant for 10x single cell sequencing
- Veerle van Hulten: Young Investigator Award during congress American Society for Bone and Mineral Research
- Robin Colpaert: Grant *'Stichting de Drie Lichten'*
- Amée Buziau: Best meeting abstract virtual NVDO/ ADDRM 2021
- Jerremy Weerts: Winner scientific abstract during the NVVC congress session 'Atrial fibrillation'
- Eline Berends: Best oral presentation during the ECCR meeting October 2021
- Gaukhar Baidildinova: Young Investigator Award 5th Euro Spring School on Pulmonary Circulation and Right Ventricular Function
- Rogier Veltrop: Interfood Award 'From the Heart'
- Aaron Iding: Early Career Award at the ISH congress and Jeanne Stibbe Bokaal during the NVTH symposium for best oral presentation

OTHER HIGHLIGHTS

CARIM COMMITMENT AWARD

Stella Thomassen (Dept. of Biochemistry) received the CARIM Commitment Award, intended for any CARIM member who has devoted his/her heart and soul to CARIM in an exceptional way, be it on an academic, managerial, service or community level. The award consists of a bronze coin of the sculptor Marina van der Kooi.

Stella has joined the Department of Biochemistry in 1989, and has since then shaped the department in a staggering positive way, both on scientific as well as social level. She was crucial in deciphering the adverse thrombotic effects of third generation oral contraceptives in the nineties and in a public-private programme on development of haemophilia therapy. She has been one of the emergency response officers for decades, and the driving force behind Biochemistry's annual normal plasma pool donations. She is also a strong believer in societal impact of science and creating awareness on cardiovascular disease and the need for research. She organises World Thrombosis Day in Maastricht since its conception in 2013, and she's regularly found on Pecha Kucha and TED-X like stages. (see pages 38-41 for a full interview with Stella).

DCVA LEADERSHIP PROGAM 2021

Prof. **Judith Sluimer,** Dr **Chahinda Ghossein-Doha** and **Rogier Veltrop** have been selected for the DCVA Leadership Program 2021. With the Leadership Program, the DCVA wants to prepare top talents from all these disciplines for a future as a leader in the cardiovascular field. See pages 12-17 for a full interview with Judith, Chahinda and Rogier.

MICHIEL HENKENS COORDINATOR OF THE HEART TISSUE BANK

Michiel Henkens has been selected as coordinator of the Heart Tissue Bank *(Hartenbank)*. The Heart Tissue Bank of the Netherlands Heart Institute (NHI), a non-profit organisation founded in June 2020, is a central biobank in which heart tissue from deceased donors and associated medical data is stored for scientific research. This heart tissue can be used to investigate how a healthy heart functions and what exactly goes wrong in various heart diseases. Both people with and without heart diseases can register as a future donor at the Heart Tissue Bank. See pages 18-21 for a full interview with Michiel.

CARIM TOP CITERS

In 2021, Prof. **Coen Stehouwer** (Dept. of Internal Medicine) and Prof. **Christian Weber** (Dept. of Biochemistry) were ranked among the top scientific scholars in the world. Prof. Stehouwer was ranked by Expertscape's PubMed-based algorithms among the top 0.15% of experts in the prediabetic state: on basis of the Maastricht Study, Stehouwer and team found that prediabetes is not quite as innocent as was perceived but coincides with considerable and measurable multiple organ damage. On basis of these results, US Preventive Task Force currently advises active monitoring and treatment of prediabetes. Prof. Weber was identified by Clarivate (Web of Science) as one of the world's most influential researchers: the select few who have been most frequently cited by their peers over the last decade. In 2021, fewer than 6,700, or about 0.1%, of the world's researchers have earned this exclusive distinction. Prof. Weber is recognised for his ground-breaking work on deciphering and treating inflammatory processes that lead to atherosclerosis.

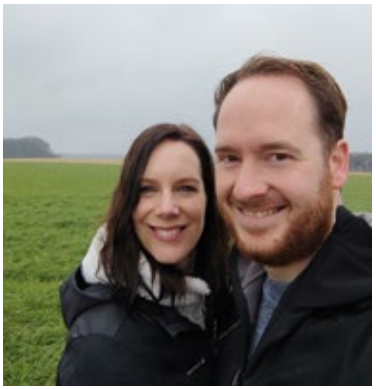
CARIM PRIORI

CARIM selected two members of the Executive Board in a special way: by draw. At the annual symposium, names were drawn from two bags, one for men and one for women. The new members will be added to the current seven-member board. All 79 scientific and 34 supportive staff members with a permanent contract competed – in principle they are all suitable for the position. Three names were drawn from each bag in the following order: 1. Carla van der Kallen; 2. Lidewij Bos; 3. Johanna Driessen; and 1. Bastiaan de Galan; 2. Wouter Verhesen; 3. Paul Schiffers. Carla and Bastiaan have accepted the membership and will join the CARIM board from 1 January until 31 December 2022. Tilman Hackeng came up with the idea while on holiday in Florence. There, during the Renaissance, every two months the city council was drawn from all guild members over 30 years of age and of impeccable conduct. At CARIM it is a one-year position. By adding two rotating members, the board will become a better reflection of the organisation, with more diversity and inclusivity. See pages 122-125 for a full interview with Carla and Bastiaan.

CARIM AT HARTSTOCHT

On 10 April, more than 30 CARIM members participated in the mostly rainy *'Hartstocht',* organised by the Dutch Heart Foundation, to raise money for cardiovascular research.

CARIM AT HARTSTOCHT



PROFESSORSHIPS

Joost Lumens (Dept. of Biomedical Engineering) - Professor of Computational Cardiology

The general objective of the Computational Cardiology chair is to better understand the pathophysiological links between cardiac arrhythmias and structural heart failure. Where possible, new insights arising from this research will be translated into improvements in the diagnosis and therapy of (electrical) heart failure. Methodologically, the emphasis is on the development and application of personalised computational models of the heart and circulation, covering different scale levels. Joost's ambition specifically includes profiling the virtual heart patient (Digital Twin) as a platform for cardiovascular research and education, and for diagnostic and therapeutic decision support in the clinical environment.

INTERVIEW

UYEN CHAU NGUYEN

Hard worker, in the guise of a lucky lady

In 2021, Uyen Chau Nguyen received a Clinical Scientist Dekker Grant from the Dutch Heart Foundation, worth 245,000 euros. “Even though I had the feeling that the interview went badly.” A few years earlier, she had been offered a position as a resident cardiology. “Whereas at the time I wasn’t yet a good doctor at all.” By the end of our interview, she says: “Perhaps it’s something typically feminine not to attribute your success to your achievements, but to luck. Although you do need some of that as well.”

It's only a week since Uyen Chau Nguyen returned from maternity leave, having given birth to her second child. She shares her room with her PhD candidate who, also just a week ago, started the research project for which Nguyen received the Dekker Grant. "For the next year I'll be doing a minimal amount of clinical duties; I've put my training on hold so I can give her the maximum guidance." The PhD candidate has come from the University of Twente, where Nguyen herself studied clinical technology. During her six-year degree programme there, which she describes as 'technical medicine', whenever she shadowed a medical doctor, she felt how much she wanted to engage in patient care too. At the end of her fifth year, she decided to go for it: she applied for the four-year Master's programme at Maastricht University called Medical Doctor–Clinical Investigator. "I decided that if I wasn't accepted, I would let it go." She was accepted, and eventually completed both programmes nearly at the same time in 2016.

PURE LUCK

Already during her medical studies, she conducted research, under the supervision of Professor Frits Prinzen. After her graduation, she continued to do so as a PhD candidate, until at the beginning of 2018 she had the opportunity to work at the cardiology clinic, which might lead to a residency ship. "By the end of 2018 I was officially accepted into the residency programme, purely by luck. I was more a researcher than a medical doctor: it was hard for me to quickly grasp the key features in the clinic, and I tended to go into all of the patient's interesting details. This was another point in her career where she found it difficult to decide how to continue. "Cardiology is a branch of medicine that involves many shifts; how can you combine that with having children later? I applied for a job in Radiotherapy, as that would fit in with my background in technical medicine. I was accepted into the programme, but when I got back to Cardiology and saw a beating heart, I literally followed my heart. To me, an ECG or a moving heart was a lot more fascinating than any other organ. And even though the future is much less secure in this discipline, I couldn't let the opportunity slip by."

NO TIME FOR RESEARCH

For the first year of her cardiology training, Nguyen had to concentrate on the clinic; there was no time for research. "Even though I already knew at the time that I wanted to combine the two later on, just like the cardiologist Vanessa van Empel, for instance." When time for research became available again, she thought that while on maternity leave for her first child, she would be able to 'just' write a proposal for a Dekker Grant. "I had no idea what it would be like to become a mother. That first time was one of the toughest things I'd ever done." By 2021, she did go for it, even though she was doing Covid shifts at the hospital and she and her whole family fell ill during the two weeks' leave she was given to write her proposal. "With hindsight I can't think how I managed to write the proposal. My first child was just one year old, so I had a bit more time to work in the evenings and particularly nights. And so I made it. Luck played a part too, I think."

BEST PAPER

She practised for the Dekker interview with the CARIM Research Council, and one day before the interview she rehearsed once more with Frits Prinzen and Matthijs Cluitmans. But even so, after the interview she felt more like crying than laughing. "The atmosphere was highly critical, at least that's how it felt to me. In the application, you had to highlight your favourite paper, and motivate your choice. I chose a relatively recent paper in which I described a technique I had further developed and translated into clinical

practice in sixteen patients. It had not been cited very often yet, and then during the interview someone said: 'Your best paper has not often been cited in the past five years….' So I explained that I had chosen this paper because it comprises the entire translational process from technical development to clinical application. To me, the impact factor and the number of citations are not the most important aspects; what counts is delivering high quality research, I said. I was surprised to get the grant after all. Maybe it's typically feminine to think it was mostly luck. In such situations I have the feeling I'm acting a part. You adapt to what people expect of you, but it doesn't always feel like who you really are deep inside."

ECG IMAGING

The research project she is going to work on with the Dekker Grant was inspired by a patient. "I was caring for a hospitalized patient in Maastricht, who had had an elaborate (biventricular) pacemaker implanted. Briefly after implantation, she developed dangerous ventricular arrhythmias, which she had never had before." Nguyen started to investigate the relation between this type of pacemaker and the development of dangerous arrhythmias. "How are they related? Can it be predicted? There appears to be a relation with the heart's relaxation phase, which seems to adapt to pacing. Can we visualise this with ECG imaging?"

ECG imaging is the technique developed by Matthijs Cluitmans, a fellow physician-engineer and researcher at both UM and Philips. Nguyen met him through Frits Prinzen. "I was trained as an engineer and medical doctor and was looking for someone with a similar hybrid background during my master thesis to exchange ideas about coding issues. Frits introduced me to Matthijs. We had a lot in common." By combining his technique with other imaging modalities like MRI and CT, Nguyen wants to investigate the heart's relaxation phase in people before and after the implantation of a biventricular pacemaker. In addition to a group of patients in Maastricht, she will also collaborate with researchers from Bordeaux, where they have collected an unique dataset of biventricular pacemaker patients who underwent ECG imaging. "Simultaneously with the patient studies, we will be collaborating with computer modellers from Lugano, where I conducted research as a master student. They develop electrophysiological models, and we intend to use the data from Maastricht patients to tailor the model. You can then virtually test what happens if you implant the pacemaker a certain way, and try to predict the risk of arrhythmias. Although I have to admit that we probably won't be able to complete all that before the Dekker Grant runs out.

IN FIVE YEARS' TIME

And then there is the matter of completing her PhD thesis, hopefully in a year's time. "A PhD degree is a requirement for the next grant I want to apply for. I've already produced the scientific publications for my thesis a number of years ago, so most of the work is done. I still have to write a general introduction and a general discussion chapter."
In five years' time, she hopes to become a cardiologist-electrophysiologist as well as a technical investigator. "What I will always carry with me is my engineering point of view. I'm looking for technological solutions for patients' physical problems." Now she knows where her destination lies, she seems to have some regrets about the circuitous route her career path turned out to be at times. "There are people my age who are already cardiologists, who have got there much faster than I. But I shouldn't compare myself with others too much."


Bared Mees

HIGHLIGHT
DIVISION VESSELS

BAREND MEES

The RegMed XB Cardiovascular Moonshot

With the aging of our population and the epidemics of hypertension, coronary artery disease and obesity, the incidence and prevalence of heart failure (HF) continue to rise. Although currently available guideline-directed medical therapy (GDMT) has helped significantly to improve symptoms and survival of patients with HF, a subset of patients with chronic HF will continue to progress and develop persistent severe symptoms despite maximum GDMT.[1] For these 'end-stage' HF patients, cardiac transplantation remains the gold standard and the only curative treatment.[1,2] Unfortunately, there is a global shortage of donor organs and there are limitations to the use of the organs that are available. Therefore, novel treatments are continuously being developed, such as a total artificial heart implantation (the first in the Netherlands) in a patient with end-stage HF who was not acceptable for heart transplantation (UMCU, 2021). This year, the first cardiac xenotransplantation (pig to human) was performed using a genetically modified porcine heart and a cardiac bioreactor. These therapies have significant side effects and have had limited success, underlining the need for alternative strategies. Therefore, the Cardiovascular Moonshot was initiated by RegMed XB.[3]

RegMed XB is a public-private partnership dedicated to bringing regenerative medicine solutions to patients. RegMed XB brings together leading scientists at Dutch and Belgian universities and a range of companies in so-called 'Moonshots', long-term visions of breakthroughs for patients, translated into research roadmaps with specific short-term milestones. There are currently four Moonshots, namely for kidney, diabetes, osteoarthritis, and cardiovascular. Each is championed by a Health Foundation and their related patient organisations, putting patient impact at the heart of RegMed XB.[4]

The RegMed XB Cardiovascular Moonshot is a collaboration between the universities of Eindhoven, Leiden, Utrecht and Maastricht, as well as several industrial partners. The ultimate goal of the Cardiovascular Moonshot is to repair or regenerate hearts *ex vivo*, creating solutions for patients with different degrees of cardiovascular disease, with the ultimate goal of preventing their transition into end-stage HF. Additionally, by learning from repairing (rejected) or preparing donor hearts and patients' own hearts facing end-stage cardiac disease, therapies will be developed that will benefit many more patients with variable causes of heart failure.

HIGHLIGHT

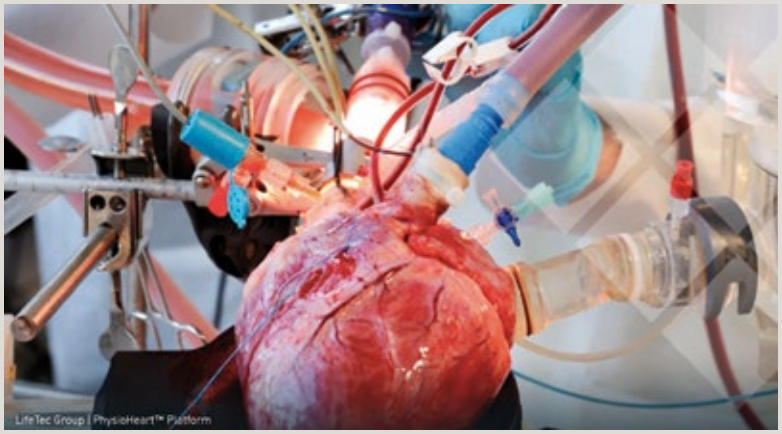


FIGURE 1 *Ex vivo* normothermic ventricular loaded porcine heart perfusion using the isolated beating heart platform (*PhysioHeart™* system) from LifeTec Group.

Currently, a donor heart is mostly stored on ice and kept alive for up to 4-6 hours. However, *ex vivo* perfusion of the heart has several potential advantages over cold storage, such as extending storage time without negative effects on function and even improving organ function, thereby offering opportunities for extending the transplantation programme to more patients. For several organs (lungs, liver, kidney), *ex vivo* perfusion is already being used to improve organ quality prior to transplantation. Yet, improved organ preservation with *ex vivo* functional improvement and options for storage time extension still need to be developed for the human heart. Therefore, the first and most important milestone of the Cardiovascular Moonshot is the development of a cardiac bioreactor.

Once the optimal protocol for the bioreactor to extend survival time and maintain the condition of perfused hearts has been identified, the bioreactor will serve as a toolbox for regenerative medicine purposes, like correction of myocardial architecture, induction of cardiomyocyte proliferation, stimulation of the micro-circulation, *ex vivo* valvular repair, arterial regeneration or replacement and correction of genetic deficits. Ongoing monitoring of cardiac function can be performed to evaluate changes over time. The *ex vivo* setting will facilitate several unique opportunities, like taking serial biopsies to judge cardiac condition and monitoring various steps in transduction, cell cycle and coupling - both physical and electrical. In addition, drug testing and gene therapy can be performed and directly monitored. There is currently no alternative approach to continuously monitor the effectiveness of gene or drug therapy at the cellular or subcellular level.

In the first two years of the Cardiovascular Moonshot, joint efforts predominantly focused on cardiac perfusion, leading to the development of five different operating heart perfusion models:

1. The Heart Box for *ex vivo* hypothermic perfusion for an extended period, suitable for transportation.
2. A ventricular *unloaded* large animal *ex vivo* perfusion model for both hypothermic and normothermic perfusion.
3. A ventricular *loaded* large animal *ex vivo* perfusion model capable of assessing cardiac function (*PhysioHeart™* system, LifeTec group, **Figure 1**).
4. A small animal (mouse) *ex vivo* perfusion system in either a ventricular loaded or unloaded state for up to 4-6 hours.
5. An *ex vivo* mini culture system in which mouse hearts can be maintained unloaded for 7 days.

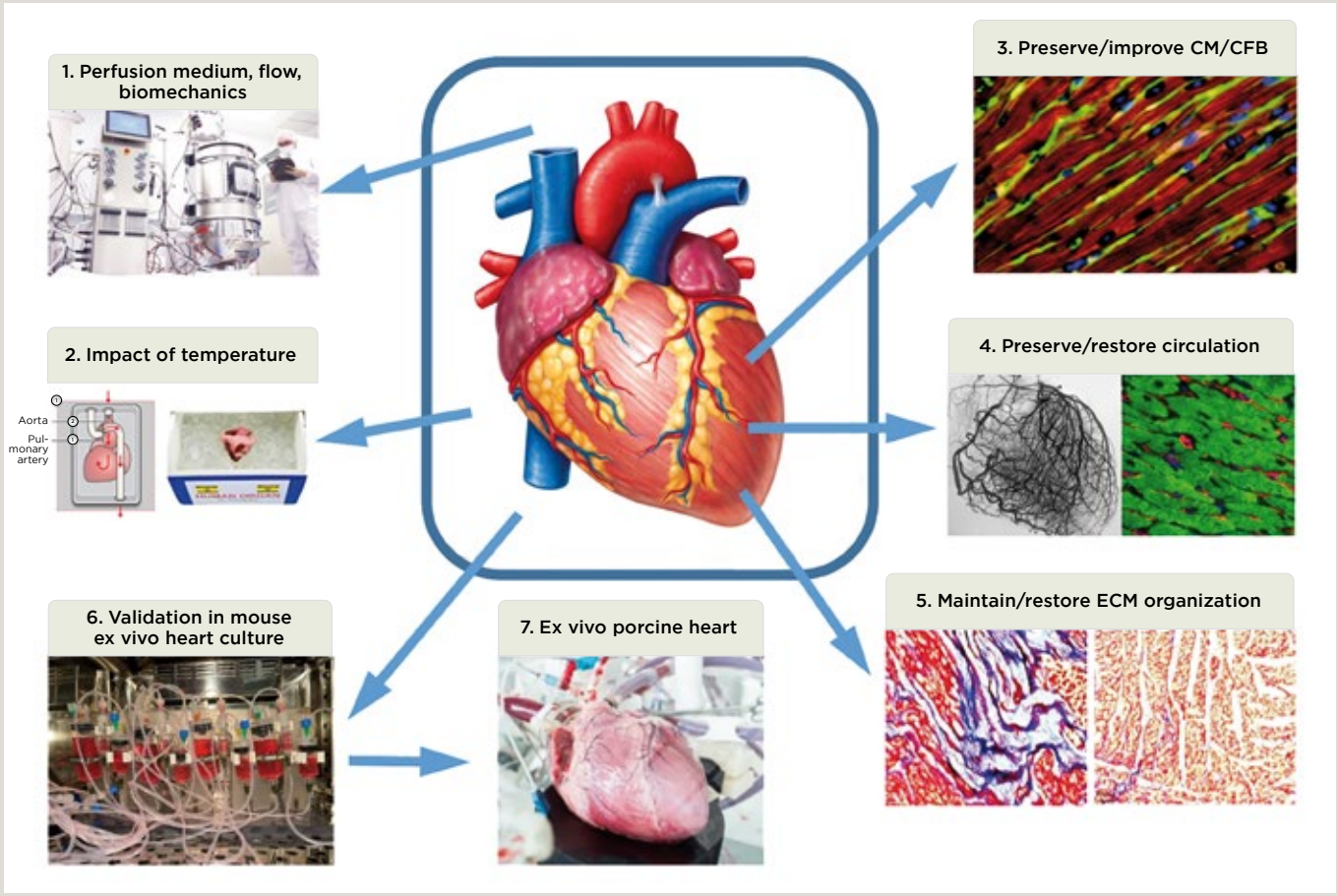


FIGURE 2 Steps in developing the optimal cardiac bioreactor as a bridge to transplantation and as a platform for regenerative medicine. 1. Define the optimal perfusion medium, flow, and biomechanical characteristics for perfusion up to 7 days for different temperatures. 2. Define the optimal temperature for perfusion and regeneration approaches. Morphology and gene expression are monitored in the porcine heart but also *in vitro* and if needed *ex vivo* in the mouse heart. 3. During culture in the box, the impact of 1 and 2 on cardiomyocyte (CM) and cardiac fibroblast (CFB) organisation is determined. 4. Micro- and macro-circulation are crucial to maintain and restore cardiac contractility, and thus the impact of culture in the box on the circulation will be monitored. 5. Matrix isotropy (ECM; extracellular matrix) is crucial for cardiac function and will be monitored during heart culture in the box. 6. Hypotheses obtained from porcine heart experiments will be investigated *in vitro* and in the mouse heart. 7. The optimal conditions determined *in vitro* and in mouse models will be validated in the *ex vivo* porcine heart model.

HIGHLIGHT

Using these five perfusion models, a step-by-step system has been set up, working towards a cardiac bioreactor and regenerative toolbox using the combined expertise (cardiac tissue, coagulation, immunology, valves, micro- and macro-circulation) of the different university and industrial partners (**Figure 2**). Maastricht University (CARIM/MERLN) is responsible for the vessels programme within the Cardiovascular Moonshot. Thus, coagulation assays in porcine heart perfusion experiments by Magdi Nagy (CARIM) have demonstrated an overall increase in coagulation activity (TAT) despite the presence of heparin in the whole blood perfusate. This activation may originate from the intrinsic coagulation activity (FXIIa:AT) caused by tissue damage and will be subject to further studies. The aim will be to counteract the negative effects of coagulation activity on myocardium preservation, using different perfusate regimens (**Figure 3**) In parallel, our other activities have focused on strategies to preserve sufficient flow to the cardiac tissue during perfusion and reperfusion. Perfusion is managed by both the micro-circulation and the macrovascular system (coronaries). We collaborate with LUMC to investigate the vascular damage to both systems due to the *ex vivo* perfusion of the heart, and strategies have been initiated to optimise perfusion fluids and techniques to minimise vascular damage and leakage.

To preserve cardiac perfusion in case of significant coronary artery disease, we are developing a decalcification technique for coronaries, which can be added during the *ex vivo* perfusion phase of the heart in the cardiac bioreactor. We have tested different decalcification methods for a variety of vascular calcifications, both in culture and in a 'vessel-on-chip' environment (Armand Jaminon, CARIM & Daniela Baptista, MERLN). We observed that for intimal, medial as well as *in vitro* calcification, different strong and weak acids and calcium chelators are capable of decalcifying both tissue and cells. However, further optimisation of this technique is needed with respect to maintaining cell viability and tissue integrity after decalcification. Finally, in the case of severely diseased coronaries, a mix of different conduits, such as in-house spun biodegradable vascular grafts (Julia Fernández, MERLN), artificial vessels or allografts, will be available to replace coronaries and restore cardiac perfusion.

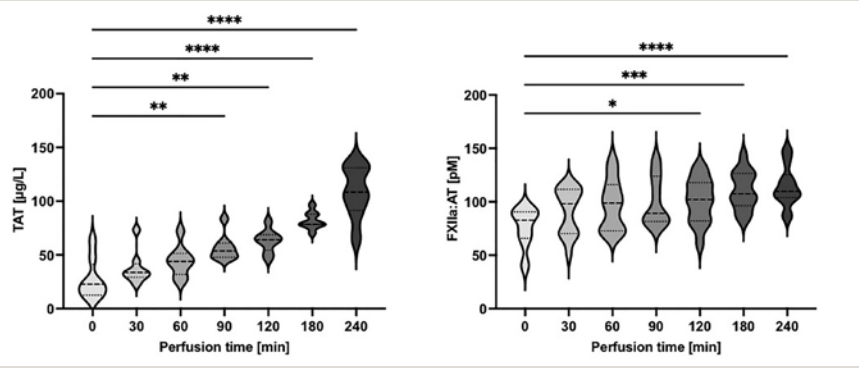


FIGURE 3 Increased coagulation activity during *ex vivo* heart perfusion. Porcine heart was perfused with autologous whole blood in normothermic condition. Blood was collected during perfusion, and coagulation activity was assessed by measuring thrombin:antithrombin [TAT] and activated coagulation factor XII:antithrombin [FXIIa:AT] complexes.
* p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

HIGHLIGHT

The RegMed XB Cardiovascular Moonshot takes us on an astonishing journey towards cardiac regeneration therapies for individual patients. In 5-10 years, we will be able to explant the hearts of most severe stage patients for *ex vivo* cardiac repair followed by reimplantation, while patients are kept alive on extracorporeal mechanical support. Hence, *ex vivo* cardiac gene therapy for inherited disease will become feasible without exposure to off-target organs. Furthermore, in less severe stage patients, we will be able to, *in situ*, stimulate endogenous repair and enhance contractility and perfusion of the myocardium (via cardiac patches and/or re-organisation of the myocardial wall), as well as improve coronary vasculature, conduction system and valve function. We are thrilled to play a role in the development of these exciting innovative technologies to help achieve our common target of reducing the burden of cardiovascular disease by 25% in 2030.[5]

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INTERVIEW

CHAHINDA GHOSSEIN-DOHA

Crowdfunding 2.0

Whereas 'crowdfunding' is usually an activity of limited duration, Chahinda's crowdfunding campaign has developed a permanent character. Crowdfunding 2.0, you might call it. And although raising money for research is of course useful and necessary, to her the contacts it has yielded, and the impact on others, are at least as valuable.

In two years' time, she hopes to have completed her cardiologist training. At the same time, she uses the evenings and weekends for research into preeclampsia (focusing on its long-term (cardiovascular) effects and its association with psychological and cognitive problems). She is also investigating whether a woman's placenta can predict future vascular problems. Many of the women who cooperate in the research move along from one study to the next, so Ghossein-Doha is actually able to follow a cohort over several decades.

NOT ALONE ANYMORE

The foundation she has started, called Queen of Hearts, involves many other activities besides this research. For instance, she wrote a Queen of Hearts book presenting stories of women's personal experiences, and she has organised concerts and a charity gala. She has raised money for research by entering with a team in the 2021 Iron Man sports event, and by selling silk-screen prints designed by an artist specially for Queen of Hearts. Ghossein-Doha: "But what's perhaps even more important: with each activity, new people join Queen of Hearts. They recognise themselves in the stories we publish, from their own experience and/or from their professional practice, and so they try to contribute something. Many of them say that for the first time in years they understand what has happened to them, and they no longer feel alone. They realise how many women are confronted with this, and want to dedicate themselves to the cause. And so it's become more of a movement rather than just a research programme. I'm at least as proud of that

IT'S BECOME MORE OF A MOVEMENT RATHER THAN JUST A RESEARCH PROGRAMME

as of the funds we raise. Maybe even more so, as it means something permanent for a whole generation of women, whereas money is transitory."

SPECIAL BOND

This is also how artist Kiki van Eijk got involved in the foundation, after having seen Ghossein-Doha in Eva Jinek's popular talkshow on Dutch TV. "Kiki also joined our Iron Man team last year, even though she was actually suffering from pneumonia. But she was determined to complete the half-marathon with me and the others." Like Jinek, Van Eijk had had preeclampsia herself, and during the 2021 Dutch Design Week she created a large art installation centring on a formalin-preserved placenta and the stories of women who had experienced complications of pregnancy. In addition, she produced a silk-screen print called 'Fragile' in an edition of 200 copies which are for sale, with part of the revenues going to the foundation. Eva Jinek was presented with the first copy last year. Ghossein-Doha: "I have a special bond with her, as she was the first woman to donate her placenta for my research. She told her story in our Queen of Hearts book of women's experiences with complications of pregnancy. She has taken part in nearly all our studies, and has used her position to contribute a lot to raising public awareness of our foundation. That's why it was an honour for me to present her with the first copy of the silkscreen print."

MOVING WOMEN

The success of the sponsored participation in the iron man event was an incentive to do more. "In 2022 we want to use our activities to get more people, especially women, to become more active. They can not only take part in the Iron Man event, but set their own sponsoring targets for any sport or activity." This brings out the activist in Ghossein-Doha. "There's been so much commotion about women in recent years, but they were often the victims, as in the Me-Too movement. That makes me think we can take control of our own destiny and determine for ourselves how we want

to position ourselves. It doesn't always have to be *about* us. We have to be part of the debate and contribute ideas, for one thing by taking control of our own health and our own life. I would like to see the image of women having to be protected changed to one of 'We need no protection; we can determine for ourselves what we do and don't want.' That starts with taking care of your own health, and the rest will develop step by step."

DIFFERENCES BETWEEN MEN AND WOMEN

The trainee cardiologist is also outspoken when it comes to focusing on the differences between men and women. During the first COVID wave, she worked in Intensive Care in Maastricht, where she saw that men and women were receiving the same treatment. "I was itching to do some research." She therefore analysed the research data of over 6,100 patients with COVID, together with her colleague Bas van Bussel. "None of the clinical studies made an a priori distinction between men and women, and only one study examined afterwards whether the patient's sex had contributed in some way to the findings. We also noticed that only 41 percent of the patients in the studies were women, and a quarter of the studies even included twice as many men as women." Whereas other research she had undertaken herself had already shown that women were less likely to die of COVID-19 than men.

GETTING THROUGH TO PEOPLE

When you hear about all the things Ghossein-Doha does alongside her full-time cardiology training, it may seem that her days have more than 24 hours. "If you carefully plan ahead and utilise each moment, there's a lot of time in one day," she says cheerfully. She is also involved in the Dutch

IT DOESN'T ALWAYS HAVE TO BE ABOUT US WE HAVE TO BE PART OF THE DEBATE AND CONTRIBUTE IDEAS

Cardiovascular Alliance's leadership programme and invests a lot of time in her Queen of Hearts foundation. "People often ask me where I got the name from, and I wish I could give them a profound answer. But unfortunately, is just the outcome of an evening of brainstorming,"

You might characterise the foundation's activities as "permanent crowdfunding", but that doesn't really do it justice. Ghossein-Doha: "I want to translate the results of our research back to the people, to get the message across to people, and one of the ways of doing that is through music, art and sports. Our scientific language is not readily transparent to everyone, so you have to look for other forms of communication. That's how you gain the trust of the people it's all about."

EDUCATION AND TALENT DEVELOPMENT

04

INTRODUCTION

CARIM offers a flexible and integrated education and training programme that suits the individual ambitions of its students. Clinical and preclinical staff of CARIM is intricately involved in the development and execution of the education programmes of the FHML Bachelor and Master studies of Biomedical Sciences, Medicine, and the Physician-Clinical Investigator Programme (MSc/MD). CARIM is also involved in 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 top researchers, while its framework has been created by senior educators of Maastricht University, who have earned an excellent international reputation for their didactic system that is 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 Schools during the start of the master phase. Members of the CARIM staff actively participate in the design and execution of the teaching programme in the second and third course. Students can attend school-specific lectures and parallel programmes organised by school researchers. In the second semester, they may become acquainted in more detail with School specific practical research. In this respect, CARIM offers students the opportunity to do a junior research internship in the field of cardiovascular sciences at one of CARIM's laboratories. In the second year, the students that are attracted to cardiovascular research can do their senior research internship and master thesis in CARIM. These internships are also accessible for students from other master programmes, provided that they have an adequate background. All too often successful master students 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 end of 2021, in total 355 (internal as well as external) PhD candidates attended our PhD programme. In 2021, 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. 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 themselves into independent and productive researchers in the cardiovascular field. To ensure high quality PhD training, CARIM offers frequent interaction of PhD candidates with skilled and experienced supervisory teams, thereby providing a stimulating and critical environment to further develop research skills. We also offer our PhD candidates a broad range of possibilities to attend general and school specific courses, to attend seminars and master classes, and provide support of a buddy (senior PhD candidates) and a coach (senior staff member). PhD candidates are stimulated to visit symposia to present their own research on national and international podia. In 2021, 32 new PhD candidates started their trajectory at CARIM and 56 defended their theses successfully.

POSTGRADUATE PROGRAMME

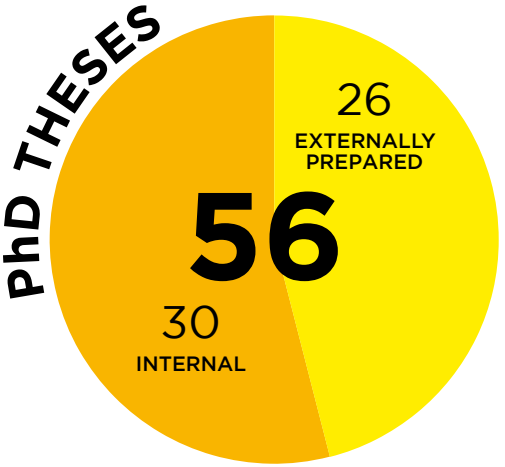
One of the key needs identified by the European Society of Cardiology is the training of future leaders in arrhythmia management and research. For this purpose, a unique two-year postgraduate educational programme entitled 'Diploma of Advanced Studies in Cardiac Arrhythmia Management' (DAS-CAM) has been established. DAS-CAM trains the future leaders in cardiac electrophysiology by integrating state-of-the-art cardiac arrhythmia management with leadership skills, biostatistics and health technology assessment. DAS-CAM is a collaboration between Maastricht University, the European Heart Academy (EHA) and the European Heart Rhythm Association (EHRA). It consists of eight modules (six of which take place in Maastricht) each chaired by two expert anchor persons supported by the Scientific Program Committee. Researchers from CARIM play a major role in the DAS-CAM programme, with four CARIM Principal Investigators serving as anchor persons and several CARIM researchers involved as members of the Scientific Program Committee and guest lecturers. In addition, a number of DAS-CAM participants will continue to be affiliated with CARIM through a PhD research project.

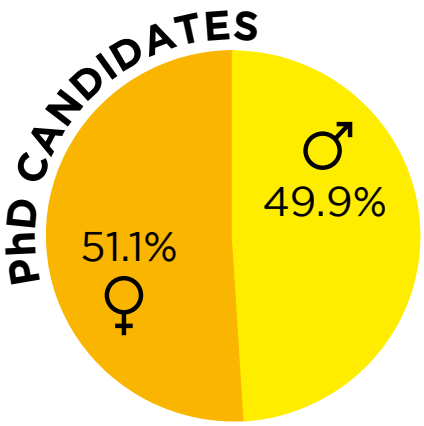
In 2021, the second successful PhD conferral of a former DAS-CAM participant took place. In addition, the final modules of the second DAS-CAM edition, which started in

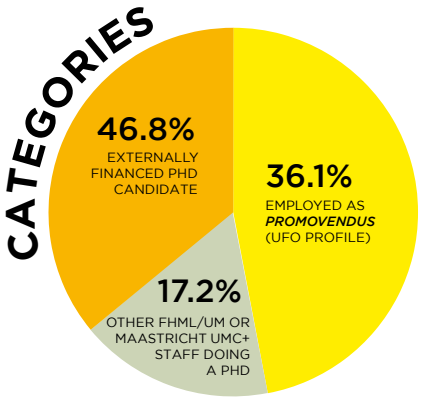
2019, were completed in a hybrid format. The graduation of this edition has been (re)scheduled for the first half of 2022, to enable maximal in-person attendance. In parallel, the third edition of DAS-CAM has started in 2021, with 31 new participants spanning time zones from Canada to Mongolia and including two CARIM researchers.

PHD STATISTICS

In 2021, 30 PhD candidates finished their theses within our institute and 26 theses were externally prepared. The male/female ratio within the group of PhD candidates is about 50/50. Almost 60% of our PhD candidates come from abroad.







CARIM THESES 2021

Naoual Bennaghmouch
Title: The use of the non-vitamin-K oral anticoagulants in patients with atrial fibrillation with(out) concomitant coronary artery disease: To be or not to be? That is the question
Supervisor: Prof. H. ten Cate
Co-supervisors: Dr J.M. ten Berg, Prof. M. Rienstra (University of Groningen)
7 January

Job Verdonschot - CUM LAUDE
Title: Causes and consequences of dilated cardiomyopathy: Integrating genotype and phenotype to redefine disease diagnostics and therapeutics
Supervisors: Prof. S.R.B. Heymans, Prof. H.G. Brunner
Co-supervisors: Dr I.P.C. Krapels, Dr M.R. Hazebroek
8 January

Frank van Rosmalen
Title: New items in the electrophysiologist's toolbox. Future improvements for electrophysiological AF treatment
Supervisors: Prof. T. Delhaas, Prof. U. Schotten
Co-supervisor: Dr S. Zeemering
13 January

Svenja Petersohn
Title: Health technology assessment of treatment for peripheral arterial disease
Supervisor: Prof. M.A. Joore
Co-supervisors: Dr A.J. ten Cate-Hoek, Dr B.L.T. Ramaekers
14 January

Henry Sutanto - CUM LAUDE
Title: Integrative Computational Modeling of Calcium Handling and Cardiac Arrhythmias
Supervisors: Dr J. Heijman, Prof. H.J.G.M. Crijns, Prof. P.G.A. Volders
15 January

Federica De Majo
Title: Healthy aging: the heart of the matter is outside of the heart
Supervisors: Prof. L.J. de Windt, Prof. M. Stoll
20 January

Floris Schreuder
Title: Non-Invasive Imaging of the Carotid Artery - From structural vessel wall to functional plaque imaging
Supervisors: Prof. W.H. Mess, Prof. M.E. Kooi, Prof. R.J. van Oostenbrugge
21 January

Nynke Simons
Title: Nonalcoholic Fatty Liver Disease in relation to Cardiovascular Disease: Is all fat equal?
Supervisors: Prof. M.C.G.J. Brouwers, Prof. C.D.A. Stehouwer, Prof. N.C. Schaper
26 February

Emilia Ruggiero
Title: Mediterranean diet and beyond: an Italian perspective
Supervisors: Prof. H. ten Cate, Prof. G. de Gaetano (Pozzilli, Italy)
Co-supervisors: Dr L. Iacoviello, Pozzilli and Varese-Como Italy, Dr M. Bonnaccio (Pozzilli, Italy)
1 March

Richard Houghton
Title: Utilisation and outcomes of treatment in Autism Spectrum Disorder
Supervisors: Prof. F de Vries, Prof. J.P. van den Bergh
4 March

Quentin Roblain
Title: The eye as a miRror: targeting microRNAs
Supervisors: Prof. S. Heymans, Prof. A. Noël (University of Liège)
Co-supervisors: Dr V. Caolo, Dr J. Lecomte (University of Liège)
15 March

Arantxa Barandiaran Aizpurua
Title: The pursuit of understanding Heart Failure with preserved Ejection Fraction (HFpEF)
Supervisor: Prof. B. Schroen
Co-supervisors: Dr V.P.M. van Empel, Dr C. Knackstedt
26 March

CARIM THESES 2021

Judith M. Hilderink
Title: Real change or natural fluctuation? Linking laboratory results to clinical practice
Supervisors: Prof. O. Bekers, Prof. R.P. Koopmans
Co-supervisor: Dr S.J.R. Meex
30 March

Laura Vergoossen
Title: Brain Network Alterations due to Cardiometabolic Risk Factors; Insights from Population Magnetic Resonance Imaging
Supervisor: Prof. W.H. Backes
Co-supervisors: Dr J.F.A. Jansen, Dr M.T. Schram
1 April

Sotirios Nedios
Title: Catheter ablation of atrial fibrillation: the association between atrial anatomy and clinical outcomes
Supervisors: Prof. H.J.G.M. Crijns, Prof. G. Hindricks (Leipzig University)
Co-supervisors: Dr J. Heijman, Prof. A. Bollman (Leipzig University), 14 April

Mark Friedberg
Title: The stressed right ventricle and its impact on the left ventricle
Supervisor: Prof. F.W. Prinzen
Co-supervisors: Em.Prof. F. Meijboom (Utrecht University), Dr J. Lumens
21 April

Lu Dai
Title: Chronic kidney disease - a clinical model of premature vascular aging
Supervisors: Prof. L. Schurgers, Prof. P. Stenvinkel (Karolinksa Institute, Stockholm), Prof. R. Kramann (RWTH Aachen University)
6 May

Nienke Verzaal
Title: Branching out: CRT beyond current concepts
Supervisors: Prof. F. Prinzen, Prof. T. Delhaas
Co-supervisor: Dr C. van Deursen
10 May

Walid Chayoua
Title: The Antiphospholipid Syndrome: The clinical importance of detecting antiphospholipid antibodies by immunoassays
Supervisors: Prof. H. ten Cate, Prof K. Devreese (Ghent University Hospital)
Co-supervisor: Dr B. de Laat
18 May

Erik Willemen
Title: A wholehearted computational assessment of cardiac pacing
Supervisors: Prof. F. Prinzen, Prof. T. Delhaas
Co-supervisor: Dr J. Lumens
21 May

Vladimir Sobota
Title: Mechanisms of Action of Atrial-Specific Anti-Arrhythmic Drugs
Supervisors: Prof. U. Schotten, Dr S. Verheule
Co-supervisor: Dr A. van Hunnik
28 May

Lara Ottaviani
Title: Extracellular vesicles at the heart of cell-cell communication
Supervisors: Prof. P. da Costa Martins, Prof. L. de Windt
28 May

Bastiaan Zwart
Title: Stent thrombosis and antithrombotic strategies in percutaneous coronary intervention
Supervisors: Prof. J.M. ten Berg, Prof. A. van 't Hof
28 May

Kim van Kuijk
Title: The effect of intra- and extracellular challenges on cellular responses in atherosclerosis
Supervisors: Prof. J.C. Sluimer, Prof. E. Biessen
Co-supervisor: Prof. A. Baker
4 June

CARIM THESES 2021

Ömer Erküner
Title: Improving the understanding of atrial fibrillation progression and the appropriate use of anticoagulants
Supervisor: Prof. H. Crijns
Co-supervisor: Dr J. Luermans
4 June

Vasco Miguel Sampaio Pinto
Title: Dissecting mechanisms of neonatal cardiac regeneration
Supervisors: Prof. P. da Costa Martins, Prof. D. dos Santos Nascimento (Porto)
Co-supervisor: Dr P. Pinto-do-Ó (Porto)
8 June

Sanne Brouns
Title: New insights in thrombus interactions: unravelling bleeding and thrombotic phenotypes
Supervisor: Prof. J.W.M. Heemskerk
Co-supervisor: Dr P. van der Meijden
14 June

Danielle Coenen
Title: Unraveling platelet function in inflammation and thrombosis. Secretory pathways and vascular interactions
Supervisor: Dr J. Cosemans
Co-supervisor: Dr R. Koenen
25 June

Jun Wan
Title: Delicate interactions between plasma factors and blood cells affect
thrombin generation
Supervisor: Prof. T. Hackeng
Co-supervisors: Dr B. de Laat, Dr M. Roest (Synapse)
29 June

Mayken Visser
Title: Unraveling the role of factor XI and plasma prekallikrein in coagulation
Supervisor: Prof. H. ten Cate
Co-supervisors: Dr H. Spronk, Dr S. Heitmeier (Bayer AG Pharmaceuticals)
30 June

Ellen Boswijk
Title: Positron emission tomography of inflammation in atherosclerosis
Supervisors: Prof. J. Wildberger, Prof. J. Sluimer, Prof. J. Bucerius (University Medical Center Göttingen)
1 July

Anouk Geraets
Title: Biological determinants of depression, the role of cerebral damage, microvascular dysfunction, and hyperglycemia: a population-based approach
Supervisors: Dr M. Schram, Prof. F. Verhey
Co-supervisor: Dr S. Köhler
2 July

Bouke Adriaans
Title: Advanced Imaging of the aortic valve and thoracic aorta. Moving beyond diameters
Supervisors: Prof. J. Wildberger, Prof. H. Crijns
Co-supervisor: Dr S. Schalla
2 July

Ahmed Hassan
Title: FAIR and bias-free network modules for mechanism-based disease redefinitions
Supervisors: Prof. H. Schmidt, Prof. M. Dumontier
7 July

Danique van den Kerkhof
Title: Exogenous factors as potential antiplatelet drugs
Supervisors: Prof. T. Hackeng, Dr I. Dijkgraaf
8 July

Rick Schreurs
Title: Novel indication and optimization strategies for cardiac pacing
Supervisors: Prof. F.W. Prinzen, Prof. J.G. Maessen
10 September

CARIM THESES 2021

Roman Zeleznik
Title: Deep learning in cardiovascular imaging using A1 to improve risk predictions and optimize clinical workflows
Supervisors: Prof. H. Aerts, Prof. U. Hoffmann (Harvard University Boston, USA)
16 September

Mariusz Kowalewski
Title: Extracorporeal Membrane Oxygenation Support in Complex Clinical Scenarios of Refractory Cardiogenic Shock in Adults
Supervisors: Prof. R. Lorusso, Prof. J.G. Maessen
Co-supervisor: Dr E. Bidar
20 September

Han Jin
Title: Tangible Heart, Silicon Brain Computational Modelling of Cardiovascular Diseases
Supervisors: Prof. E.A.L. Biessen, Prof. J.C. Sluimer
Co-supervisor: Dr E. Smirnov
21 September

Maria Piazza
Title: Novel aspects of the Renin Angiotensin-Aldosterone System; A focus on hyperaldosteronism and glycation
Supervisors: Prof. C. Schalkwijk, Prof. G. Rossi (University of Padua)
Co-supervisors: Prof. T. Seccia (University of Padua), Dr N. Hanssen (Amsterdam UMC)
4 October

Nienke Eijsvoogel
Title: Optimisation of scan and injection protocols to the individual patient in CT angiography
Supervisors: Prof. J. Wildberger, Prof M. Das (Helios Klinikum, Duisburg)
Co-supervisor: Dr C. Mihl
5 October

Bibian Tullemans
Title: Tyrosine kinase inhibitors for cancer treatment: effects on platelets
Supervisor: Prof. J.W.M. Heemskerk
Co-supervisors: Dr M.J.E. Kuijpers, Dr M.J.B Aarts
6 October

Floris van den Brink
Title: Intra-cardiac infections, coronary interventions and mechanical circulatory support
Supervisors: Prof. A. van 't Hof, Prof. J. ten Berg
20 October

Yuri Declan Foreman
Title: The measurement and consequences of daily glucose variability; a meaningful addition to the mean?
Supervisors: Prof. C. Stehouwer, Prof. M. Brouwers, Prof. N. Schaper
20 October

Dongmei Yin
Title: Evaluation and optimalisation of laboratory criteria for APS diagnosis
Supervisors: Prof. H. ten Cate, Prof K. Devreese (Ghent University)
Co-Supervisor: Dr B. de Laat
27 October

Sahab Abtahi
Title: Osteoporotic Fractures: Relation to Mortality, Medication Use, and Rheumatoid Arthritis
Supervisors: Prof. F. de Vries, Prof. A. Boonen
28 October

Michele Di Mauro
Title: Tricuspid Valve Regurgitation: its Interplay with the right Ventricle, Prognostic Role, and Surgical Results in Various Settings
Supervisors: Prof. R. Lorusso, Prof. J. Maessen
Co-supervisor: Dr B. Maesen
11 November

Marianthi Kalafati
Title: Investigating insulin resistance in human obesity with transcriptomics: Towards precision-based strategies
Supervisor: Prof. E. Blaak
Co-supervisors: Dr M. van Greevenbroek, Dr M. Summer-Kutmon, Dr M. Adriaens
12 November

CARIM THESES 2021

Annika Kuhn
Title: Metabolic rewiring of the failing heart - unraveling cause and effect
Supervisor: Prof. B. Schroen
Co-supervisor: Dr M. van Bilsen
18 November

Alexandra Heinzmann
Title: Interplay of platelets, chemokines, and extracellular vesicles in the propagation of vascular inflammation
Supervisors: Prof. T. Hackeng, Dr R. Koenen
Co-supervisor: Dr J. Cosemans
26 November

Daniel Claassens
Title: Implementing pharmacogenetics to personalize antiplatelet therapy after myocardial infarction
Supervisors: Prof. J. ten Berg, Prof. A. van 't Hof
Co-supervisors: Dr V. Deneer (UMC Utrecht), Dr R. Hermanides (Isala Zwolle)
3 December

Till Seime
Title: The role of smooth muscle cells in calcification of atherosclerotic plaques
Supervisors: Prof. L. Schurgers, Prof. U. Hedin (Karolinska Institute, Stockholm)
Co-supervisor: Dr L. Perisic Matic (Karolinska Institute, Stockholm)
7 December

Joris Winters
Title: Large scale analysis of atrial structure and gene expression in patients with atrial fibrillation
Supervisors: Prof. U. Schotten, Prof. M. Stoll
Co-supervisor: Dr S. Verheule
8 December

Xiaosong Liu
Title: Implementation of Structural Bioinformatics in Thromboinflammation Studies
Supervisors: Dr G. Nicolaes, Prof. C. Reutelingsperger
Co-supervisor: Dr K. Wichapong
9 December

Francesco Matteucci
Title: Bipolar biparietal bidirectional application of radiofrequency in experimental in vitro/in vivo environment
Supervisors: Prof. S. Gelsomino, Prof. M. Lemair (Vrije universiteit Brussel)
Co-supervisor: Dr B. Maesen
14 December

Christian Nogales Calvo
Title: Network Modules as Novel Molecular Disease Definitions for Precision Theranostics
Supervisors: Prof. H. Schmidt, Dr A. Casas Guijarro
16 December

DISSERTATION PRIZE 2020

Dr **Martijn Smulders** (Dept. of Cardiology) received the CARIM Dissertation Award 2020 for his thesis 'Diagnostic Evaluation of Chest Pain. The Role of Non-Invasive Cardiac Imaging'. Martijn started his scientific career as a medical student at Maastricht University. He analysed clinical and cardiac magnetic resonance (CMR) data of patients who had suffered an acute myocardial infarction. His remarkable ambition and dedication led to successful co-authorships of several manuscripts. Immediately after his MD degree, he continued as researcher at the Department of Cardiology.

In 2015 he received a Netherlands Heart Foundation Dekker grant, allowing him to setup the 'CARMENTA trial'. This landmark trial on patients suffering from a non-ST elevation myocardial infarction showed that an early non-invasive imaging strategy (CT or CMR) was feasible and safe compared to an early invasive strategy. In 2017, Martijn won the 22nd Pélerin prize of Maastricht UMC+, on basis of this project. The final results were published in the prestigious Journal of the American College of Cardiology in 2019 and later implemented in the 2020 ESC guidelines. During his PhD trajectory, Martijn was awarded twice (2016 and 2019) the best oral presentation prize at the annual congress of the Netherlands Society of Cardiology. In 2020, he was nominated among the three best dissertations of the Einthoven Dissertation Prizes (Netherlands Society of Cardiology).

KNOWLEDGE TRANSFER

CARIM COURSES

From 14 until 18 June, the annual CARIM Course Week took place online. The week consisted of parallel courses, covering several aspects of CARIM's research and a social programme organised by I'M CARIM, the organisation of CARIM's PhD candidates. In 2021, two courses were organised by CARIM researchers: 'Non-invasive cardiovascular imaging' and 'Heart Failure 2021 – crossing bridges. Almost 70 PhD candidates participated. Furthermore, the course 'Advanced Microscopy and Vital Imaging', which is accessible to CARIM PhD candidates, was organised.

The aim of the course 'Non-invasive cardiovascular imaging' is to acquire insight into the basic theory and cardiovascular applications of non-invasive imaging methods. The course focuses on the most frequently applied imaging modalities, being ultrasound, CT, PET and SPECT, X-ray angiography, MRI, and hybrid imaging modalities. Aspects that are covered during this course are the basic physical principles, the imaging characteristics, the requirements for human as well as animal studies, and the possibilities and limitations of each of these imaging modalities in relation to specific cardiovascular research questions. The course 'Heart Failure 2021 - crossing bridges' deals with clinical and preclinical approaches towards understanding heart failure, and especially the way it is modulated by electrical and microcirculatory disorders.

CARDIOVASCULAR GRAND ROUNDS AND CARIM SYMPOSIUM 2021

The Cardiovascular Grand Rounds Maastricht and the yearly CARIM symposium are means to update the knowledge of our PhD candidates, our researchers and other external people with interest in the field of cardiovascular research.

Despite the challenges posed by the pandemic, the Cardiovascular Grand Rounds Maastricht lecture series hosting national and international experts, was successfully continued on a bi-weekly basis in 2021. These lectures traditionally take place on Friday during the morning meetings from 8 am until 9 am and are of very high scientific level. In 2021, the lectures were either completely online or organised in hybrid format, with options to attend in-person in the morning meeting room or online via Zoom, depending on the COVID restrictions. Also in this new format, the lectures have been well attended and have addressed a wide range of topics relevant to all CARIM divisions. The Cardiovascular Grand Rounds are currently organised by a working group representing all CARIM divisions, with Prof. Blanche Schroen and Dr Jordi Heijman acting as the primary scientific contacts. For the current programme and the composition of the organising committee, please visit our website.

CARIM's hybrid annual symposium was held on 24 November, as it was not possible to have the entire CARIM community together due to the corona measures. An interesting afternoon programme was organised that could be followed online via livestream. Our recent laureates presented their research and a session on alternative research funding, including the presentation of the Harry Crijns Research Grant, was organised. The Robert Reneman Lecture that

takes place during the annual CARIM Symposium 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.

The 2021 Robert Reneman Lecture was presented by Prof. Barbara Casadei. Barbara Casadei is a British Heart Foundation (BHF) Professor of Cardiovascular Medicine at the University of Oxford and Honorary Consultant Cardiologist at the Oxford University Hospitals NHS Trust where she leads the Cardiovascular Theme of the National Institute for Health Research (NIHR) Biomedical Research Centre and is Steering Committee Member of the BHF Centre for Research Excellence. Professor Casadei graduated in Medicine (cum Laude & Gold Medal) at the University of Pavia, Italy and moved to Oxford in 1989 to undertake her clinical and research training.

She was awarded the Joan and Richard Doll Fellowship at Green College in 1991, a DPhil in Cardiovascular Medicine in 1995, and a BHF Senior Research Fellowship in 2001. She is Fellow of the UK Academy of Medical Sciences, holds the highest honour of the British Cardiovascular Society (The Mackenzie Medal) and of the European Society of Cardiology (Gold Medal), and is the Immediate Past President of the ESC. Professor Casadei is member of several Scientific Advisory (e.g., the Fondation Leducq, the Netherlands Heart Institute, and the LIRYC Research Institute) and Editorial Boards (e.g., Cardiovascular Research; Circulation; European Heart Journal; Circulation Research) and has delivered numerous international prize lectures including, The William Harvey Lecture on Basic Science and Silver Medal of the ESC, 2013; The Thomas Lewis Lecture and Silver Medal of the British Cardiovascular Society, 2014; The Carmeliet-Coraboeuf-Weidmann Lecture of the European Heart Rhythm Association, 2015; The Brutsaert Lecture of the European Heart Failure Association, The William H Gaasch Lecture, University of Massachusetts, 2017, The Michael Sole Lecture, University of Toronto, 2019 and the Roman W. DeSanctis Lecture, Harvard Medical School, US, 2021.

She provides a clinical service at the John Radcliffe Hospital and leads a bench-to-bedside translational research programme, which spans from bench-based investigation in human tissue and cells to clinical trials.

Finally, the CARIM Commitment Award (see page 57) and Dissertation prize (see page 86) were awarded and the CARIM priori (see page 58) were drawn by lot.

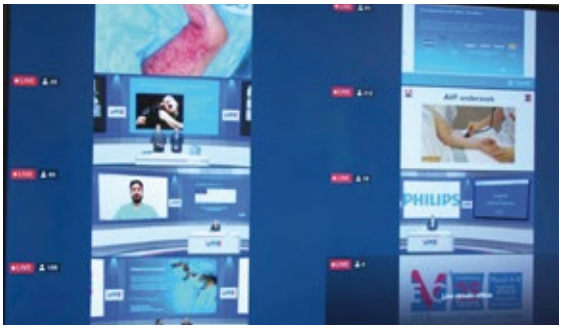
OTHER CARIM LECTURES, SEMINARS AND SYMPOSIA 2021

Complementary to the regular lecture series and CARIM symposium, several lectures, seminars and conferences were organised by our research staff in 2021. Some of them are presented below. All of these events were organised online.

The **Cardiorenal Seminars** is a joint lecture series of CARIM and the Institute of Cardiovascular Research (IMCAR) of the University Hospital RWTH Aachen (headed by Prof. Joachim Jankowski) and offers a platform for international top scientists in the field of vascular biology and nephrology to present their recent work. The lecture series is alternately held in Aachen and Maastricht. In 2021, nine keynote lectures were given by Katey Rayner (University of Ottawa, 25 February), Bart Ghesquière (KU Leuven, 15 April),

Makoto Kuro-o (Jichi Medical University, 27 May), Chrishan Ramachandra (Duke-NUS Medical School, 24 June), Johan Heemskerk (Maastricht UMC+, 1 July), Junichi Sandoshima (Rutgers New Jersey Medical School, 19 August), Andreas Herrmann (RWTH Aachen, 23 September), Arnold von Eckardstein (University Hospital Zürich, 4 November) and Oliver Söhnlein (Ludwig-Maximilians-Universität München, 16 December).

In March 2021, the **24th European Vascular Course (EVC)** was organised in the Maastricht convention center. EVC is globally the largest vascular surgery training event, normally hosting some 2,000 participants from more than 50 different countries. MedTech Europe classifies EVC as an official training event, confirming EVC as an established official training and education platform. Theoretical and practical training concentrates on arterial, venous, vascular access and cardiovascular topics, and consists of scientific 'state-of-the-art' lectures and interactive case discussions, and workshops on surgical anatomy, non-invasive diagnostics, clinical decision making, virtual reality techniques and open and endovascular surgical procedures. In 2021 however, due to the COVID pandemic, EVC was completely digitally organised using a novel remote training concept. For the first time ever, technicians managed to stream 148 LIVE hands-on workshops from 8 studios in the Maastricht convention center, connecting tutors with delegates digitally present in the studio and delegates with observational seats. Using this innovative technology and interactive content we were able to train and educate more than 2,200 participants that occupied 13,000 workshop seats. Despite this tremendous success, in 2022 EVC will be organised live again and celebrate its 25th anniversary.



On 19 May, the **CARIM Crijns Crowdfunding kick-off took** place. Guido Vanderbroeck (SWOL) opened the meeting by introducing 'Crowdfunding@UM: How to create a successful campaign', followed by Rogier Veltrop with 'From patient to research, a life with laminopathy'. The session was concluded by Chahinda Ghossein-Doha on 'From spark to sparkle: the role of storytelling in crowdfunding'. The CARIM Crijns Crowdfunding Doubler offers enthusiastic researchers financial support in reaching their crowdfunding goals by doubling one CARIM crowdfunding initiative to € 50,000 when it has reached € 25,000. In 2021, the CARIM Crijns Crowdfunding Doubler was given to Chahinda.

On 2 October, the sponsor event *'Loop met je dokter'* was organised by the Health Foundation Limburg and the Maastricht UMC+ for the 13th time. During a 5 or 10 km-walk in the beautiful countryside of Banholt and its surroundings, patients and their doctors meet in a different, informal way where the doctors show the importance of a healthy lifestyle by setting a good example themselves. In total, € 52,894 was raised for groundbreaking research into cardiovascular diseases at Maastricht UMC+ and the Limburg partner hospitals.

On 13 October, the 7th **World Thrombosis Day (WTD)** was celebrated worldwide. Seven years ago the International Society on Thrombosis and Haemostasis decided to dedicate the birthday of the German physician Rudolf Virchow (1821-1902) to increase awareness on thrombosis among the general population. CARIM's Department of Biochemistry together with Maastricht UMC+ uses this day to bring their research results to the general public and inform our society on important signs that predict or coincide with this dangerous and prevalent disease. As

From left to right: Patient Bert, Drs Anne Willers.

in 2020, we took our 2021 campaign to an online format from our University Studios. In preparation for this, flyers and info charts were distributed, and newspaper articles in newspapers and hospital magazines were published. World Thrombosis Day 2021 was organised by Lidewij Bos, Dionne Braeken, Stella Thomassen, Hugo ten Cate, and Tilman Hackeng. The theme for World Thrombosis Day 2021 was myocardial infarction. After an introduction by Prof. Tilman Hackeng on the scope of WTD and theme, people could enjoy clear lectures by Dr Martijn Smulders on essential

diagnosis of heart attack, or not. Next, Prof. Eline Kooi presented on clinical imaging of atherosclerosis, a condition leading to heart attack or stroke. Prof. Arnoud van 't Hof introduced us on the critical actions between the site of a heart attack and the hospital in which every minute counts. Lastly, Drs Anne Willers interviewed a patient with an aortic dissection and who later received an artificial aortic valve and who shared his experiences on anti-thrombotic therapy with the audience. World Thrombosis Day 2021 registered over 200 attendees, and was again concluded to be a great success.

INAUGURAL LECTURES 2021

8 October - Prof. Paula da Costa Martins (Dept. of Cardiology): 'Little messages, Big hearts'

12 November - Prof. Kevin Vernooy (Dept. of Cardiology) '*Ritme zit in alle mensen*'

19 November - Prof. Yvonne Henskens (Dept. of Clinical Chemistry): '*Van bloedstollend naar testminnend*'

26 November - Prof. Bastiaan de Galan (Dept. of Internal Medicine): '*Hoge pieken, diepe dalen*'

From left to right: Prof. Arnoud van' t Hof, Prof. Eline Kooi, Dr Martijn Smulders, Prof. Tilman Hackeng.

CARIM'S DEVELOPMENT TALENT PROGRAMME

Early recognition of talent is one of the key strategies of CARIM to coach and prepare gifted young academics for their future academic career. CARIM stimulates and supports talented students and staff by offering grants for research 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 is intended for three groups of young scientific researchers.

1. HS-BAFTA TALENTED FUTURE PHD CANDIDATES

The fellowship is intended for:

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

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

c. 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 amounts to max. € 21,000 (in accordance with scale 7-0) and € 3,000 for exploitation costs and is meant for a period of max. 6 months. For Ba/Ma students the regular curriculum should be interrupted to perform the research project within CARIM. The PI concerned has to match an equal amount of money for the candidate for an equal period of max. 6 months. This brings the max. total annual amount for the HS-BAFTA on € 48,000 for a total of 12 months.

2017 William van Doorn

2018 Jasper Demandt

2019 Mohamed Kassem

2020 Anne-Marije Hulshof, Yentl Brandt

2021 Daniek Meijs

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 to € 7,500 based on actual costs of max. € 1,000 for (extra) living allowance per month and travel costs, for a period of max. 6 months. The fellowship can be performed during any period within the PhD trajectory.

2018 Mueez Aizaz, Jens Posma

2019 Federica de Majo, Cengiz Akbulut, Walid Chayouya, 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

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

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 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

“Pick up the BAFTA’s 2019-2021” - from left to right: Job Verdonschot; Job Stoks; Yentl Brandt; CARIM director; Cengiz Akbulut; Kim Maasen; Rob Holtackers; Anne-Marije Hulshof and Rogier Veltrop.

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

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	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 - 2022	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

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

I'MCARIM 2021

from left to right: Myrthe van der Bruggen, Renée Tillie, Valeria Saar-Kovrov and Adele Ruder

I'MCARIM 2021

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.

In 2021, as in 2020, the COVID-19 pandemic made it a challenge to organise many live activities. We therefore dedicated our time and energy to other ideas that would benefit CARIM PhD candidates. In the past year, together with CARIM, we focused on projects that would help new PhD candidates find their way around more easily.

We developed a buddy system in which new PhD candidates are paired with a more experienced PhD candidate from a different department. This ensures that the new PhD candidate has a designated buddy they can ask questions to while getting started, and helps expand their social network. Additionally, matching PhD candidates from different departments stimulates contacts between CARIM departments.

We are also excited to be in the final stages of completing a CARIM introduction video. The video is meant to introduce CARIM and its PhD programme to interested candidates and to warmly welcome new PhD candidates. It will provide information about CARIM itself and important facilities that CARIM offers to new PhD candidates. We hope they will like it.

Furthermore, we thought 2021 was the perfect year to revive the CARIM PhD Guide. We created a booklet about CARIM, the PhD programme and everything that comes with it, such as the available courses, the PhDs' social life, young researcher grants, and graduation. In other words, this booklet contains information that is essential for both starting and experienced PhD candidates and will be updated yearly. We are currently putting the finishing touches on the booklet and think it will prove very useful for all current and future CARIM PhD candidates!

Fortunately, we were still able to organise some social activities in 2021, albeit in a modified form. During the CARIM course week, there was stiff competition at our online pub quiz. We supplied drinks and snacks that could be picked up by the PhD candidates beforehand. The pub quiz turned out a great success, and the members of the winning team were awarded a trophy.

The online edition of our popular career event, in collaboration with NUTRIM's PhD representatives, was another hit. We invited several NUTRIM and CARIM alumni from academia, industry and health care to give a presentation about their career path and how and why they got their current jobs. This provided valuable ideas and insights in an informal atmosphere.

We are very happy to have the opportunity to contribute to all the important projects described above, which promote the professional development of fellow PhD candidates and offer support. Moreover, we think it is important to stimulate the social interaction between CARIM PhD candidates in a fun and educational way. If you share the same enthusiasm, do not hesitate to contact us, as I'mCARIM is always open to new members! Let us make 2022 an even better year.

I'mCARIM 2021
Myrthe van der Bruggen, Kim Maasen, Adele Ruder
Valeria Saar-Kovrov and Renée Tillie

INTERVIEW

INTRICARE

"I'd do it again.
Why not?"

Imagine: you have reached the end of your life and you are ordered to live it again, exactly the same as the first time. Would you be happy, or feel cursed? Looking back on an almost completed PhD track, Cengiz Akbulut reflects on this imaginary situation. He was one of the six Maastricht-based PhD scandidates in a group of fifteen who were trained within the INTRICARE consortium that CARIM coordinated. We are meeting four of them in a Zoom interview.

Did this larger consortium play a role for you, when looking for a PhD project?

Olivia Waring: "Not really, no. I originally applied for a different project and when I met with the professors for the interview, they liked me, but they had two candidates that they liked. So they put me forward for this position. I did like that there was a lot of emphasis on the international aspects of the project, so this was a good fit as well."

Mueez Aizaz: "I knew about the Marie Curie scheme and the collaborating universities and that it's a prestigious and preferred position, but I mainly applied to positions that were very relevant to my work and what I wanted to do. I saw it as an added benefit, when I was accepted."

What's the difference between doing a PhD in one department and in a consortium like this?

Aizaz: "I think one of the bigger advantages is that it's much easier to collaborate. There are 15 of us, working on similar topics. I got the opportunity to work with a group at King's College London for five months. That looks good on your CV too and it enables you to publish more. In a regular PhD, I think setting up a collaboration with a group abroad is much more difficult."

Anouk Gentier: "It was also easier, I think, to get more training in different fields. Because there was an umbrella of these three institutes, with their own specialities, and they could provide courses focused on, for example, the basics of analysing micro-CT, or some introduction to RNA sequencing and vascular imaging. Plus it trained my soft skills, like giving a Ted talk: how to present work to a non-scientific audience."

Cengiz Akbulut: "It offers more variety compared to a regular PhD track. You spend three years in different countries, instead of just one. That's a cultural experience, which can be quite enriching, or challenging, depending on the country you're going to. It's a nice extra."

Was there collaboration between the PhD candidates too?

Gentier: "Yes, definitely. One person will have more experience with, for instance, microscopy, while the other has more skills in analysing big data through computational technology. You can easily write a paper together, based on everyone's strengths, and that leads to a higher quality paper. Because we all know each other from the courses, but also have a lot of contacts outside the professional setting, it makes it easier to set these things up. That's a big benefit of the consortium."

Aizaz: "One PhD candidate who works in Aachen as a medical doctor wanted to test a particular dietary supplement. And I had some imaging protocols that I wanted to test. Because our focus is on the same topic, he can test his supplement and I test my imaging protocols on the same project. When you meet every six months, you know what everyone is working on, and it makes working together easier."

Waring: "The social aspect was also quite encouraged, spending time to get to know each other."

After you have completed your PhD, you'll have a double degree. What does that mean to you?

Gentier: "People I talk to about it tell me it's pretty rare, so I think that's good for your CV. Sometimes it's a bit stressful and a lot of paperwork between the different universities, although we did get some good support from both the secretary at our department here and Tara de Koster, our programme manager of INTRICARE in Maastricht."

Akbulut: "Now we're about to write our thesis, we experience that, for example, the graduation terms differ between the participating universities, which was not clear

from the beginning. That's a bit annoying, but it's a challenge for all these consortia. It's the first time universities are embarking on these kinds of processes. There are a million things to do, in order to get the funding, get the projects going, hire the candidates. Some things get missed, but well, it's lessons learned for the institutions."

Although you're not completely finished yet, may I ask how you look back on this period so far?

Waring: "I started my PhD when I was 23, now I'm almost 28. It's been a large part of my life and I'm proud of the work I've done. There were a lot of opportunities and research freedom during the project, which was really nice. And the bench fees are definitely very good, so I also felt I had enough money to do whatever I wanted to do, which is a luxury many colleagues don't have. Training was emphasised, which was nice for my personal development. I'm a more rounded researcher now at the end of my PhD."
Gentier: "It was a learning experience. We've learned to work and behave in an academic group, which I didn't experience before. For me it was a big adjustment, but it was interesting. I think a PhD for a big part is learning to deal with failures and to correct what went wrong. When I started, I wasn't that good at it, because I could really get frustrated, but now I'm a bit more relaxed about it. The biggest thing I've learned is finding strategies to work around issues, and sometimes just letting go of what doesn't work, shifting focus. Next to getting more comfortable in public speaking."
Akbulut: "Looking back at my PhD, I'm happy for every moment. I encountered a quote by Nietzsche about the question 'How are you living your life?' The PhD has been a part of our lives. Nietzsche said: 'If you come to the end of your life and an angel or daemon comes up to you and says: "You're going to re-live that, every high and every low." Would you bless them and say: thank you, I look forward to that? Or would you curse them, and say: how dare you make me live that again?' Looking at my PhD, I wouldn't want it any other way. I'd do it again. Why not?"
Aizaz: "Overall, it's been a great experience and a very social thing as well. I did already spend some time in the industry before I started the PhD. I didn't exactly know what it would really mean from day to day. It's like having a baby for the first time, my first daughter was born last year. Everybody tells you and warns you, but only when you get into it, you understand. So I feel like I'm doing two PhDs at the same time and the one at home is even more challenging. In the end, the freedom the PhD provided allowed me to be the master of my own boat and steer it in the direction I wanted, of course while staying inside certain boundaries. It has polished different facets of my personality and I look forward to the next phase."

What will your next step be? Would you like to stay in academia?

Aizaz: "I'll be joining Philips as of 1 July 2022. For the type of work I do, Philips is one of the best places to go to. I'll be developing commercial software for image guided therapy machines. I do love research, but this was also an exciting opportunity, because I can work on something that will benefit patients in the end. I'm not sure if my PhD work will realise that anytime soon. That's how I justify it to myself."
Akbulut: "I consider myself to be one of the luckiest PhDs to come out of the university. During my PhD trajectory, I established a series of protocols to work with stem cells and this has exploded within our group and department. We are practically a stem cell group these days. So the Faculty of Health, Medicine and Life Sciences has established a new laboratory, where they want to make of stem cells a facility and I've been offered a managing position of that. So I'm staying in Maastricht University, in a stable position.

It's an incredibly unique opportunity, a matter of right time, right place, and the hard work on stem cells was more than worth it. Next to managing the laboratory, I will continue my research with Professor Schurgers too."

Aizaz: "Cengiz has been very important to our group and he really deserves all this. He's being modest here."

Waring: "He was always putting in the hours to take care of his stem cells, day and night. It's really deserved. I'm trying to finish the thesis and I'm looking for jobs, also outside of academia. I don't think the pressure and the uncertainty of it fit me well in the end."

Gentier: "What I like about academia is that you can choose what you research, and hours are flexible too. I don't know how that would be in industry. I'm looking for postdoc positions, but I'm also talking to companies, to keep my options open."

Cengiz Akbulut focused on how smooth muscle cell phenotype switching affects microcalcifications in his INTRICARE PhD project. Olivia Waring studied the link between inflammation and calcification in the atherosclerotic plaque. Anouk Gentier focused on the development of smart peptide/protein-based diagnostics and drugs that target microcalcifications. She has been recently offered a 5-y postdoc position in the Bay Area, CA. Mueez Aizaz worked on developing new techniques to assess plaque vulnerability in carotid and coronary arteries, using state of the art non-invasive imaging (PET/MRI).

INTRICARE is funded by the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement. It is a consortium in which CARIM, RWTH Aachen University and Karolinska Institute, Stockholm cooperate. The International Network for Training on Risks of Vascular Intimal Calcification and roads to Regression of Cardiovascular Disease (INTRICARE) started in March 2017 and finished in August 2021. The objective of INTRICARE was to train a new generation of scientists to help advance the understanding of vulnerable plaque formation, with a particular focus on microcalcification, and to develop innovative solutions for the early prevention, diagnosis and treatment of atherosclerosis.

THE BIGGEST THING I'VE LEARNED IS FINDING STRATEGIES TO WORK AROUND ISSUES, AND SOMETIMES JUST LETTING GO OF WHAT DOESN'T WORK, SHIFTING FOCUS

HIGHLIGHT DIVISION HEART

JUSTIN LUERMANS

A Giant LEAP in Cardiac Pacing

In 1958, Åke Senning, a Swedish thoracic surgeon, implanted the first pacemaker in a human being. Today, permanent cardiac pacing is still the only available therapy in patients with a slow heart rhythm (bradycardia) and it can be life-saving. Each year around 13,000 patients in the Netherlands undergo a pacemaker implantation, and the need for cardiac pacing will continue to increase as our population ages. Four years ago, I was part of the organising committee of a symposium in the Netherlands on the occasion of the 60th anniversary of bradycardia pacing. At that time, we had just started applying an exciting new clinical pacing strategy at Maastricht UMC+. In this article I describe how years of preclinical CARIM research has led to the clinical application of an innovative pacing method, as well as the design of a multicentre randomised clinical pacing trial which is currently ongoing.

RIGHT VENTRICULAR PACING

In cardiac pacing, the right ventricular (RV) apex has for decades been the preferred site for ventricular stimulation.[1] The RV apex has proven to be an easily accessible and stable site for lead fixation. However, up to 36% of patients receiving RV pacing develop a reduced heart function, which can lead to morbidities such as heart failure and atrial fibrillation.[2-5] These derangements are caused by RV pacing-induced non-physiologic, dyssynchronous activation of the ventricles.[4, 6-8]

ALTERNATIVE PACING SITE?

Following the recognition of the possible adverse effects of RV pacing, new pacing strategies to maintain or restore inter- and intraventricular synchrony have been sought for. In 1970, Durrer et al. described the physiological electrical activation of the left ventricle in seven isolated human hearts.[9] They demonstrated that during sinus rhythm with normal ventricular activation through the heart's specialised conduction (His-Purkinje) system, the electrical impulse first exits the Purkinje system at sites on the left ventricular endocardial surface of the interventricular septum. It was therefore hypothesised that pacing near these exit sites would result in a more physiological activation of the left ventricle (LV).

LEFT VENTRICULAR SEPTAL PACING

Animal studies

In the 1990s, a series of canine experiments were initiated at CARIM's Department of Physiology to further investigate this hypothesis. In a study conducted in the laboratory of Prof. Prinzen, invasively measured LV stroke volume and contractility in seven anesthetised open-chest dogs with healthy hearts were found to be better during left ventricular septal pacing (LVSP) when compared to RV pacing.[10] A subsequent study, comparing different sites of left ventricular pacing, RV pacing, and normal sinus rhythm in anaesthetised, open-chest dogs, showed that LV function, measured in terms of LV dP/dT max and LV stroke work, was indeed maintained during LVSP to a level comparable to normal sinus rhythm.[11] The longer-term effects of LVSP were studied in canine hearts after 16 weeks of pacing, and were compared with RV pacing and normal sinus rhythm.[12] It was demonstrated that LVSP maintained regional cardiac mechanics, contractility, relaxation and efficiency at near native levels, whereas RV pacing reduced these variables.

First human study

After these preclinical CARIM studies had successfully demonstrated the advantages of LVSP over RV pacing (RVP), and even showed that electrical and mechanical activation and their subsequent haemodynamic effects were comparable to normal sinus rhythm, clinical studies were needed. The first study applying LVSP in patients was conducted by Prof. Vernooy at our Department of Cardiology at Maastricht UMC+. The study included ten patients with structurally normal hearts with mainly a pacing indication because of sick sinus syndrome. LVSP was applied using a custom bipolar, fixed-screw, ventricular pacing lead (Model 09066; Medtronic Inc, Minneapolis, MN), which was exclusively delivered for this study **(Figure 1A)**[13]

The lead was introduced transvenously into the RV and, after positioning against the RV septum, driven through the interventricular septum (IVS) under fluoroscopic and echocardiographic guidance until the LV septum was reached, without perforating the IVS **(Figure 1B).** The lead Model 09066 is a modification of the market-released Select Secure model 3830 (Medtronic Inc, Minneapolis, MN) with an extended helix **(Figure 1A).** Instead of the short 1.8-mm helix of the Model 3830, the Model 09066 has been fitted with a longer 4-mm helix to provide better lead fixation and a higher pull-through force for deeper penetration into the IVS. Acute haemodynamic measurements showed that values of LV function in LVSP were maintained to levels comparable to baseline atrial pacing with normal ventricular conduction **(Figure 2).**[13] Moreover, the acute haemodynamic benefits of LVSP over RVP were consistently observed in all patients.

This study was the first to confirm in humans the potential beneficial effects of LVSP over RVP.

LEFT BUNDLE BRANCH PACING

At that time, around 2016, larger clinical studies demonstrating the advantageous effects of LVSP were hampered by the fact that the Model 09066 lead for performing LVSP was not commercially available.

In 2017, however, Prof. Weijian Huang, a Chinese cardiologist, published a case report on a novel pacing strategy.[14] In a patient with heart failure he succeeded in placing the commercially available Select Secure Model 3830 lead at the LV septal area, after conventional cardiac resynchronisation pacing methods (i.e. biventricular pacing) had failed in this particular patient. Moreover, he demonstrated that he was able to capture the heart's specialised conduction system (i.e. the left bundle branch) after advancing the lead through the IVS. The proximal left bundle branches run through the

HIGHLIGHT

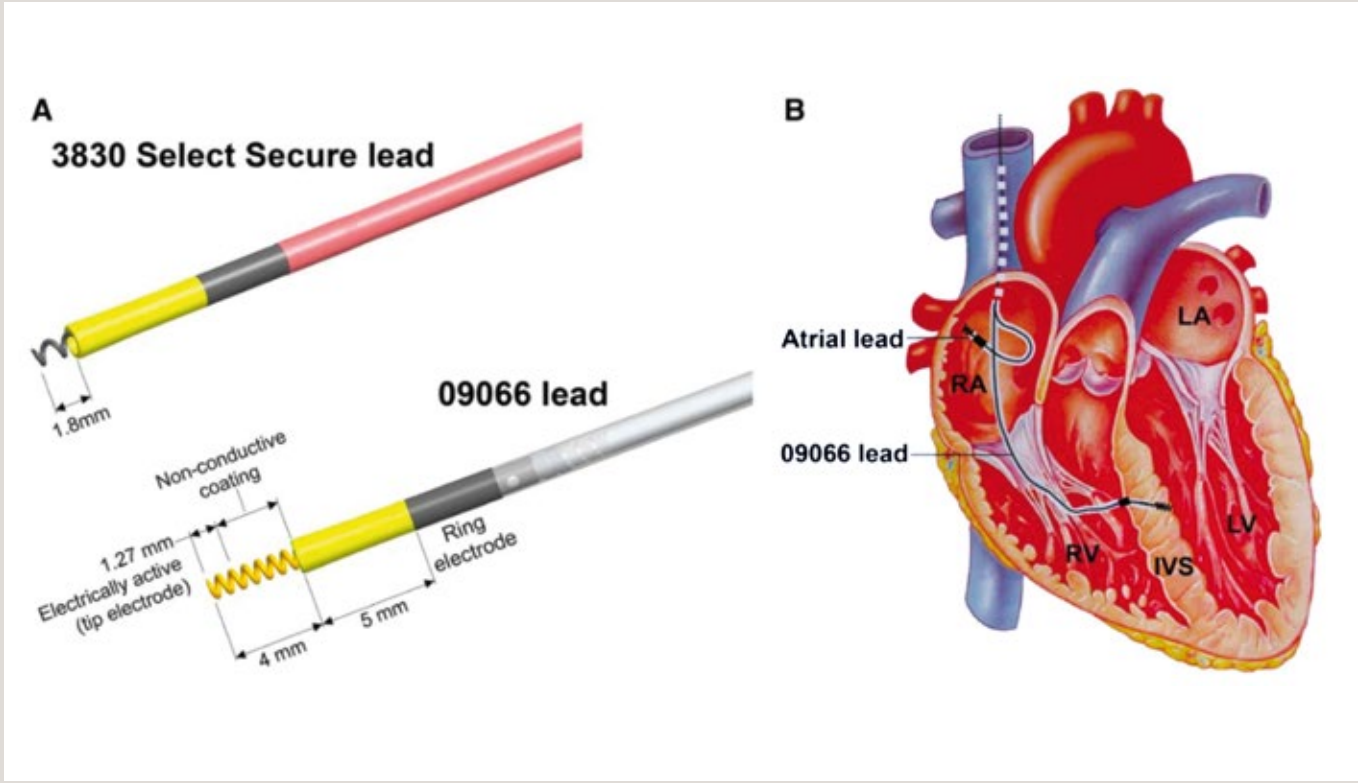


FIGURE 1 A, Lead design of the Model 09066. The lead is a modification of the market-released Select Secure Model 3830 with an extended helix. The lead has been fitted with a 4-mm helix instead of the standard 1.8-mm helix of the Model 3830. The helix is partially insulated so as to ensure that the electrically active portion is limited to the distal 1.27 mm. **B,** Schematic representation of lead positioning.

The lead Model 09066 is introduced transvenously into the right ventricle (RV) and, after positioning against the RV septum, driven through the interventricular septum (IVS) with the screw-in tip until the left ventricular (LV) septum is reached, without perforating the IVS. The ring stimulates the RV side and the tip the LV side of the IVS. LA indicates left atrium; and RA, right atrium.

left ventricular septum and fan out to form a potentially wide target for the physiological pacing of the conduction system **(Figure 3).** Following this case report, more papers and registries on this so-called "left bundle branch pacing" (LBBP) appeared.[15, 16] It was now demonstrated that it was feasible to perform LVSP and to even capture the left bundle branch with commercially available materials, and the technique was to a large extent based on our earlier scientific work on LVSP.

In 2019, Prof. Vernooy and I travelled to Prof. Huang in Wenzhou, China **(Picture 1),** to learn more about LBBP, and we introduced the technique in the Netherlands in 2019. While gaining experience we set up a registry of all patients receiving LBBP at Maastricht UMC+. So far we have included more than 150 patients in our registry. Soon, physicians around the world became interested in this new LBBP technique, and we and others set up educational programmes to teach them.

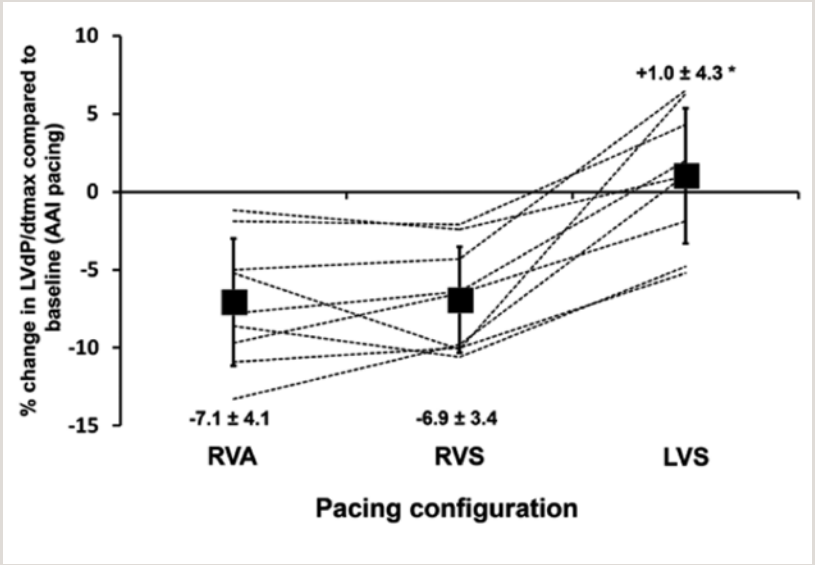


FIGURE 2 Acute change in left ventricular (LV) dP/dtmax (mean±SD) during pacing at different ventricular sites relative to baseline atrial pacing. Dashed lines represent individual haemodynamic responses to pacing at different ventricular sites. LVS indicates left ventricular septum; RVA, right ventricular apex; and RVS, right ventricular septum. *P=0.001 vs RVA and RVS.

NEW STUDIES AND COLLABORATIONS

We are currently conducting several mechanistic studies and modelling experiments in a close collaboration between the Departments of Cardiology, Physiology and Biomedical Engineering (CARIM) in order to obtain more electro-mechanical insights into LBBP. A large European collaboration of experienced physicians performing LBBP has led to the presentation of the largest study to date reporting outcomes of LBBP (MELOS registry) at EHRA 2022.

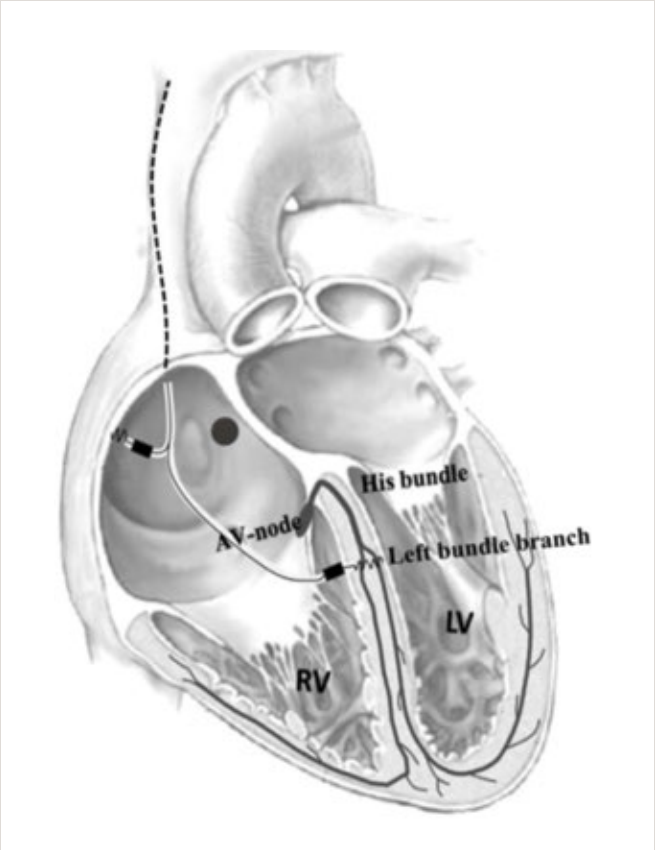


FIGURE 3 Schematic overview of the heart and the conduction system. The proximal left bundle branches run through the left ventricular septum and fan out to form a potentially wide target for the physiological pacing of the conduction system. When the Left Bundle Branch is captured during Left Ventricular Septal Pacing (LVSP) it is defined as Left Bundle Branch Pacing (LBBP).

Importantly, 2020 saw us receive a grant of € 800 k in the context of ZonMw's 'Efficiency Studies' programme, for the project entitled 'Permanent left ventricular septal pacing versus right ventricular pacing in patients with advanced atrioventricular block: a multicentre randomised trial': LEAP trial (Project number 852002101). The LEAP trial is registered in clinicaltrials.gov (NCT04595487) and the Netherlands Trial Register (NTR9672). The LEAP trial is an international, multi-centre investigator-initiated, prospective, randomised, controlled, open label, blinded endpoint evaluation (PROBE) study that compares LVSP (in practice LBBP) with conventional RVP. A total of 470 patients with a class I or IIa indication for pacemaker implantation due to atrioventricular conduction disorders will be randomised 1:1 to LVSP or RVP. The primary endpoint is a composite endpoint of all-cause mortality, hospitalisation for heart failure and an echocardiographic measure of pacing-induced cardiomyopathy. LVSP is hypothesised to result in improved outcomes. Secondary objectives are to evaluate whether LVSP is cost-effective and associated with improved quality of life as compared to RVP. The study is currently ongoing and we have so far included more than 50 patients.

The LEAP trial is the first large randomised clinical trial on LVSP and is the direct result of years of scientific preclinical work at CARIM. We think this is a perfect example of translational CARIM research and we truly hope that LVSP will be "a giant leap in cardiac pacing" serving many patients in the future.

PICTURE 1 Prof. Huang, Prof. Vernooy and Dr Luermans at the Department of Cardiology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

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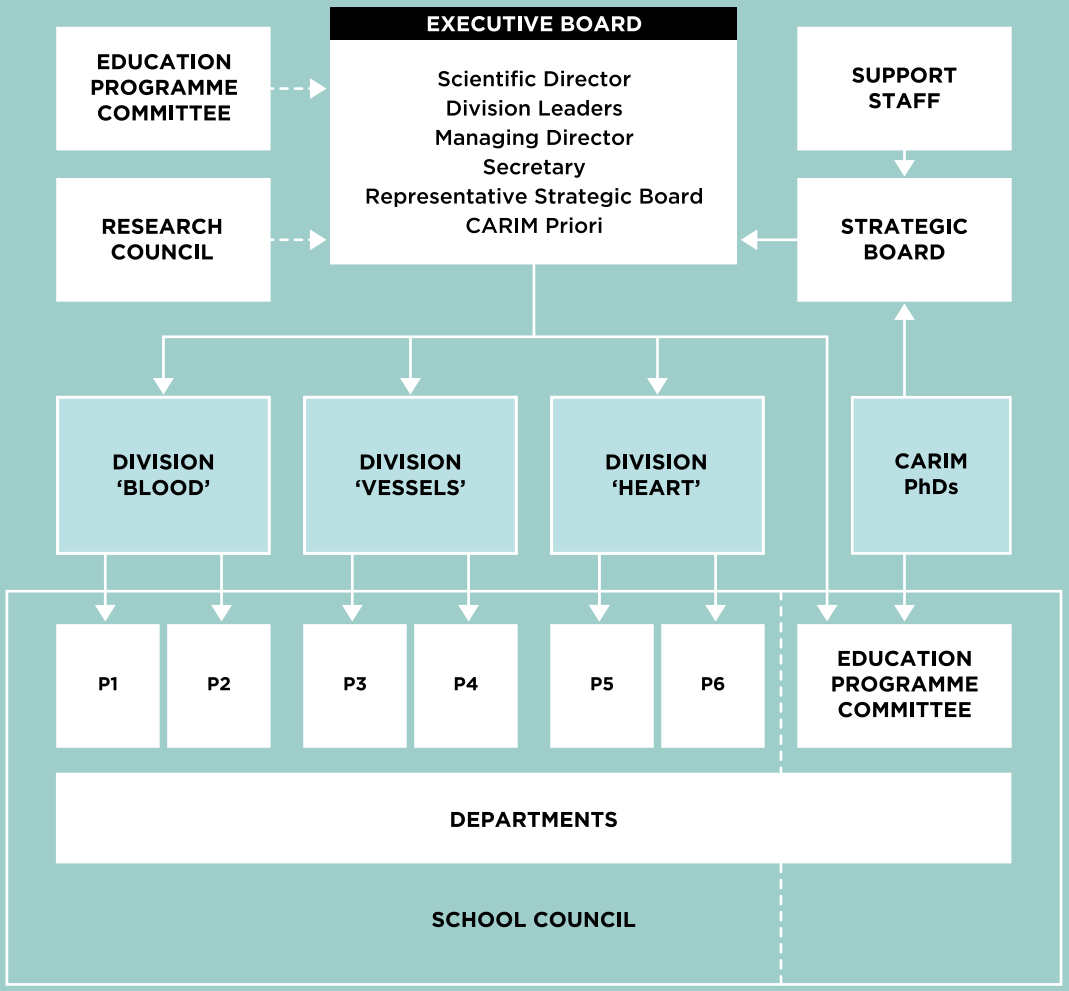
ORGANISATION

05

ORGANISATION



The Scientific Director has the final responsibility for the research institute, including the organisation and management of the research programme, the scientific output, the training of Master's and graduate students and post-doctoral fellows, the financial management and the public relations of the institute. The Scientific Director is assisted by the Managing Director, who takes care of the financial, legal and human resource issues, and by the secretary to the Board, whom together represent the Management Team (MT). The MT meets weekly to discuss daily matters. Together with the three leaders of the divisions, and a representative from the Strategic Board, the MT constitutes the Executive Board (DB) of the institute. The DB meets monthly to discuss and decide upon issues at strategic and operational level. The DB 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 is a discussion forum and generates written visions of the future of CARIM and its survival in an increasingly competitive international scientific environment. The SB meets monthly to discuss issues such as grant programmes, national and international collaboration networks, interdisciplinary communication and CARIM's visibility in the national and international cardiovascular fields.

The EPC coordinates both the PhD and master's training programmes and advises the DB on all issues regarding these educational programmes. The chairperson is also CARIM's PhD coordinator and advises the DB on 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 DB on the quality of research proposals and meets regularly to discuss and guide grant applications. In 2019, the CARIM 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 School Council consists of all PIs and Department Heads and meets four times a year. The School Council is informed by the Executive Board on ongoing matters and advises the Scientific Director on research within the school and the related education programmes.

EXECUTIVE BOARD

- Prof. Tilman Hackeng, Scientific Director
- Prof. Hugo ten Cate, Leader Division Blood
- Prof. Coen Stehouwer, Leader Division Vessels
- Prof. Harry Crijns, Leader Division Heart (until April 2021)
- Prof. Kevin Vernooy, Leader Division Heart (from May 2021)
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- Wouter Hankel, Managing Director
- Tara de Koster, secretary to the Board

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- Prof. Leon de Windt, Dept. of Molecular Genetics

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- Prof. Frits Prinzen
- Prof. Chris Reutelingsperger
- Dr Marjo Donners
- Dr Gerry Nicolaes

CARIM OFFICE

The CARIM Office consists of specialists that support the organisation and its researchers with administrative, financial and legal issues, including HRM and funding. Tara de Koster, Riet Daamen (until April 2021), Esther Willigers and Barbara Przybylski (from February 2021) are responsible for administrative issues, including supporting the DB. The controllers of CARIM are Lynn Lemeer and Hans Slenter. The Finance Department of Maastricht University provides support on accounting the CARIM research projects with Henny Kerckhoffs, Esther van Heel (until October 2021), Johan Noordijk and Jacqueline Roufs-Scheepers (from October 2021). Petra Suurmond and Anke Neekmann of the Human Resources Department of Maastricht University are dedicated to CARIM. In legal affairs, Cindy Schröder, Monique Soons-Smeets and Suzanne ten Hoeve support CARIM. Willem Wolters is responsible for funding acquisition. Managing Director Wouter Hankel is the head of the CARIM office.

The research in CARIM's divisions involves the research activities of employees working in 17 (six basic and eleven clinical) departments of Maastricht UMC+.

6
BASIC DEPARTMENTS

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

11
CLINICAL DEPARTMENTS

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


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INTERVIEW

CARLA VAN DER KALLEN
BASTIAAN DE GALAN

One year on the CARIM Executive Board

They both heard from a colleague that their name had been drawn during the 2021 CARIM symposium, which meant that they would be 'PRIORI-members' of the Executive Board for the whole of 2022.
Internist Prof. Bastiaan de Galan heard it on the day of his inaugural address, while Dr Carla van der Kallen, researcher and coordinator of the Maastricht Study, was told in a message. "A good way of getting to know the organisation a bit better", is what they both thought. "Hope it's not too time-consuming."

It was during a holiday in Florence that CARIM director Tilman Hackeng got the idea that it would be nice to have an annual lottery to select two CARIM colleagues who would be members of the school's Executive Board. In the Renaissance, this was how the composition of the municipal council in the Italian city was determined every two months. The idea for CARIM was that this system would lead to a board that would be more representative of the organisation and would contribute to greater diversity and inclusivity. All 79 members of the scientific staff and all 34 members of the support staff with a permanent contract would be eligible. During the symposium, one name would be drawn from all male candidates and one from all female candidates.

COFFEE MACHINE

Both Carla van der Kallen and Bastiaan de Galan were absent at the symposium and so heard about being selected from a colleague. The message on her phone simply read "You're in the Executive Board." "I know CARIM pretty well, as I used to work in an office next door to the CARIM office for a number of years. We shared the coffee machine, which is a good way to get to know each other quite well. So I thought this would be a nice additional opportunity." Bastiaan de Galan, who had been working at Radboud University Nijmegen for the past twenty years, and still works at the hospital there, did not know the structure of the research school at all. "We do have research themes in Nijmegen, but no budget is being allocated along that line. It goes to individual researchers and departments. In that sense, the kind of competition for funding that you see to some extent between CARIM and NUTRIM is new to me. So I thought this would be a good opportunity to gain some more insight into the way things work here, though I hoped it wouldn't take up too much of my time", he admits with a smile.

DIVERSITY

The CARIM Executive Board meets for two hours each month, and of course members are expected to have studied the necessary documents beforehand. Van der Kallen: "Of course you can always join the discussion about a subject like diversity and have an opinion on it, but for some topics on the agenda it's difficult to make a sensible contribution." De Galan: "If the discussion is about projects that have started a few years ago, it's sometimes difficult as you've missed what went before." Van der Kallen: "But it's interesting to see what sort of things are discussed. People often think, and that goes for the Maastricht Study too, that management is something magical, but in practice it's not that complicated. It's fascinating to see what themes are discussed, and all the things that managing such an organisation entails." De Galan: "You do find, however, that it takes time to get a handle on things. If CARIM should want to get more out of this scheme, a year is perhaps too short. Which doesn't mean I'm asking for an extra year, mind you! Although I must say the atmosphere at the meetings is excellent."

A GOOD WAY OF GETTING TO KNOW THE ORGANISATION A BIT BETTER

"E chiamoronsi Priori delle Arti:
e stettono rinchiusi nelle Torre della Castagna
appresso alla Badia, acciò non temessero
le minacce dei potenti"

Dino Compagni

INTERVIEW

CHRIS HUGHES

“I love to talk science”

The best days for Professor Chris Hughes from the University of California, Irvine (UCI), are when he can ‘talk science’ with PhD candidates, colleagues or even lay people. “When I give a talk to experts in my field, I can predict 90% what the questions will be. If I give a talk to a lay audience, or scientists in another area, they will ask questions I’ve never thought about before.” The role of visiting professor at CARIM and Maastricht Heart+Vascular Center fits him like his old British sports car does the California climate.

Chris Hughes is a pioneering expert in the field of blood vessel development and growth. His lab was one of the first in the world to grow micro-organs in the lab, each with its own blood vessel network. His connection with Maastricht started with a visit to UCI by a delegation from CARIM and the MERLN Institute for Technology-Inspired Regenerative Medicine. “Next Tilman Hackeng, Leon Schurgers and Marianne van der Steen, MERLN’s Chief Business Development Officer, came over to discuss the possibilities of collaborating, and I got on well with all three. I was invited to give a talk in Maastricht and one thing led to another. Tilman suggested I should become a visiting professor, which we set up just before Covid happened.”

Why did you accept the offer?

“Multiple reasons, actually. Tilman and Leon are great scientists who do really nice work and Marianne has an amazing entrepreneurial spirit. If I hadn’t become good friends with them, it probably wouldn’t have happened. I’m collaborating with Leon, on a project of mutual interest. It’s good to see each other live and talk about research, so the visiting professorship is very helpful for that. And then, I just love talking science. So anytime I’m in a room with a bunch of young scientists and talk science, that’s a great day.”

Have you been able to do that, in view of Covid?

“Yes, I’ve been over twice and will return in September 2022. When I come over, I meet with the PhD students for a couple of hours and we go through their projects. I try to provide a new perspective on their work, based on the direct knowledge from projects that we’ve done, or just from years of experience. Last time, we talked for many more hours than originally scheduled. I really enjoyed it, and learned a lot of good science from the students. All the good ideas come when you’re talking to colleagues or explaining a scientific point to someone – it’s much more intellectually stimulating to talk about science than it is to sit, stare at the wall and think. I’ve never had a single good idea sitting alone in my office! OK, well maybe I’ve had one! Also, my perspective is opened up when talking to people not in my field. As I mentioned before, lay audiences can ask you really challenging questions, and that’s just fine with me.”

What exactly are you working on with Professor Schurgers?

“I have an interest in vascular malformations, so that’s when blood vessels go wrong. Instead of being a nice neat tube, they form big tangled messes of tubes, or they become this really big cavern-like structure. I’m interested in how those form. One of the proteins Leon works on, MGP, has been implicated as being involved in one of these vascular malformations. We try to understand how. In my lab we can grow human blood vessels as part of human tissues in a so-called organ-on-chip platform. We do brain, liver, lung, pancreas, tumours: all organs in tiny versions. They all have their own blood vessels, either normal or diseased. We’re basically trying to understand how MGP is involved in this vascular malformation, which is a big problem for patients with the rare disease HHT. Our technology and

Leon's protein helps us to understand the disease better and hopefully will lead us to new drugs for patients. This project started with a Seed Grant from UCI and UM."

What's that exactly?

"Aileen Anderson, the director of the stem cell centre here at UCI, decided together with CARIM and MERLN to have a seed grant programme. Aileen puts money in, CARIM and MERLN do too. Once a year, the people from Irvine and Maastricht get together to review the submitted proposals for funding as seed grants, with the aim of stimulating collaboration on some aspects of stem cell biology."

What will the future of your collaboration look like?

"Marianne, Tilman and Leon contributed to a grant to build a facility in Maastricht where tissue is generated from stem cells, the so-called Induced Pluripotent Stem Cells. I'm part of that as a consultant, and potentially my company would have some space in this facility too. I have a company that's commercialising our organ-on-chip devices, named Aracari, after a pretty bird I like... I'm a birdwatcher!"

Why did you start this spin-off?

"Because I'm really excited about the technology. I think it can make a difference in the world and I want lots of people to be able to use it, to develop better drugs. And I like new challenges; I get bored if I do the same thing all the time. The company is very successful. We work with clients both from large pharma to small biotech companies to improve the accuracy of their drug development pipelines. Our goal is also to provide tools that will reduce the use of animals for drug testing. UCI is becoming very entrepreneurial: we've got a big focus on moving technologies into the commercial space and that's what Maastricht is getting better at as well."

Are there more similarities between UCI and Maastricht University?

"The universities have a similar size and age, both have many international students, we're both growing and becoming more well known, we're both a public university. I don't think it really matters for the collaboration, to be honest. It's more the research goals that we share, the personal interactions with people and the fact that resources are well matched too. It's not like one university is super rich and the other super poor."

Final question: CARIM suggested I ask you about your TR6, is that a grant you were able to obtain?

"Ha-ha, no, it's my old British sports car, a Triumph TR6. It's my pride and joy: I always loved them when I was a kid and then I got to the point I actually was able to buy one. Southern California is the perfect place for it: it's always sunny. I've been here on the West Coast since 1996, but I still feel very British, and sound British too. I'm just a Brit living in America."

FACES

BLOOD P1

BLOOD COAGULATION,
VENOUS THROMBOSIS & BLEEDING


AARON ISAACS


ALMA MINGELS


ARINA TEN CATE-HOEK


CECILE MAASSEN


CONSTANCE BAATEN


ELISABETTA CASTOLDI


ERIK BECKERS


FRAUKE SWIERINGA


GERRY NICOLAES


HANS IPPEL


HEIDI NOELS


HENRI SPRONK


HUGO TEN CATE


INGRID DIJKGRAAF


JENS POSMA


JUDITH COSEMANS


JUR TEN BERG


KANIN WICHAPONG


KRISTIEN WINCKERS


MAGDI NAGY


MARIJKE KUIJPERS


MONIKA STOLL


OTTO BEKERS


PAOLA VAN DER MEIJDEN


RENSKE OLIE


RORY KOENEN


STEVEN MEEX


STIJN AGTEN


TILMAN HACKENG


YVONNE HENSKENS

FACES

BLOOD P2 ATHEROSCLEROSIS, ARTERIAL THROMBOSIS & STROKE


BAS BEKKERS


CASPER MIHL


CHRISTIAN WEBER


DIETBERT NEUMANN


ELINE KOOI


EMIEL VAN DER VORST


ERIK BIESSEN


FELIX MOTTAGHY


JACK CLEUTJENS


JOACHIM JANKOWSKI


JOACHIM WILDBERGER


JUDITH SLUIMER


LIEVE TEMMERMAN


MARC VAN ZANDVOORT


MARJO DONNERS


PIETER GOOSSENS


PIETER VAN PAASSEN


REMCO MEGENS


ROBERT VAN OOSTENBRUGGE


SIMON SCHALLA


SUZAN WETZELS


SYLVIA HEENEMAN


WERNER MESS


WIM VAN ZWAM

FACES

VESSELS P3 VASCULAR COMPLICATIONS OF DIABETES & HYPERTENSION


ANNEMARIEK DRIESSEN


BASTIAAN DE GALAN


BOY HOUBEN


BRAM KROON


CARLA VAN DER KALLEN


CASPER SCHALKWIJK


COEN STEHOUWER


ELLEN FRANKORT


JULIE STAALS


KRISTIAAN WOUTERS


MARC HEMMELDER

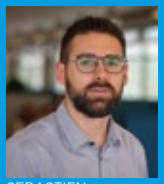

MARLEEN VAN GREEVENBROEK


MARTIJN BROUWERS


MIRANDA SCHRAM


NORDIN HANSSEN


RONALD HENRY


SEBASTIEN FOULQUIER


SIMONE EUSSEN


THOMAS VAN SLOTEN


THOMAS UNGER


YVETTE DERKS

FACES

VESSELS P4 REGENERATIVE & RECONSTRUCTIVE CARDIOVASCULAR MEDICINE


BAREND MEES


BART MAESEN


CHRIS REUTELINGSPERGER


DANIEL MOLIN


ED ERINGA


ELHAM BIDAR


IWAN VAN DER HORST


JOS MAESSEN


LEON SCHURGERS


LISETTE UNGETHUM


MAARTEN SNOEIJS


MARK POST


NIKO DECKERS


MICHAEL JACOBS


NYNKE VAN DEN AKKER


PEYMAN SARDARI NIA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ROBERTO LORUSSO


SANDRO GELSOMINO


SYLVIA MARIANI

FACES

HEART P5 STRUCTURAL HEART FAILURE


BEN JANSSEN


BLANCHE SCHROEN


CHRISTIAN KNACKSTEDT


GUIDO HAENEN


HANS PETER BRUNNER-LA ROCCA


JOB VERDONSCHOT


LEON DE WINDT


LIZ JONES


MARC VAN BILSEN


MARK HAZEBROEK


MARTIJN HOES


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SEBASTIEN FOULQUIER


STEPHANE HEYMANS


VANESSA VAN EMPEL


WARD HEGGERMONT

FACES

HEART P6 COMPLEX ARRHYTHMIAS


ARNOUD VAN 'T HOF


AURORE LYON


BART SPRONCK


BAS BEKKERS


BASTIAAN BOUKENS


CHAHINDA GHOSSEIN-DOHA


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