CARIM ANNUAL REPORT 2016

SCHOOL FOR CARDIOVASCULAR DISEASES

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CONTENTS

PREFACE
NOURISH YOUR NETWORKS; IT'S WORTH IT...

Recently, during a research partnership kick-off meeting with Big Pharma, we were asked the question: "Why do most projects fail?" The audience blamed lack of progress; funding; or applications, but the answer struck with simplicity and clarity: more than 80% of public-private initiatives fail due to a lack of communication.

This is undoubtedly true. Optimal communication leading to sustainable and reliable networks is key to today's successful research endeavours. In contrast, research progress in large consortia is far too often hampered by dividing funds and tasks between partners that subsequently go about performing essentially independent research in their own institutes. Annual meetings are then used to inform each other about the status of each group's respective activities, which, in most cases, does not result in meeting overall research objectives.

Currently, complex unmet research objectives require the engagement of multidisciplinary approaches mostly performed in large research teams. It is therefore necessary to choose your partners wisely, meaning choices should not be based solely on technical skills and track record, but also on communication skills and loyalty to the research consortium. After establishing a strongly performing network with non-competing partners, complementary disciplines, and the necessary personal 'clicks', you need to protect it by investing time and energy in maintaining relationships and loyalty to the group. Active interaction through consortium, or regular international, meetings between all consortium members - junior and senior - boosts research activities and, importantly, allows more fun.

CARIM - in its own way - is such an optimal consortium, albeit on local turf. CARIM is people working together to understand the full spectrum of cardiovascular disease in blood, heart and vessels by studying it from a chemical, biophysical, biological, mathematical, genetic, and clinical point of view. The three themes (blood, heart and vessels) exist purely for organisational purposes and investigators exchange ideas, techniques and viewpoints and collaborate regardless of theme boundaries to decipher how cardiovascular disease can be diagnosed and prevented at an early stage.

CARIM is performing to a high level; in 2016 it was judged as 'excellent' among its national peers. It was reported that "Maastricht UMC+ has a very high citation score and a strong cardiovascular research profile" and that "In Maastricht, cardiovascular research is clustered in the School for Cardiovascular Diseases (CARIM), one of the top institutes for translational cardiovascular research in Europe" (Neth Heart J 2016; 24: 308-316). In the same year, numerous prestigious personal grants and prizes were obtained, and crucial steps were taken to restructure CARIM.

Europe has recognized CARIM's excellence by funding many consortia in which CARIM plays a leading role, as will be outlined in this annual report. In addition, profiles of individual investigators, research networks and concepts developed through translational and, importantly, curiosity driven efforts will be highlighted, which will give you a flavour of our work and our passion.

This is CARIM 2016.

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 two and a half decade as a leading research institute in the field of cardiovascular disease. At CARIM, basic mechanisms as well as early diagnosis and individual risk stratification of cardiovascular diseases are studied, allowing faster translation of new research concepts to clinical practice. New findings, products and techniques which can be applied in healthcare are evaluated, often in collaboration with private companies, and the results of scientific research are published in high-ranking international journals. Master's students, PhD students and MD students are trained to become independent researchers, and post-docs are trained to become leading scientists in the field of cardiovascular disease.

CARIM is built around three broader research themes, each led by a program leader: I) Thrombosis and Haemostasis, II) Complex Arrhythmias and Structural Heart Disease and III) Vascular Biology and Medicine. These three themes comprise 23 basic and clinical programs, each led by a Principal Investigator (PI). The PIs are responsible for the scientific progress of their program, for linking activities and seeking collaborations between PIs and themes, for mentoring of PhD students and post-docs and, finally, for the financial basis of the program. All three themes involve basic and clinical programs. Cardiovascular scientists from around the world join CARIM because it values open communication, close cooperation, high ambitions, good facilities and a critical learning. CARIM is one of the six research schools of the Faculty of Health, Medicine and Life Sciences (FHML) of Maastricht University and is embedded within the Maastricht University Medical Centre+ (MUMC+). CARIM is appointed as research school by the Royal Netherlands Academy of Arts and Sciences (KNAW) and recognised as an international training site for Early Stage Researchers by the European Union.

CARIM researchers have been very active in EU networking activities and forming (inter)national alliances. In total CARIM is currently involved in about 30 European projects. CARIM is involved in eight Innovative Training Networks (ITN) with a total number of 22 Early Stage Researchers allocated to CARIM. Of one of these Horizon 2020 ITNs, INTRICARE (3.8 M€), CARIM is coordinator. See pages 40-69 for more information on CARIM's involvement in EU networks.
CARIM has a long-lasting tradition of executing programmes in collaboration with industry, sharing its expertise but maintaining its independence as reflected by the right to publish. Ongoing collaborations include, among others, Bayer HealthCare, Roche, Medtronic Bakken Research Center BV, and Abbott. Furthermore, CARIM researchers are involved in other Public Private collaborations through Interreg programs and the Weijerhorst Foundation, and takes part in (inter)national networks such as NHF CVON, Horizon 2020, EUPlan, and Leducq Transatlantic Network.

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

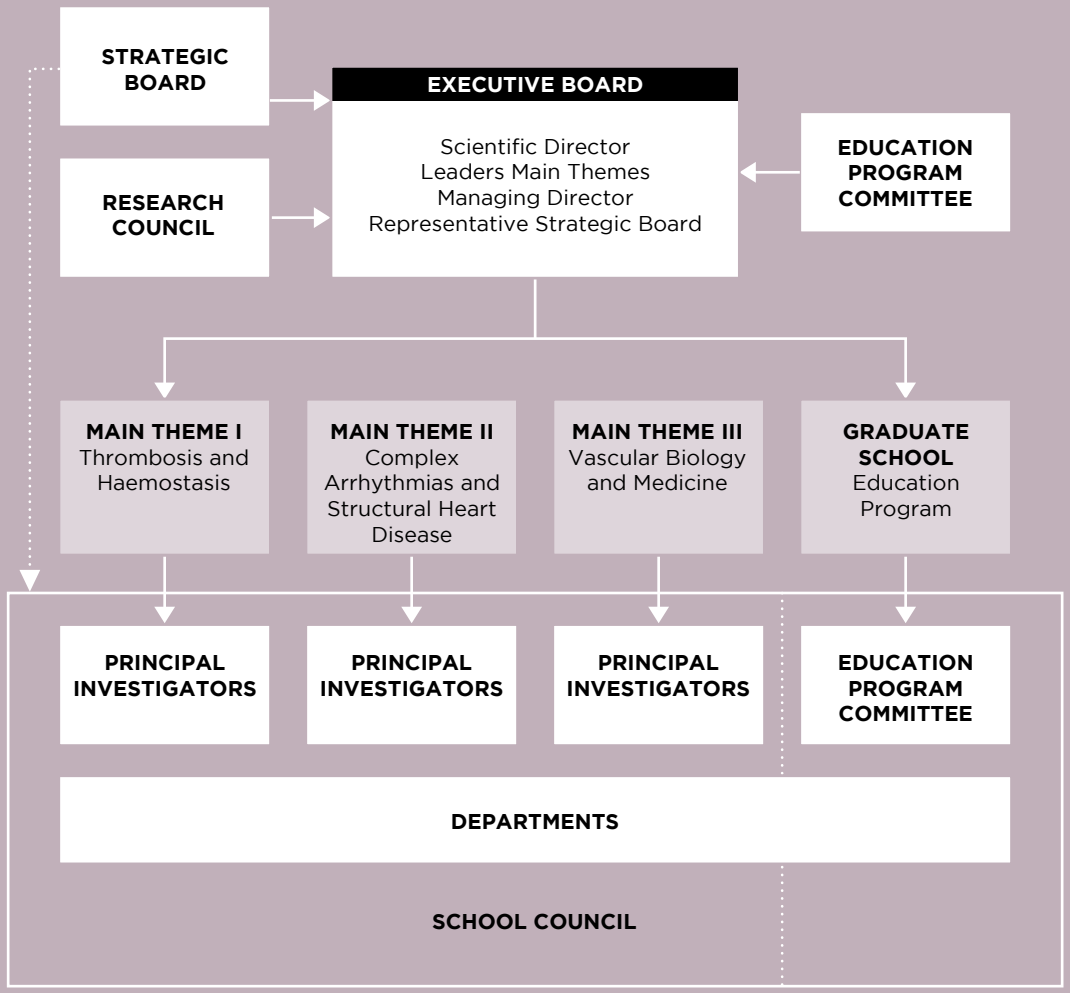
KEY FIGURES 2016

ANNUAL BUDGET: **21,076** K€	DEPARTMENTS/DISCIPLINES: **15**
NEW CONTRACTS AND GRANTS: **15,567** K€	SCIENTIFIC ARTICLES: **577** (Wi-1: 535)
RESEARCHERS: **144** FTE	PHD THESES: **55**
TECHNICAL AND SUPPORTING STAFF: **48** FTE	PATENTS: **2**

ORGANISATION

02

ORGANISATION



In April 2017, Professor Tilman Hackeng took over CARIM's Scientific Directorship from Professor Thomas Unger. The Scientific Director has the final responsibility for the research institute, including the organisation and management of the research programme, the scientific output, the training of Master's and graduate students and post-doctoral fellows, and the financial management and the public relations of the institute. A Strategic Board is in place to advise and support the Scientific Director in managing long term policy. The board is also a discussion forum and generates written visions of the future of CARIM and its survival in an increasingly competitive European scientific environment. The Strategic Board meets regularly to discuss issues such as grant applications, national and international collaboration networks, interdisciplinary communication and CARIM's visibility in the national and international cardiovascular fields.

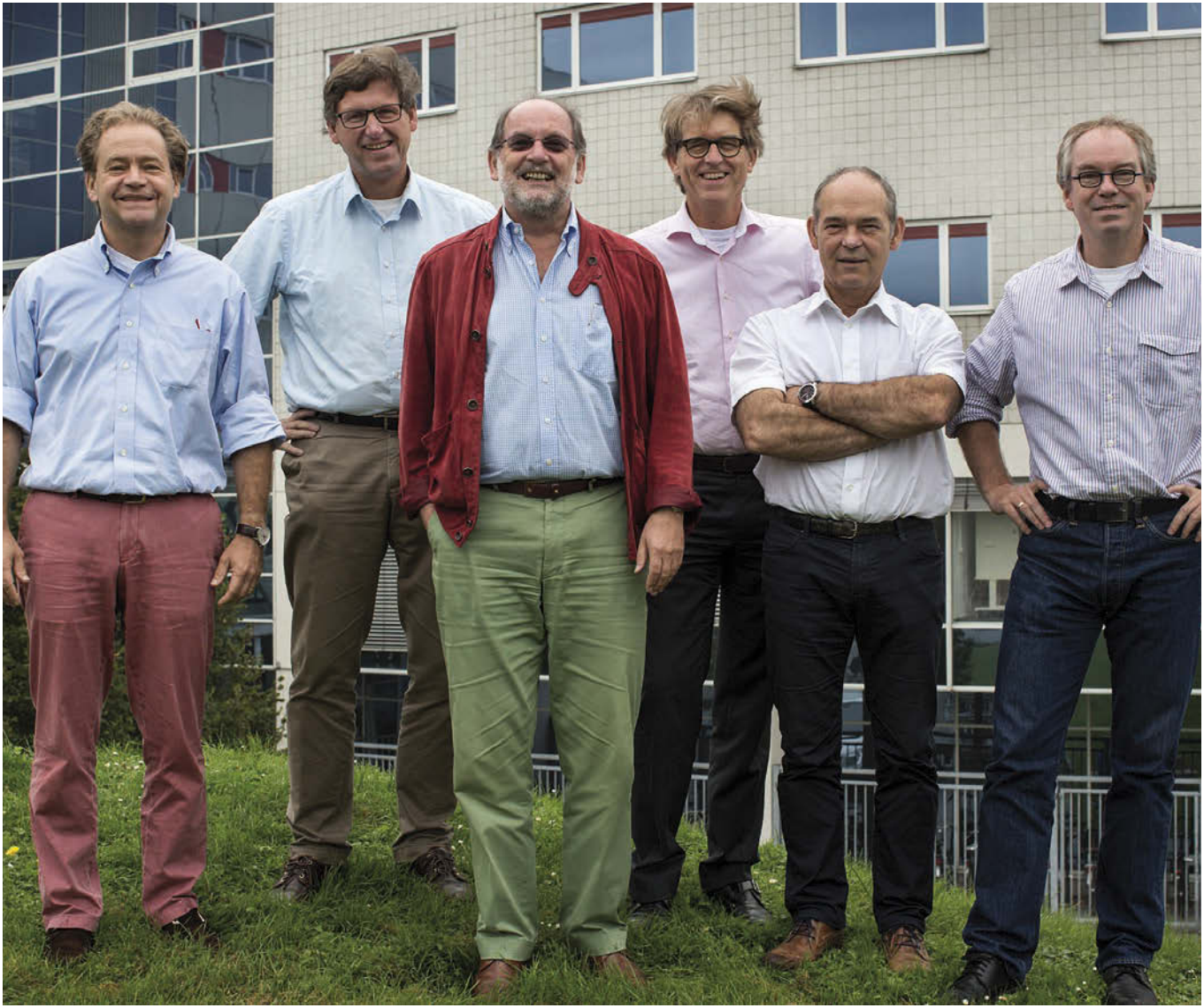
The Scientific Director is assisted by the Managing Director, Rob van der Zander, who takes care of the financial and human resource management. Together with the three leaders of the main themes and a representative from the Strategic Board, the Scientific and Managing directors make up the Executive Board of the institute. The Executive Board meets monthly to discuss and decide upon issues at strategic and operational level. The Executive Board is advised by three councils/committees: the Strategic Board, the Education Program Committee and the CARIM Research Council. The Education Program Committee coordinates both the PhD- and Master's training programs and consists of the PhD Program Coordinator, the Master Program coordinator, 3 CARIM staff members and 3 PhD students. The committee advises the Executive Board on all issues regarding the PhD and Master's programs. The Research Council advises the Executive Board and Principal Investigators on the quality of all research proposals and meets regularly to discuss grant applications. Finally, the School Council consists of the Principal Investigators and Department Chairs and meets four times a year. Since the end of 2016, junior staff members are also invited to the School Council meetings, but are excluded from voting rights. The School Council is informed by the Executive Board on ongoing matters and advices 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 Main Theme I
- Prof. Harry Crijns, Leader Main Theme II
- Prof. Harry Struijker-Boudier, Leader Main Theme III
- Prof. Coen Stehouwer
- Prof. Uli Schotten, representative Strategic Board
- Rob van der Zander, Managing Director

STRATEGIC BOARD

- Prof. Uli Schotten, Chairman
- Prof. Hugo ten Cate
- Prof. Leon de Windt
- Prof. Chris Reutelingsperger
- Prof. Robert van Oostenbrugge
- Dr Judith Sluimer
- Rob van der Zander



PRINCIPAL INVESTIGATORS

- Prof. Ilja Arts, Dept. of Epidemiology
- Prof. Erik Biessen, Dept. of Pathology
- Prof. Matthijs Blankesteijn, Dept. of Pharmacology & Toxicology
- Prof. Harry Crijns, Dept. of Cardiology
- Prof. Hugo ten Cate, Dept. of Biochemistry
- Prof. Tammo Delhaas, Dept. of Biomedical Engineering
- Prof. Tilman Hackeng, Dept. of Biochemistry
- Prof. Johan Heemskerk, Dept. of Biochemistry
- Prof. Stephane Heymans, Dept. of Cardiology
- Prof. Bram Kroon, Dept. of Internal Medicine
- Prof. Jos Maessen, Dept. of Cardiothoracic Surgery
- Prof. Robert van Oostenbrugge, Dept. of Neurology
- Prof. Mark Post, Dept. of Physiology
- Prof. Frits Prinzen, Dept. of Physiology
- Prof. Chris Reutelingsperger, Dept. of Biochemistry
- Prof. Uli Schotten, Dept. of Physiology
- Prof. Coen Stehouwer, Dept. of Internal Medicine
- Prof. Monika Stoll, Dept. of Biochemistry
- Prof. Harry Struijker-Boudier, Dept. of Pharmacology & Toxicology
- Prof. Paul Volders, Dept. of Cardiology
- Prof. Christian Weber, Dept. of Biochemistry
- Prof. Joachim Wildberger, Dept. of Radiology
- Prof. Leon de Windt, Dept. of Cardiology

RESEARCH COUNCIL

- Prof. Frits Prinzen, chairman
- Dr Kristiaan Wouters, secretary
- Prof. Erik Biessen
- Dr Matthijs Blankesteijn
- Dr Marjo Donners
- Dr Gerry Nicolaes
- Dr Henri Spronk (until June 2017)
- Prof. Chris Reutelingsperger

EDUCATION PROGRAM COMMITTEE

- Dr Marc van Bilsen, chairman, PhD Coordinator
- Dr Adriaan Duijvestijn, Coordinator Biomedical Sciences Master (until October 2017)
- Dr Matthijs Blankesteijn, Coordinator Biomedical Sciences Master (since October 2017)
- Dr Eline Kooi, staff member
- Dr Hans Vink, staff member
- Lauren Dupuis, PhD student
- Armand Jaminon, PhD student
- Margaux Fontaine, PhD student

CARIM OFFICE

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

HR-SUPPORT

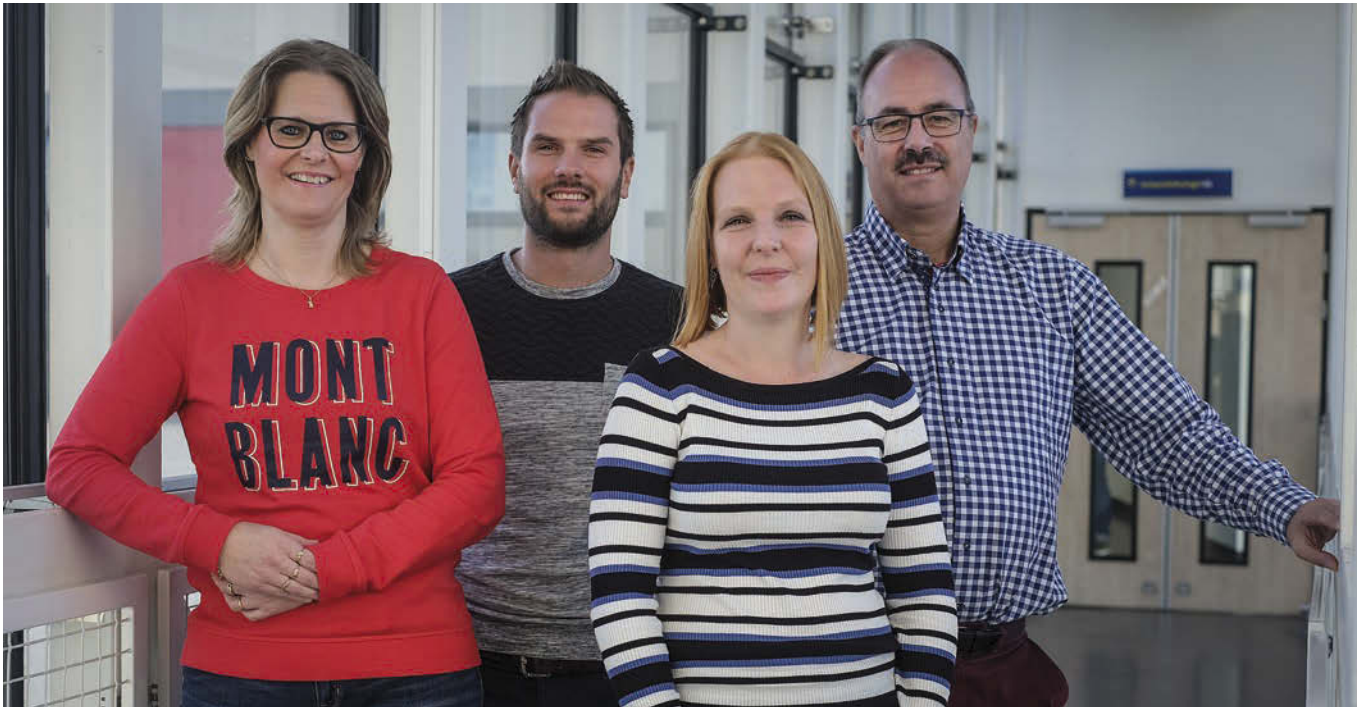
Patrick Janssen and Dennis Aarts of the Human Resources Department of Maastricht University are dedicated to CARIM.

ADMINISTRATIVE SUPPORT

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

PARTICIPATING DEPARTMENTS AND DISCIPLINES

The research in the CARIM's three main themes involves the research activities of employees working in 15 basic and clinical departments/disciplines of MUMC+.



BASIC RESEARCH DEPARTMENTS

- BIOCHEMISTRY
- BIOMEDICAL ENGINEERING
- EPIDEMIOLOGY
- GENETICS & CELL BIOLOGY
- PHARMACOLOGY & TOXICOLOGY
- PHYSIOLOGY

CLINICAL DEPARTMENTS

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

CONTROLLER AND ADMINISTRATIVE SUPPORT:
Esther van Heel, Mark van Gisteren, Lynn Lemeer, Henny Kerckhoffs

HIGHLIGHT THEME I

PAOLA VAN DER MEIJDEN

DEPARTMENT OF BIOCHEMISTRY

Acquired alterations in platelet haemostatic function

Platelets are derived from megakaryocytes in the bone marrow or, as recently described for mice, in the lungs, and fulfil a multitude of roles in haemostasis and thrombosis, vascular repair, inflammation, innate immunity and tumour metastasis. There is increasing evidence that the platelets in one individual are heterogeneous in terms of composition and function, resulting in the existence of different platelet populations with specific functions. We can distinguish adhesive and aggregating platelets (activated integrins), secretory platelets (granule secretion) and procoagulant platelets (surface exposure of phosphatidylserine). Platelet fate is determined by both intrinsic factors and the local environment. With regard to intrinsic factors, megakaryocytes can vary greatly in cytoplasmic content and receptor expression on their membrane, which is likely to be reflected in the platelets formed from them. Also, platelet size and platelet age correlate with platelet activity, with larger platelets and newly formed platelets being the more active ones. The lifespan of platelets is tightly regulated by the balance between pro- and anti-apoptotic proteins, and upon ageing apoptotic platelets appear with severely reduced function. In addition to intrinsic platelet factors, the environment also greatly influences the platelet response and can vary, depending on local levels of platelet agonists, the location of the vascular bed, the type of injury and the physiological (or pathophysiological) state of the vessel.

Heterogeneity in platelet activation, and thereby also in fibrin distribution, is especially apparent in thrombi formed *in vitro* or *in vivo* in flowing blood. The thrombus core typically consists of adhesive/aggregating and secretory platelets surrounded by procoagulant platelets, while loosely adhering platelets are present in the outer shell. By applying our microspot method of thrombus formation in parallel-plate flow chambers under coagulant conditions, we were able to assess the distribution of platelets and fibrin throughout the thrombus by analysing *z*-stacks of two-colour confocal images. Limitation of the platelet-activating surface or the platelet number results in increased accumulation of fibrin in the centre and top (luminal) regions of the thrombus (Figure 1). Using nano-indentation, we showed increased microelasticity of these thrombi, which is presumed to enhance the haemostatic process.

HIGHLIGHT THEME I

It is known that certain pathological conditions, such as prothrombotic or haematological diseases, affect platelet activation, but the treatment of these diseases can also alter platelet function and/or coagulation, and thereby tip the haemostatic balance towards bleeding.

DUAL ANTIPLATELET THERAPY IN VULNERABLE CORONARY ARTERY DISEASE PATIENTS

Patients with coronary artery disease are treated with dual antiplatelet therapy (DAPT), consisting of aspirin and an inhibitor of the ADP receptor P2Y12, to prevent secondary atherothrombotic events. DAPT is associated with an increased risk of bleeding, especially in patients with decreased platelet reactivity during treatment, so-called low on-treatment platelet reactivity. It is still not completely clear whether monitoring the platelet function and subsequently adjusting the antiplatelet therapy in high-risk patients is beneficial in preventing bleeding complications. Several platelet function tests can be used to measure the residual platelet reactivity while on DAPT, but there is no consensus on the preferred type of platelet function test and the accompanying therapeutic window. We have therefore set up a regional referral clinic for bleeding complications of antithrombotic therapy for high-risk patients with coronary artery disease who have undergone percutaneous coronary intervention. Cardiologists refer to us those patients who have two or more common risk factors for bleeding and/or ischaemic events and are treated with DAPT or single anti-platelet therapy (P2Y12 inhibitor) combined with an oral anticoagulant. The aim of this clinic within the Thrombosis Expertise Centre of the MUMC+ is to identify patients with high bleeding risk during DAPT by combining patient characteristics (e.g. risk scores, genetic polymorphisms) with platelet function tests and, possibly, global haemostatic tests and then tailor their treatment.

In a group of 145 patients, we first explored the level of agreement between three different platelet function tests (VerifyNow, Multiplate and light transmission aggregometry) using the therapeutic windows proposed by consensus documents. After classifying the patients into low, optimal and high platelet reactivity groups according to the three tests, we found that 26% of the patients had been classified in the same category, while 70% of the patients had been classified in two different categories and 4% even in three categories. These results indicate that there is only slight to moderate agreement between the three platelet function tests we applied, so the tests are not interchangeable. Furthermore, we found that the level of agreement between the assays was significantly influenced by the type of antiplatelet drug, patient characteristics (e.g. age) and laboratory parameters (e.g. haemoglobin level).

The next step will be to assess the predictive value of each platelet function test for clinical outcomes and to define the therapeutic window for the vulnerable patient population. Since the mechanisms that increase the risk of bleeding in patients are multifaceted, assessment of platelet function alone will not be sufficient to identify patients at risk. Addition of other (integrative) tools, such as coagulation and fibrinolysis markers, may aid in the risk assessment. We have proposed a research algorithm (Figure 2) for identifying patients with high bleeding risk and subsequent tailoring of therapy, which eventually requires clinical validation.

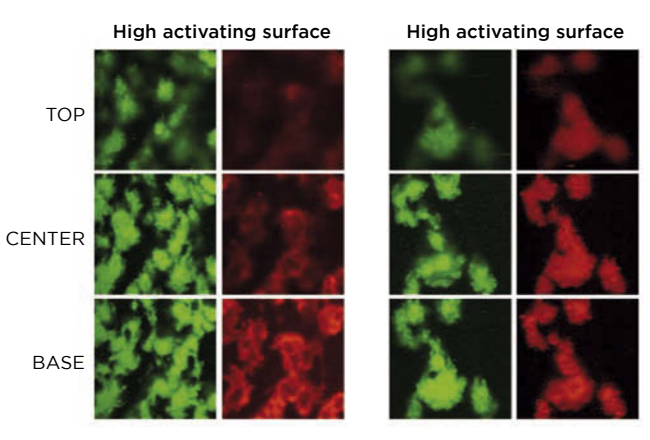


FIGURE 1

The platelet-activating surface determines the distribution of fibrin across a thrombus. Thrombi containing platelets ($DiOC_6$ in green) and fibrin (AF647-fibrin(ogen) in red) were formed by flowing blood over microspots containing high or low collagen content in combination with tissue factor. Representative fluorescence images of optical slices at the base, centre and top regions of thrombi.

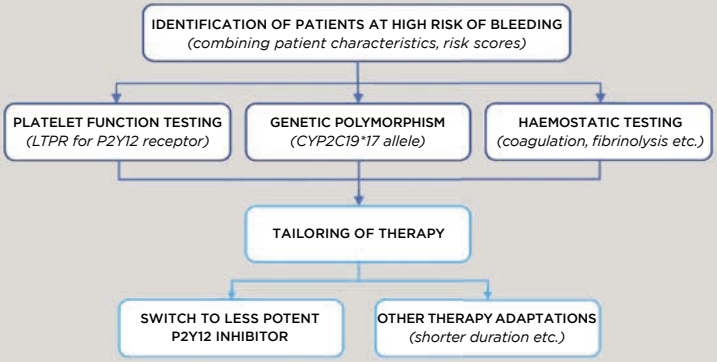


FIGURE 2

Research algorithm (simplified) for identifying patients with high bleeding risk and tailoring of therapy. LTPR= low on-treatment platelet reactivity.

CHEMOTHERAPY IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

Patients with haematological malignancies, such as leukaemia, myeloma and lymphoma, are treated with intensive chemotherapy targeting the malignant cells in the bone marrow. Consequently, these patients develop severe thrombocytopenia, i.e. a platelet count below $50x10^9$/L, which is associated with an increased risk of clinically significant bleeding. The current standard to prevent bleeding in such patients is prophylactic transfusion with platelet concentrate if the platelet count drops below $10x10^9$/L. Still, a significant number of patients experience bleeding events despite prophylactic platelet transfusion. Since the bleeding risk cannot be predicted by the platelet count only, we hypothesised that other haemostatic factors would be involved.

Being awarded the EHA-ISTH (European Haematology Association- International Society on Thrombosis and Haemostasis) Joint Research Fellowship gave me the opportunity to evaluate platelet and coagulant function in patients with chemotherapy-induced thrombocytopenia. This is especially of interest since myelosuppressive chemotherapy affects both intrinsic platelet factors (platelet production in the bone marrow) and the activating environment by inducing vascular damage. Together with the Department of Haematology and the Central Diagnostic Laboratory of MUMC+, we included 93 patients with acute leukaemia, myeloma and lymphoma who had not received a platelet transfusion within the previous three days. An interesting finding, revealed by flow-cytometric analysis of platelet activation markers, is that the platelets from these patients were to a varying degree dysfunctional, and

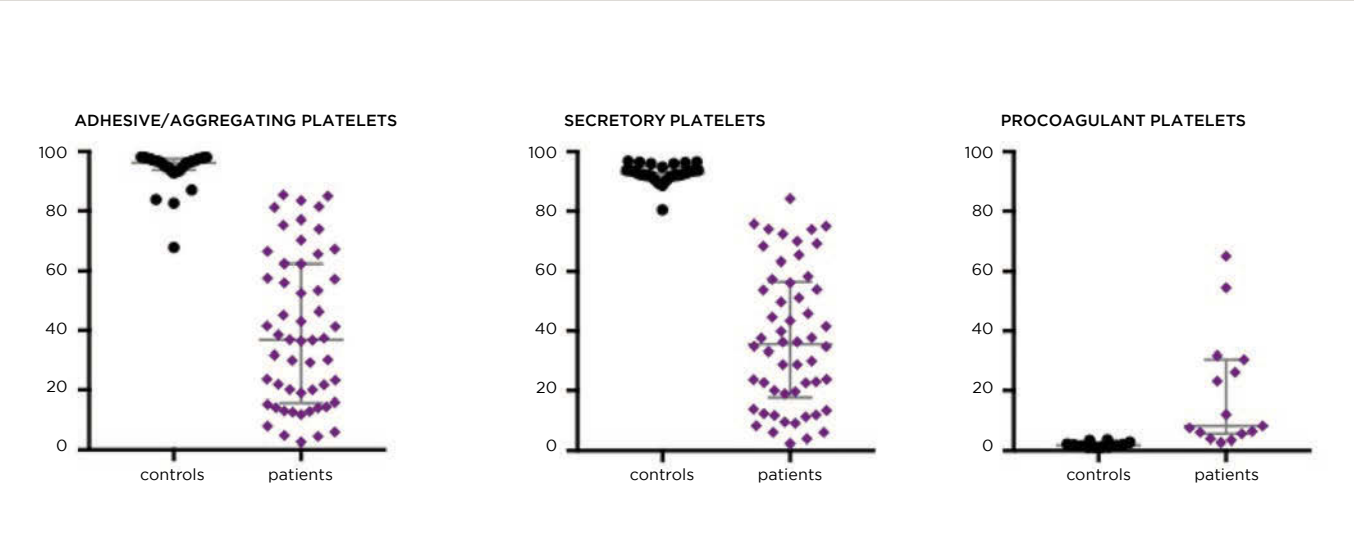


FIGURE 3

Functional impairments of platelets from thrombocytopenic patients with haematological malignancies after chemotherapy treatment. After stimulation with thrombin, platelets from patients showed decreased integrin αIIbβ3 activation (PAC-1 antibody binding) and α-granule secretion (P-selectin antibody binding). In the absence of stimuli, these patients showed an increased fraction of platelets exposing phosphatidylserine (PS).

this appeared to be independent of disease or treatment type. Platelet dysfunctionality was more evident during the phase of decreasing platelet count than during the recovery of platelet count, while severe thrombocytopenia was present. When analysing the different platelet populations after the addition of agonists, the fractions of adhesive/aggregating platelets and secretory platelets in these patients were found to be reduced. Surprisingly, in the absence of activating stimuli there was an increased fraction of procoagulant platelets exposing phosphatidylserine on their membrane surface (Figure 3). However, these platelets showed no signs of apoptotic signalling, which could have explained the phosphatidylserine exposure and decreased platelet function. By using high-resolution respirometry, we revealed that impaired mitochondrial activity and subsequent defective receptor signalling caused the overall dysfunction of platelets from thrombocytopenic cancer patients treated with chemotherapy. After patients received

transfusion with platelet concentrate, their thrombus and fibrin formation under flow was increased, indicating improved haemostasis.

Since platelet transfusion comes with undesirable side effects and high costs, improved identification of patients at risk of bleeding is necessary. The first step will be to confirm the association between markers of platelet dysfunction and bleeding complications. This could ultimately lead to more efficient transfusion practice based on platelet function rather than platelet count.

INTERVIEW
ULI SCHOTTEN

To stay ahead, embrace change

"As a scientist, I like to think in evolutionary terms. Basically this means that you are more successful if you adapt quickly to changes in your environment. The basic principle of natural selection also holds true for scientists and research schools."
These are the words of Prof. Uli Schotten, chairman of CARIM's Strategic Board (SB). The SB was created five years ago to support the Executive Board in its strategic planning for the Research School.

What exactly does the Strategic Board do?
"Our main task is to keep track of changes in our scientific environment in a very broad sense of the word. What new technologies are emerging? In what direction is the research field developing? What new grant opportunities occur? Are we good at taking advantage of these opportunities or how could we facilitate this? How do the EU calls change, content-wise and in terms of scientific approach? But we also deal with the way we work together. How do we organise our research programmes? Do we pay enough attention to young talent? How do we and how do we want to communicate and exchange ideas and technology? We try to translate the results of our discussions into tangible action points and suggest them to the Executive Board. "

And does the Executive Board follow your suggestions?
Often they do, sometimes they don't – usually not because they wouldn't want to, but because of constraints we have to deal with. Overall, this is how it should be. We have an advisory role but I think we have triggered quite some fruitful discussions in the past.

How exactly do you go about doing that?
"It depends quite a bit on the question at hand. Sometimes we organise strategic days, some kind of retreat to discuss strategic aspects with all scientists of the school. In other cases we organise workshops or we initiate new working groups. Right now we work on a strategy document in which we give recommendations for future investments of CARIM. We hope to finish this document by the end of the year.

So where does CARIM stand?
"Compared with other cardiovascular institutes in the Netherlands, and with other research schools at Maastricht, we're doing quite well. But regardless of the current results, the ambition should always be to perform even better. For example, it should be possible to further enhance the scientific coherence between CARIM scientists while at the same time we should increase our methodological diversity. For example, we see room for improvement in developing algorithms and code for computer modelling and large scale signal analysis, primarily for better patient characterisation. This may facilitate linking various data modalities with each other and assembling clinically well-characterised patient cohorts that at the same time allow for studies on individual molecular disease mechanisms. I believe that's where we need to invest now, if we want to remain competitive in current and upcoming European calls for grant proposals."

Can you expand on that?
"Under the FP7 programme, grant proposals often focussed on a particular disease entity. In the new framework, the calls are much more broadly defined and focus more on a particular approach or technology. This means that researchers from completely different fields of science can respond to the same call, resulting in large numbers of applying consortia and low acceptance rates, often below 5%. Nevertheless, we try to encourage researchers to apply and offer support during the application process. Most importantly, we have to make sure that we develop and refine expertise in key technologies that often are requested in these calls, such as non-invasive diagnostics, research with organoids, alternative approaches to animal experiments, gender issues, or systems approaches. A general trend is that exchange of data of existing databases is strongly encouraged, particularly in cohorts with well characterised patients."

Are you worried about young researchers in the current grants climate?
"There are quite some grant opportunities for young

researchers both on the national and the European level. The problem is that mostly scientists that follow a very straightforward and standard career benefit from those instruments. Researchers working on the interface between disciplines or those who – for whatever reason – develop a successful career relatively late have difficulties to take advantage of them. This example shows how urgently our system for career incentives and promotion needs to account much more for the large diversity of career trajectories in biomedical sciences and for the fact that top research is usually the result of a team effort rather than the achievement of a single hero. Also, the competition is very tough and a young researcher's career is often dominated by systematically building up a competitive curriculum vitae but not necessarily by curiosity-driven research. Ambition that in the past often focussed on specific scientific questions nowadays is adsorbed by achieving yet another milestone. We appreciate that many PIs involve their younger colleagues in the larger networks where the bigger picture leads the strategy and where there is still more room for the one and other experiment following a side-path. "

A few years ago, some young researchers in CARIM felt they were insufficiently being listened to or not given enough information.

"That's right, and I think the School has made considerable progress in that respect over the years. There's much more communication, transparency and reflection about what we do, how we work, and why we take decisions. Junior staff members, who are not yet PIs, are now more closely involved in decision-making, and research staff is more frequently given a platform, like the School Council, to discuss matters that are important to them. We also integrate younger colleagues much more in the administrative bodies of our school, such as the SB. Besides, we have many more bottom-up working groups right now than 10 years ago."

WE KEEP TRACK OF CHANGES IN OUR SCIENTIFIC ENVIRONMENT IN A VERY BROAD SENSE OF THE WORD

What do you see as the main challenge CARIM is facing in the near future?

"In CARIM we deal with complex syndromes of cardiovascular diseases, often with relatively uniform clinical presentation, such as hypertension, heart failure, or atrial fibrillation. The underlying mechanisms however are likely very diverse making effective therapy difficult. One of the most important challenges in the field is to bridge the gap between the individual mechanisms on the cellular or molecular level on the one hand and the clinical presentation on the other. The new 2018/19 working programme from Brussels is full of calls addressing this important challenge. I think that most researchers in CARIM are fully aware of this trend and have recently expressed this in a survey by suggesting that investments in computer modelling, signal analysis, bioinformatics and expertise linking different layers of information in cohorts of well characterised patients are needed in CARIM."

Composition of the Strategic Board

The SB recently underwent restructuring. Currently it has 10 members, two members representing each of the main research themes, two members of the CARIM management team, one member representing MaCSBio and one responsible for the HVC-CARIM interaction.

FACTS AND FIGURES

03

FUNDING AND EXPENDITURE AT INSTITUTIONAL LEVEL 2011-2016

	2011	2012	2013	2014	2015	2016
	K€	K€	K€	K€	K€	K€
FUNDING						
Direct Funding structural	8,242	7,391	7,419	7,500	7,443	7,096
Direct Funding specific programs	2,830	2,717	2,272	1,309	1,492	2,751
Total Direct Funding (1)	**11,072**	**10,108**	**9,691**	**8,809**	**8,935**	**9,847**
Research grants (2)	1,284	1,566	1,730	1,481	1,850	2,053
Contract research (3)	13,202	13,464	13,456	11,117	11,612	9,167
	14,486	**15,030**	**15,186**	**12,598**	**13,462**	**11,220**
Total funding	**25,558**	**25,138**	**24,877**	**21,407**	**22,397**	**21,067**
EXPENDITURE						
Personnel costs	15,984	16,492	17,501	16,343	15,039	14,098
Other costs	7,855	8,475	8,379	6,392	5,986	6,406
Total Expenditure	**23,839**	**24,967**	**25,880**	**22,736**	**21,025**	**20,504**
RESULT	**1,719**	**171**	**-1,003**	**-1,328**	**1,372**	**563**

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

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

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

RESEARCH OUTPUT IN 2011-2016

	2011	2012	2013	2014	2015	2016
SCHOOL LEVEL						
Scientific publications	571	635	605	584	586	577
Other publications	53	80	50	70	48	69
PhD theses	39	50	34	35	43	55
Total* (I)	**666**	**765**	**689**	**689**	**677**	**701**
Academic staff** (II)	34.3	33.1	32.4	33.4	32.6	28.7
Ratio I and II	19.4	23.1	21.3	20.6	20.8	24.4
THEME I						
Scientific publications	107	108	111	109	125	152
Other publications	12	12	13	19	8	13
PhD theses	8	8	7	10	10	14
Total	**127**	**128**	**131**	**138**	**143**	**179**
THEME II						
Scientific publications	214	246	240	239	249	212
Other publications	13	25	20	34	13	28
PhD theses	14	20	17	10	21	23
Total	**241**	**291**	**277**	**283**	**283**	**263**
THEME III						
Scientific publications	309	353	331	313	301	269
Other publications	28	45	22	32	31	26
PhD theses	17	22	12	17	12	22
Total	**354**	**420**	**365**	**362**	**344**	**317**

* Please note that the sum of the publications in Themes I, II and III exceeds the total number of publications at School level, due to a double counting of publications with authors from different themes

** Academic staff: PhD students and post-docs not included

PhD theses: including PhD theses externally prepared

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

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

Due to the implementation of the FHML Pure output assessment tool, the final data for 2016 were not available at the time of print.

NEW CONTRACTS AND GRANTS CONCLUDED IN 2016

FUNDING	THEME I	THEME II	THEME III	TOTAL SUPPORT
	K€	K€	K€	K€
Type 2	800	489	-	1,289
Type 3	5	4,336	1,718	11,168
Type 4	1,577	406	377	2,360
Type 5	250	250	250	750
Total	**7,742**	**5,481**	**2,345**	**15,567**

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

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

Type 4 Industry, excl. CTCM (turn over in 2016: 2,088 K€)

Type 5 Annual support MUMC+ (750 k€) Cardiovascular Center-CARIM 'Pieken in de Breedte'

SUMMARY OF SCIENTIFIC AND TECHNICAL STAFF CARIM 2016 (IN FTE)

RESEARCH AREA	WP1			WP2			WP3			WP4			MUMC+	TOTAL
	Faculty	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	FTE
Thrombosis and Haemostasis	6.6	2.1	1.0	2.1	2.0	1.6	0.3	6.9	4.2	-	2.8	0.1	2.3	31.9
Complex Arrhythmias and Structural Heart Disease	11.9	1.1	1.1	1.1	6.5	3.4	0.0	19.2	7.2	-	4.0	2.0	5.4	62.8
Vascular Biology and Medicine	10.1	1.3	0.5	0.0	2.7	1.1	0.1	17.3	9.6	-	0.5	0.7	5.8	49.6
TOTAL	**28.7**	**4.4**	**2.6**	**3.2**	**11.2**	**6.1**	**0.4**	**43.3**	**20.9**	**-**	**7.3**	**2.7**	**13.5**	**144.3**

RESEARCH AREA	OBP 1	OBP 2	OBP 3	OBP 4	MUMC+	TOTAL
Thrombosis and Haemostasis	4.4	1.0	1.2	1.0	2.2	9.8
Complex Arrhythmias and Structural Heart Disease	14.2	-	2.7	-	-	16.9
Vacular Biology and Medicine	10.9	0.5	6.6	1.9	1.6	21.6
TOTAL	**29.5**	**1.5**	**10.5**	**2.9**	**3.8**	**48.3**

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

HIGHLIGHT THEME II

GUDRUN ANTOONS

DEPARTMENT OF CARDIOLOGY

Regulation of atrial function and rhythm: a nanoscale perspective

INTRODUCTION

Atrial fibrillation (AF) is the most common clinically relevant arrhythmia that presents major therapeutic challenges. AF is a progressive disease that occurs and maintains itself in the context of a structurally and functionally remodelled substrate. Stressors and modulators include autonomic imbalance and mechanical-electrical interactions. At several stages of disease progression, a role for aberrant calcium (Ca^{2+}) handling has been suggested in the initiation and maintenance of AF, being a critical element in ectopic activity, re-entry and atrial remodelling.

In cardiac myocytes, Ca^{2+}-induced Ca^{2+} release (CICR) is a fundamental process of excitation-contraction (EC) coupling, which is necessary for beat-to-beat contraction. CICR is supported by dedicated nanostructures, so-called dyads, localized at tubular membranes. The dyad functions in the spatiotemporal control of subcellular Ca^{2+} dynamics. If uncontrolled, arrhythmogenic Ca^{2+} events arise. Dyadic structures, including the tubular components, are subject to remodelling. In the context of AF, most research has focused on functional remodelling of signalling complexes that converge at the dyad, including ryanodine receptor (RyR) dysregulation by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and reactive oxygen species (ROS). The structural element of atrial-specific dyadic organisation and Ca^{2+} regulatory subdomains has been under-addressed in studies of Ca^{2+} dynamics in AF. In addition, the mechanical component is usually overlooked in cellular studies.

The main focus of our current work is the structure-function analysis and regulation of atrial-specific subdomains of Ca^{2+} release in relation to global atrial function and arrhythmias. We specifically address subdomain-specific mechanisms of autonomic regulation and mechanical stretch, and examine whether form, function and regulation are altered in disease.

ATRIAL-SPECIFIC REGULATORY MECHANISMS OF EXCITATION-CONTRACTION COUPLING

Cardiac myocytes have a unique network of invaginating membrane structures composed of interconnected transverse and longitudinal tubules. These tubules contain hubs of ion channels and signalling molecules that propagate action potentials throughout the entire cytosol and form functional contacts with neighbouring RyR (Figure 1). These coupled regions, dyadic microdomains, are structurally essential for

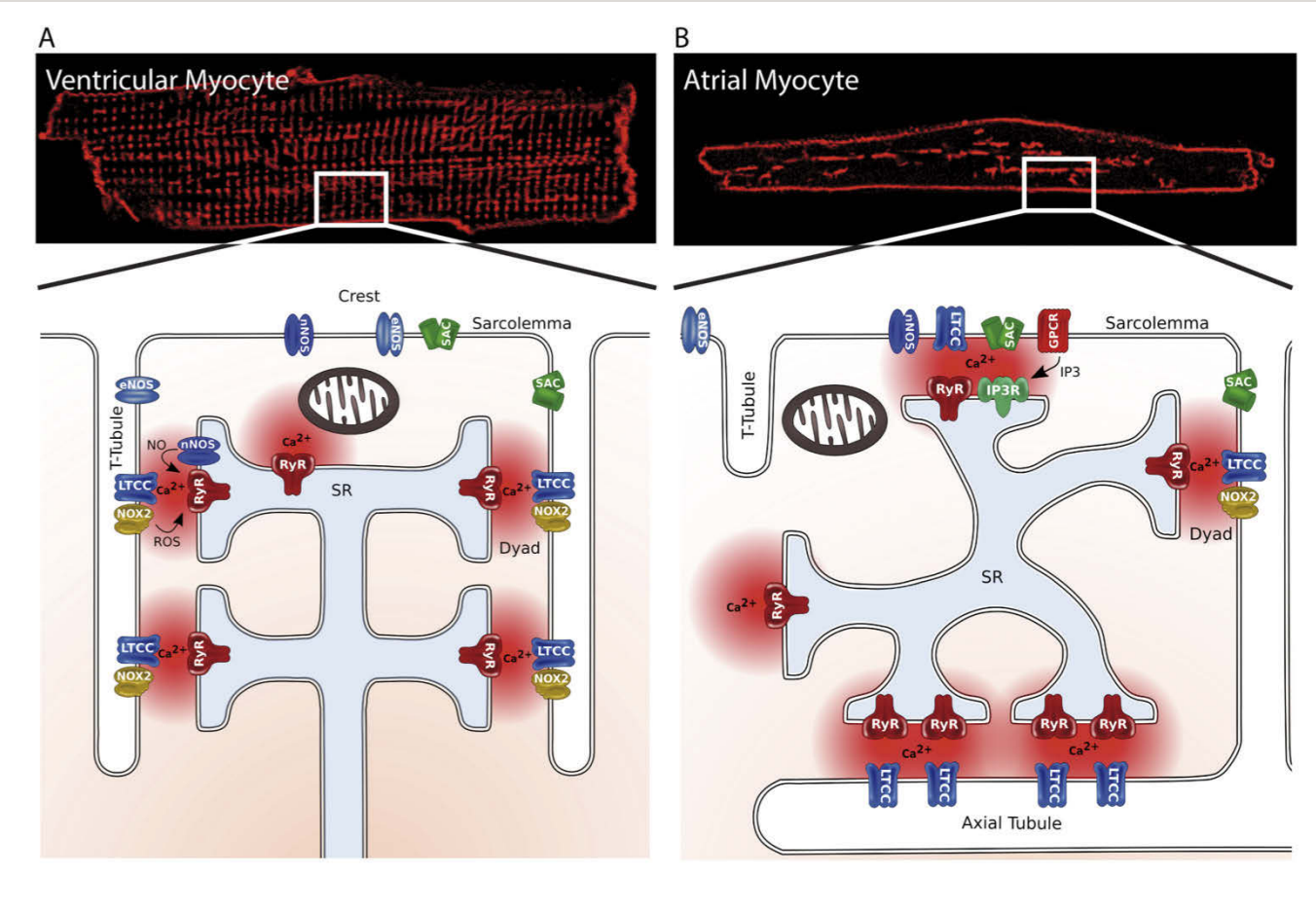


FIGURE 1

Structural organisation of Ca^{2+} microdomains in ventricular (A) and atrial myocytes (B). The schematic representation shows an enlarged detail of subcellular structures between adjacent sarcomeres in a ventricular and an atrial myocyte. The organisation of transverse tubules (TT) and axial tubules (AT) is based on membrane stainings of rabbit myocytes (Di-8ANEPPS).

optimal CICR and contractile synchrony. Dyads are also sites of compartmentalised regulation of Ca^{2+} signalling by kinases, ROS and mechanotransduction.

The structural arrangement of the tubule network in atria is remarkably different from that in the ventricles. Ventricular myocytes typically have a dense and regularly spaced network of transverse tubules (TT) near sarcomeric Z-lines, ensuring uniform Ca^{2+} release and contraction. In atrial myocytes, tubule density is sparse and more irregular, and as a consequence, there are fewer dyadic junctions in the central regions of the cell. As a result, Ca^{2+} for the initiation of contraction is provided by fast release from junctional RyR and slow propagating release from non-junctional RyR. In addition, the atrial tubule network contains a larger population of axial tubules (AT). Thus in atrial cells, there are multiple types of Ca^{2+} release subdomains. This spatial heterogeneity is expected to cause local Ca^{2+} release inhomogeneities, delayed global Ca^{2+} transients and slow contractions. Paradoxically, we find that Ca^{2+} transient and contractile force development is faster in atria than in ventricles.

Given the large heterogeneity of transverse-axial tubule (TAT) density and organisation, studying dyadic structure-function relationships in atrial myocytes is challenging. We have developed live-cell imaging methods to measure spatially resolved Ca^{2+} transients in relation to proximity to membrane structures (axial and transverse components, subsarcolemma and non-coupled regions) combined with force measurements (Figure 2). This allowed us to decode domain-specific Ca^{2+} signals in relation to global force. Such spatiotemporal analysis revealed substantial heterogeneity of local Ca^{2+} transients. Strikingly, Ca^{2+} release at axial couplons is faster and larger than in subcellular regions

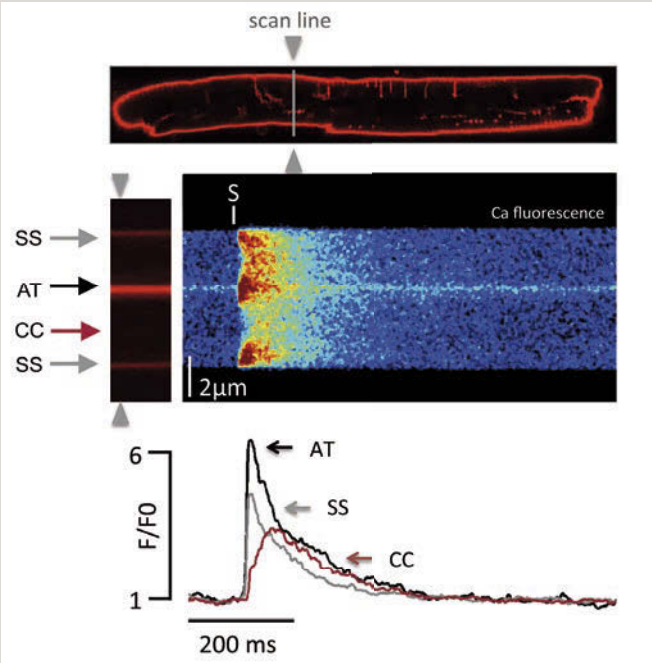


FIGURE 2

Structure-function analysis of subcellular Ca^{2+} dynamics using live-cell imaging. Atrial myocytes are labelled with a membrane (Di-8ANEPPS) and Ca^{2+} dye (Fluo-4). During an electrically stimulated beat (S), Ca^{2+} fluorescence is imaged along a transversal line passing through an axial tubule. Local Ca^{2+} transients are analysed at axial tubules (AT), subsarcolemma (SS), and cytosolic uncoupled regions (CC).

coupled to TT. Thus, axial couplons represent a distinct type of Ca^{2+} release domains that function as highways for rapid Ca^{2+} signalling, providing the structural foundation for fast and efficient contraction in atrial cells.

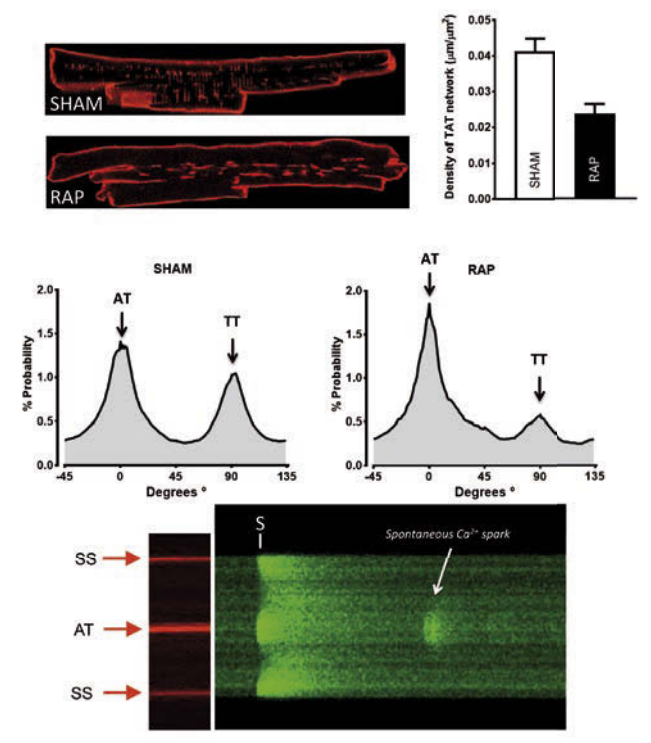


FIGURE 3

Remodelling of tubular membrane system in atrial fibrillation showing preferential loss of transverse tubules (TT) in a rabbit model of rapid atrial pacing. Axial tubules (AT) are the preferential sites of Ca^{2+} spark generation in atrial cells. AT predominance in atrial fibrillation may therefore contribute to arrhythmia initiation.

REMODELLING OF TRANSVERSE-AXIAL TUBULE NETWORK IN ATRIAL FIBRILLATION

The cardiomyocyte tubular network is sensitive to increased wall stress and remodelling. In heart failure, disruption and loss of TT in ventricular myocytes is often associated with uncontrolled Ca2+ signalling, contractile dysfunction and ventricular arrhythmias. In atrial disease, the importance of TAT remodelling in relation to spatiotemporal dynamics of Ca2+ release and arrhythmogenic Ca2+ wave initiation has been largely overlooked thus far. In a rabbit model of AF, we have optimised membrane-preserving workflows for cell isolation and found robust expression of transverse-axial tubule structures in isolated atrial myocytes. After 1 week of rapid atrial pacing, atria were dilated, which was associated with a substantial loss of total tubular network density (Figure 3). Interestingly, there was a greater and preferential loss of transverse tubules compared to axial tubules, resulting in a predominance of axial components. In addition, we identified axial tubules as the preferential site of Ca2+ spark generation. Our findings suggest that the unique atrial TAT remodelling in AF, possibly compensating for contractile dysfunction, may have a functional role in triggered activity and AF initiation.

MECHANO-ELECTRICAL FEEDBACK AND ATRIAL ARRHYTHMIAS

Studies in ventricular cells have shown sarcoplasmic reticulum Ca^{2+} release to be stretch-sensitive. The proposed mechanism includes activation of membrane-bound Type 2 NADPH oxidase (NOX2) followed by a transient rise in ROS that oxidizes RyR and sensitizes the Ca^{2+} release process. In ventricular myocytes, the process is confined to the dyad and independent of stretch-activated sarcolemmal ion channels.

Atrial dilatation occurs in heart failure and atrial fibrillation. In these conditions, the mechanosensitive component

of Ca^{2+} release may become highly relevant when investigating the role of Ca^{2+} signalling in the initiation of atrial arrhythmias. Therefore we combine uni-axial stretch with confocal Ca^{2+} imaging to study mechanosensitivity of local Ca^{2+} release events, Ca^{2+} sparks, in atrial myocytes (Figure 4). Mechanical stretch induces an increase in Ca^{2+} sparks and arrhythmogenic Ca^{2+} waves. Unlike in ventricular myocytes, the stretch response is independent of NOX2, but requires transsarcolemmal Ca^{2+} influx. Stretch-induced Ca^{2+} sparks are suppressed by the spider peptide GsMTx4, indicating involvement of stretch-activated channels. Thus, atrial mechanisms of mechanosensitivity underlying stretch-induced arrhythmias appear to be distinct from those in the ventricle. Our future work will focus on the molecular identity of atrial-specific mechanosensitive ion channels as a potential atrial-specific anti-arrhythmic target.

PROSPECTS

A new picture of atrial-specific EC coupling is emerging, and is an active subject in basic AF research. The current concept that an abundant and uniform tubular network is required for optimal Ca^{2+}-induced Ca^{2+} release has been challenged by new insights in atrial dyadic structure-function relationships. The recent observations of unique axial patterns that are sites of fast and spontaneous Ca^{2+} release have opened up a new avenue for future research into the regulatory mechanisms of these atrial-specific subdomains, including autonomic regulation, CaMKII and ROS signalling, and mechanotransduction. Our future work will examine the functional role of axial couplons in aberrant subcellular Ca^{2+} dynamics in AF and will particularly focus on the mechanical regulation and identification of stretch-activated channels at these specific sites.

AF remains a difficult and important clinical problem in terms of prediction, prevention and management. New mechanistic insights into the regulatory mechanisms of EC coupling in normal atrial physiology and disease have the potential to suggest new concepts for future AF therapy based on subdomain-specific drug targeting, for instance CaMKII signalling, tubular formation and maintenance, and/or mechanotransduction.

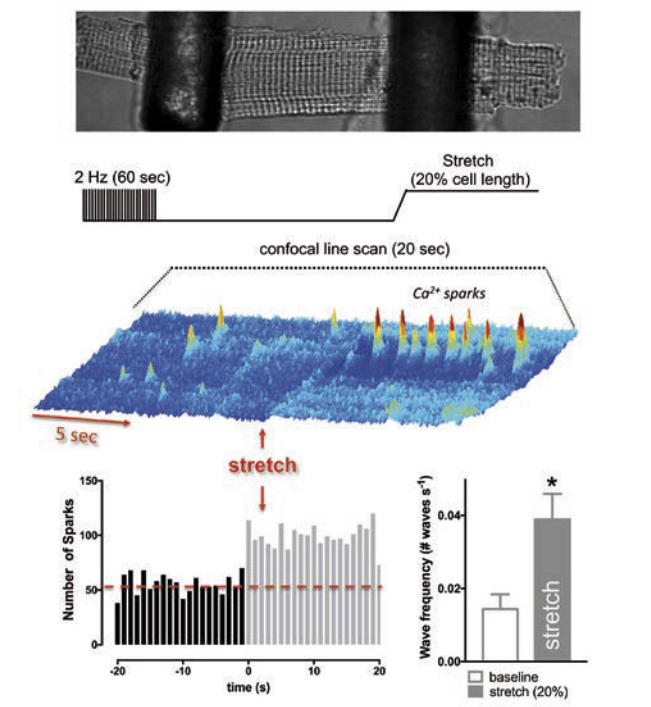


FIGURE 4

Stretch-induced Ca^{2+} sparks and waves in atrial myocytes. Light image of an atrial cell glued to glass rods with a biological adhesive (MyoTak). Uni-axial stretch is applied by moving one rod in the longitudinal direction. Stretch (20% of cell length) induces an immediate burst of Ca^{2+} sparks and increases the incidence of Ca^{2+} waves.

INTERVIEW
MIRANDA SCHRAM

Depression, a vascular disease?

When an epidemiologist is offered the chance to set up her "own" large cohort study, she doesn't have to think twice. Miranda Schram came to Maastricht in 2008 to set up the Maastricht Study, which is embedded in CARIM's research programme. She stepped down as project leader in 2014, to have time for her own research again, which concerns the vascular components of diabetes-related brain disorders. A paper published in the prestigious journal *JAMA* this year concluded that damage to minor blood vessels in the brain (microvascular dysfunction) predicts not only whether people will develop dementia, but also whether they will get a depression. "So depression might be a vascular disease, particularly if you have diabetes."

In hindsight, Miranda Schram was possibly a bit naive when she began setting up the Maastricht Study. “I had somewhat underestimated how much work it would be. Next to the study design and methodology, the funding had to be arranged, and it involved a lot of politics as well, so the preparations took three instead of the envisaged one to two years. Nevertheless, I’d do it again immediately, as it was great fun and I learned a lot.” The goal of this large cohort study, which aims to include 8,000 people aged 40 to 75 years from the Maastricht-Heuvelland region between 2010 and 2019, is to study the prevalence, causes and treatment of type 2 diabetes, cardiovascular diseases and other chronic disorders. One of the things she learned was that, in retrospection, the study could also have been organised jointly by multiple research schools. Another was that “you can’t give enough attention to the details. If we had for instance used LEAN for our data collection from day one, it would have saved us a lot of searching.”

Schram is an active member of the Management Team, which among other things, considers requests for collaboration and addresses data processing challenges that crop up. For instance, whereas measuring the microcirculation by means of an eye test takes five to ten minutes, it takes half an hour to analyse the results. How can this be streamlined?

HARVEST

By now, 7500 people have been included in the Maastricht Study, and have undergone elaborate measurements that can be analysed, so now it is harvest time. “And that’s very exciting,” beams the epidemiologist, whose own interest is mainly in comorbidities of diabetes, especially those involving the brain. “In a previous job at the National Institute for Public Health and the Environment (RIVM), I investigated the incidences of diabetes and depression. The two turned out to be closely associated, but we don’t yet have a biological explanation for this. Among the known complications of diabetes are microvascular problems like eye and nerve damage. It now looks as if the brain can also be damaged further down the line. But we don’t yet understand how it works.” In the *JAMA* paper published this year, Schram and colleagues describe how a wide review of the literature allows the conclusion that vascular damage can predict depression at a later age. “There might be a causal relationship; perhaps depression is actually a vascular disease, especially among people with diabetes.
I think that the vascular component is a major determining factor particularly among people who get a depression later in life. Older people with a depression often respond less well to the current antidepressants than younger people. If vascular damage is indeed the cause of the depression, it’s not surprising that drugs that address serotonin levels are ineffective in this group of patients. The crucial elements might be the very smallest blood vessels.” These are some of the questions she is studying with data from the Maastricht Study, which includes not only elaborate vascular measurements, but also MRI images of vascular damage in the brain and detailed interviews and questionnaires about depression. The data analysis is now in full swing.

'DIABETES PEARL'

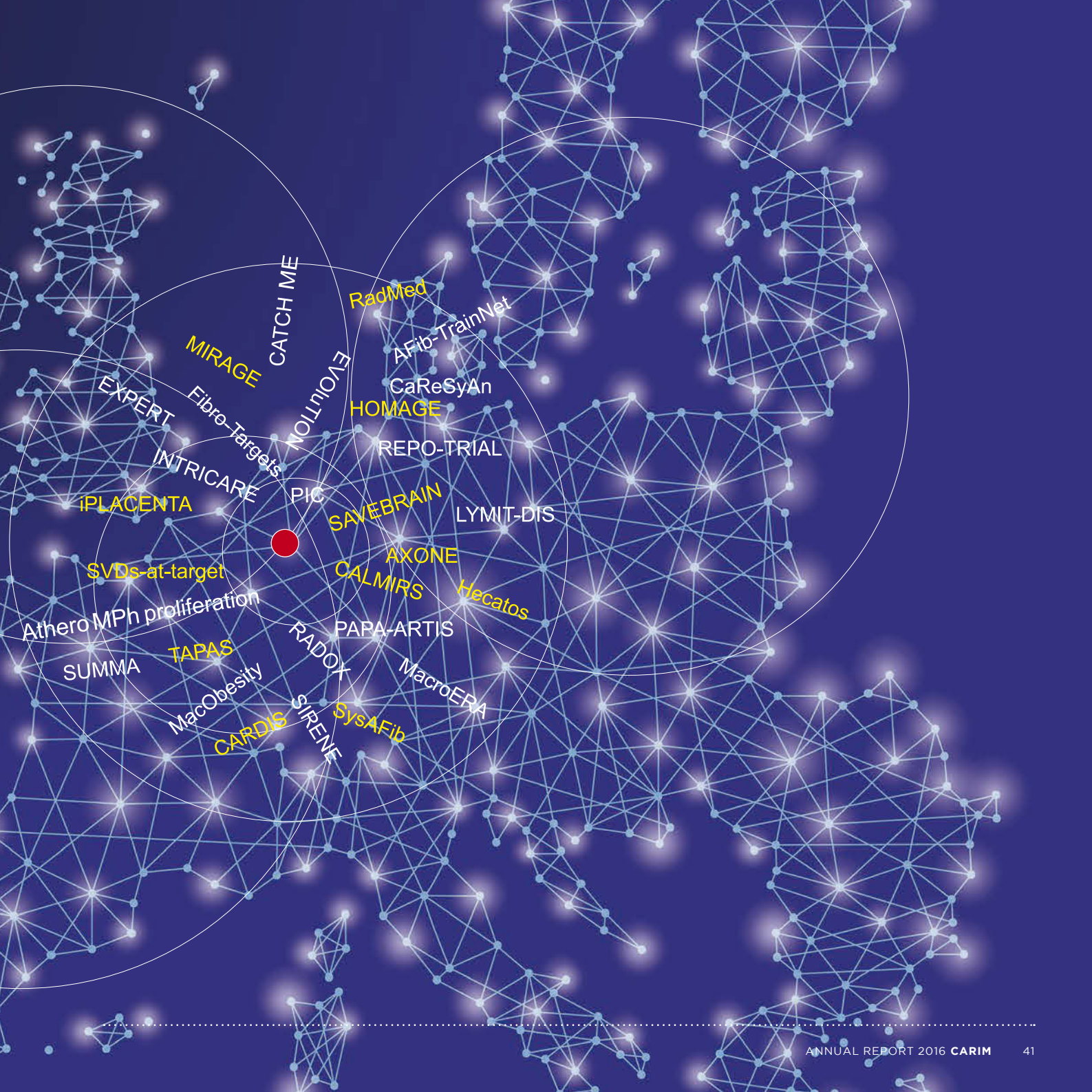
Whether diabetes itself can also cause feelings of depression and stress is a question which Schram is trying to answer in another study, called the 'Diabetes Pearl'. All eight university medical centres in the Netherlands have joined forces in an initiative known as the 'String of Pearls Initiative' (*Parelsnoer Initiatief*), which involves them jointly contributing to a biobank, while each of them focuses on a different disease entity (the 'pearls' in the string). Together with VU Medical

centre in Amsterdam, MUMC+ is leading the investigations on diabetes. The Diabetes Pearl is one of the pillars of the Maastricht Study, and the two studies are fully integrated. All participants of the Maastricht Study who have diabetes are also included in the Diabetes Pearl. The *Parelsnoer* cohort currently includes 6,000 people, and the analyses of their data are now yielding the first publications.

"For our first paper on this study we have asked all patients with diabetes how hard they find it to manage their disease. How much stress is it causing them? Do they ever worry about complications? How well are they communicating with their doctor? In this paper we focused on ethnic minorities, including people of Moroccan, Turkish, Asian and Hindustani descent. Our findings show that there is far more diabetes-related stress among these ethnic groups than among the group of Dutch descent. The differences are remarkable." The researchers do not think this difference is caused by language problems, as potential participants were required to have a specified level of command of Dutch to be eligible for inclusion in the study. "Perhaps these groups have a different clinical picture or disease perception? We don't have an explanation yet. But for the time being our message to doctors is: if you've got a patient with diabetes from an ethnic minority, you should give special attention to their level of stress in order to control their diabetes as effectively as possible."

"YOU CAN'T GIVE ENOUGH ATTENTION TO THE DETAILS"

EU SPECIAL


CATCH ME
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Fibre-Targets
INTRICARE
iPLACENTA
PIC
RadMed
AFib-TrainNet
CaReSyAn
HOMAGE
REPO-TRIAL
SAVEBRAIN
LYMIT-DIS
AXONE
CALMIRS
Hecatos
SVDs-at-target
Athero MPh proliferation
PAPA-ARTIS
RADOX
TAPAS
SUMMA
MacObesity
MacroERA
CARDIS
SIRENE
SysAFib

PROGRAMME
H2020

PROJECT ID
661099

Athero Mph proliferation

Macrophage proliferation and ontogeny in murine models of atherosclerosis

Personal Grant

DR PIETER GOOSSENS

Atherosclerosis is a slowly progressing inflammatory disease that underlies some of the most common causes of death in western society. The central role of macrophages throughout its pathogenesis makes this cell an eminent target for therapeutic intervention. Recent studies have subverted the classical view that atherosclerotic plaque macrophages mainly originate from recruited circulating monocytes, launching the new notion that macrophages could also be derived from clonal expansion of resident macrophages or even trans-differentiated vascular smooth muscle cells. The relative importance of these mechanisms to the pathogenesis remains however unclear, due to a lack of adequate animal models that allow assessing this question.

In this project, we introduce a recently developed fate mapping model, the LysMCre-Ubow +/+ mouse, into the atherosclerosis field to conclusively identify regions within the plaque that were formed through local proliferation rather than monocyte recruitment. Apart from quantifying its relative contribution to plaque growth during disease progression and regression, we will furthermore characterise the localisation, transcriptional activity and the lipidic makeup of these proliferated cells versus invaded monocytes.

In a second part of this project, we will deploy adoptive bone marrow transfers from WT to Ubow mice and vice versa as a model to quantify intraplaque myeloid versus stromal-cell derived macrophages. We will compare proliferative capacity, phenotype, transcriptomics and lipidomics of these two subsets and link this information to their functionality.

With this strategy we will be the first to reveal the impact of the three macrophage accumulation mechanisms throughout the disease course, to couple this to their function and to exploit this knowledge for targeted experimental therapeutic interventions.

This project includes a collaboration with the Centre d'Immunologie de Marseille-Luminy (CIML, Marseille, France).

AIMS
- Map intraplaque macrophage heterogeneity in ontogeny and proliferation.
- Characterise the different macrophage subsets (kinetics, transcriptomics, lipidomics,...).
- Identify subset-specific markers and functions for targeted therapeutic approaches.

PROGRAMME
H2020

PROJECT ID
764474

CaReSyAn

Combatting the CardioRenal Syndrome: towards an integrative Analysis to reduce cardiovascular burden in chronic kidney disease

DR LEON SCHURGERS

CaReSyAn will integrate proteomics, clinical, experimental and bioinformatical competences to enhance our understanding, diagnosis and therapy of the cardiorenal syndrome (CRS). CRS comprises disorders of the heart, vessels and kidneys, including the increased development of cardiovascular disease (CVD) in patients with chronic kidney disease (CKD). With ~45% of all deaths in CKD patients caused by CVD, the socioeconomic burden of CRS is extremely high.

CaReSyAn builds on already available patient cohorts, advanced technologies and established cooperations. CaReSyAn is complementary to ongoing European programs focusing solely on CKD or CVD and strives to synergistically improve structural training on European level. CaReSyAn will nurture the development of young, broadly-trained scientists able to successfully bridge clinical with basic research as well as academia and industry. This is a cornerstone in effectively combatting complex diseases as CRS, a major killer of this century. CaReSyAn will train scientists in a close cooperation between academia, SME and industry partners.

KEY OBJECTIVES ARE TO PROVIDE
- Excellent scientific training on CRS pathology, integrating clinical/mechanistic knowledge with technological skills (animals and in vitro, molecular and functional studies, proteomics and bioinformatics) to generate innovative insights triggering the understanding, diagnosis and treatment of the CRS;
- Excellent complementary skills in personal and career development as well as business training required to extend beyond scientific research; and
- Exposure to both academic and non-academic environments, required to build bridges between researchers and entrepreneurs and support the future translation of research findings in innovative products and services.

BENEFICIARIES
- Universitätsklinikum Aachen Germany (lead)
- Idryma Iatroviologikon Ereunon Akademias Athinon Greece
- Mosaiques Diagnostics GmbH Germany
- Medizinische Universität Wien Austria
- RD Nephrologie SAS France
- Institut National de la Sante et de la Recherche Medicale France
- Universiteit Maastricht The Netherlands
- Karolinska Institutet Sweden
- DSM R&D Solutions BV The Netherlands

PROGRAMME
H2020

PROJECT ID
675111

EVOluTION

European Vascular Interventions and Therapeutic Innovation Network

PROF. CHRIS REUTELINGSPERGER

DR LEON SCHURGERS

EVOluTION is a European Vascular Interventions and Therapeutic Innovation Network supported by the Horizon 2020-ITN program.

It is a pioneering network within EU in view of its focus on endogenous protective mechanisms and it is established to provide training for 11 young researchers in innovative therapeutic strategies, integrating early detection and prevention, to yield novel approaches to the management of chronic vascular and metabolic diseases that affect the increasing ageing population of Western societies. Fully aligned with the knowledge triangle (business, research and higher education) platform being developed at the EU level, EVOluTION-trained young scientists will gain valuable knowledge and multi-disciplinary skills: only interdisciplinary and cross-cutting research can lead to novel therapeutic tools and scientific angles to address these challenging medical, societal and industrial issues.
EVOluTION provides a conductive structure by bringing 5 leading academic institutions and 2 SMEs, together with 5 pharma and biotech companies, 1 policy-maker, and 1 patent & trade firm as Partner Organisations, from 6 EU countries.

The science of EVOluTION evolves around the innovative concept of boosting natural protective mechanisms operating in our body, focusing on the vasculature, to answer 3 key questions: Can we exploit mediators and targets of endogenous tissue protection? Can we exploit these pathways to yield innovative therapeutic strategies? Can dietary approaches boost these endogenous protective processes? The Network Partners guarantee delivery of training through knowledge creation, knowledge exploitation and knowledge communication.
Scientific and educational expertise of the partners, leaders in areas like computational chemistry, nutraceuticals, resolution pharmacology and vascular therapies will be maximally exploited.
The EVOluTION training platform is based on state-of-the-art lab-based and network-wide and local training activities, including secondments and scientific visits and specialized transferable skills focussed in entrepreneurship and societal engagement. CARIM hosts 3 talented Early Stage Researchers: Angelina Pavlic (Targeted treatment of vascular calcification), Jan Nagenborg (Re-instructing the atherosclerotic plaque macrophage) and Ploingarm Petsophonsakul (Nutraceuticals modulating the vascular vitamin K-system).

BENEFICIARIES
- Queen Mary University of London UK (lead)
- Ludwig-Maximilians-Universität München Germany
- Universiteit Maastricht The Netherlands
- Lifearc UK
- Karonlinska Institutet Stockholm Sweden
- University College Dublin, National University of Ireland

PROGRAMME
H2020

PROJECT ID
765274

iPLACENTA

Innovation in modelling Placenta for Maternal and Fetal Health

PROF. LEON DE WINDT

iPLACENTA is a European Training Network (ETN), and will act as a springboard for promoting international, intersectoral and multi/inter-disciplinary training, career development and collaboration of fifteen early-stage researchers in Maternal and Fetal Health. iPLACENTA will improve our ability to study, model and visualise the placenta. iPLACENTA focuses on doctoral-level training and will be delivered by eleven participating universities located in ten different European countries.

It coordinates research and training collaboration among world-leading academic institutions in Europe, providing a new combination of in-depth international expertise. iPLACENTA's unique network aims are to improve our ability to study the placenta through in vitro and mathematical modelling. Whilst enhancing visualisation and assessment of the placenta in animal models and the clinic, thus enhancing investigation and prognosis of complicated pregnancies.

To link the research to industrial exploitation, the network brings together four different businesses; two established companies as beneficiaries Mimetas (organ-on-achip developer) and Moor, a clinical-technology specialist, together with two partners that are industrial global brands Samsung and Fujif-Film VisualSonics. Together they will work with academics and clinicians to develop new placenta-on-a-chip technology, in silico placenta modelling, new modalities of laser technology to visualise the placenta in vivoimprove maternal-cardiovascular assessment and validate novel ultrasound tools for diagnosis of complicated pregnancies. Cross-sectorial training delivered by Business and Law Schools, Industry, Clinical specialist and European leaders in OpenScience-OpenInnovation.

BENEFICIARIES
- Aston University UK (lead)
- Katholieke Universiteit Leuven Belgium
- Universita degli Studi di Torino Italy
- Universiteit Maastricht The Netherlands
- Universität Rostock Germany
- Mimetas BV The Netherlands
- St. George's Hosptial Medical School UK
- Institut National de la Sante et de la Recherche Medicale France
- Fundacion para la Investigacion del Hospital Universitario la Fe de la Comunidad Valanciana Spain
- University College Cork – National University of Ireland

PROGRAMME
H2020

PROJECT ID
766118

TAPAS

TArgeting Platelet Adhesion receptors in thrombosis

PROF. JOHAN HEEMSKERK

PROF. HUGO TEN CATE

DR PAOLA VAN DER MEIJDEN

DR MARIJKE KUIJPERS

TAPAS will position Europe at the forefront of innovative research to prevent thrombosis and thrombo-inflammation, and will train a uniquely qualified cohort of ESRs in a highly intersectorial and multidisciplinary programme that will equip them with the knowledge and transferable skills required in the broad biomedical sector. The research will focus on platelets which are small cells in the blood that play a critical role in prevention of excessive bleeding following injury (haemostasis). Activation of platelets in diseased vessels gives rise to thrombotic disorders such as heart attack and stroke, two of the major causes of morbidity and mortality. Patients at risk of thrombosis are treated with medicines that inhibit platelets for life, but many patients still undergo thrombotic episodes or encounter serious bleeds through diminished haemostasis. There is thus an urgent need for novel and safe anti-platelet medicines that powerfully target thrombosis but preserve haemostasis.

In TAPAS, an original and innovative approach will be undertaken to find new ways to target thrombosis through co-operation of academic experts in distinct disciplines with key skills from the private sector. TAPAS will generate and integrate knowledge from analytical complex 'omics', advanced microscopy, cell biology, microfluidics, in vivo models, contemporary systems biology and high throughput screens to identify new targets for therapeutic intervention and novel lead compounds or biologics.

The research skills developed in this programme are applicable to other complex diseases and represent essential training in modern day research for the next cohort of academic and private sector scientists that are able to convert complex biological understanding into new medicines. The shared knowledge and close interaction between beneficiaries and partners makes this programme ideally suited to an EJD and will deliver 15 ESRs in 21st century biomedical research.

RESEARCH HYPOTHESIS
The degree and mechanisms of platelet adhesion receptor clustering and signalling are crucial determinants of platelet activation states in thrombotic environments and that these can be selectively targeted by biologics and small molecules, whilst preserving haemostasis.

AIMS
(1) to develop and use new methods for high-resolution detection of platelet receptor clustering; (2) to model the clustered receptor-ligand interactions and downstream signalling networks, and screen biologics and small molecules for modulation; (3) to validate the identified receptor epitopes and clustering mechanisms; and (4) to use in vivo models of haemostasis and thrombosis to select the most suitable therapeutic targets.

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

PROGRAMME
H2020

PROJECT ID
644798

CARDIS

Early stage CARdio Vascular DISease Detection with Integrated Silicon Photonics

PROF. FRITS PRINZEN

Early identification of individuals at risk for cardio-vascular diseases (CVD) allows early intervention to halt or reverse the pathological process. This is the driver of the abovementioned partners to develop a mobile, low-cost, non-invasive, point-of-care screening device for CVD.
The objective of CARDIS is to investigate and demonstrate the concept of a mobile, low-cost device based on a silicon photonics integrated laser Doppler vibrometer and validate the concept for the screening of arterial stiffness, detection of stenosis and heart failure.

WE WILL
- Investigate, design and fabricate the optical subsystems and components: silicon photonics chip with integrated Ge-detectors, micro-optics, micro-optical laser bench, optical package;
- Integrate the subsystems and build a multi-array laser interferometer system;
- Develop a process flow scalable to high volumes for all sub-systems and their integration steps;
- Investigate and develop the biomechanical model to translate optical signals related to skin-level vibrations into underlying CVD physiological events;
- Validate the system in clinical settings.

Photonics integration is needed to enable a device that is mobile (small size, small weight, robust (no moving parts)), low cost (high volume scalable process flow) and allows fast screening (laser array) and battery operated.

BENEFICIARIES
- Medtronic Bakken Research Center BV The Netherlands (lead)
- SIOS Meßtechnik GmbH Germany
- Interuniversitair Mirco-Electronica Centrum Belgium
- Tyndall National Institute Ireland
- Ghent University Belgium
- Institut National de la Sante et de la Recherche Medicale France
- Queen Mary University of London UK
- Universiteit Maastricht The Netherlands

PROGRAMME
H2020

PROJECT ID
6660440

MIRAGE

MicroRNAs as therapeutic targets for ARVC

PROF. LEON DE WINDT

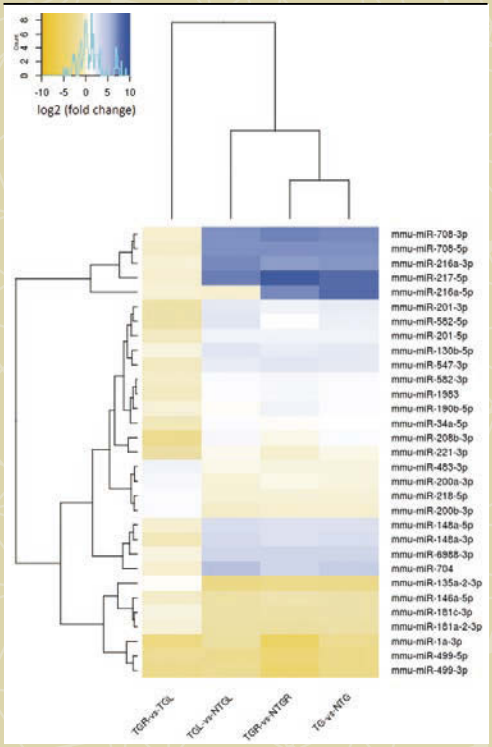
DR MARTINA CALORE

Among the causes of heart failure, arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic form of human heart disease classified as the second most common cause of unexpected sudden cardiac death in the young and may account for as many as 22,4% of heart failure among athletes. To date, 15 ARVC genes have been discovered, with 40% of mutations identified in 3 major genes, encoding for plakophilin-2 (PKP2), desmoplakin (DSP), and desmoglein-2 (DSG2). Advances in understanding the molecular disease mechanisms underlying ACM and earlier detection are urgently needed.

In the context of MCSA-IF MIRAGE, in collaboration with Prof. A. Rampazzo from Padova, we provided an inventory of microRNAs (miRNAs) that were differentially expressed in hearts from a transgenic model for ARVC overexpressing a nonsense mutation in DSG2 gene found in a human patient (see figure). The identification of these deregulated miRNAs will provide novel insights into the complex and still undetermined pathogenesis of ARVC and will allow to develop novel tailored therapeutic approaches which will take into account the genetic diversity of ARVC patients. As remarkably stable molecules in body fluids, like the bloodstream, circulating miRNAs have the potential of being used as biomarkers for several pathophysiological conditions, including ARVC.

In collaboration with Prof. T. Thum from Hannover, we provided a signature of circulating miRNAs in ARVC patients. This result will help in supporting the complex ARVC diagnosis, patient stratification and treatment monitoring.

COLLABORATORS
- Prof. Alessandra Rampazzo, Padova University (Italy);
- Prof. Thomas Thum, Institute of Molecular and Translational Therapeutic Strategies;
- Cristal Therapeutics, Department of Pharmaceutical Development, Maastricht.



Hierarchical clustering of differentially expressed miRNAs from RNA-Seq data. We performed genome wide RNA-Seq in right and left ventricles separately of 3 transgenic animals (TG) and 3 non transgenic control animals (NTG). A total of 31 miRNAs were identified as significantly differentially expressed across four different comparisons; transgenic compared to non-transgenic model (Tg-Vs- NonTg), right ventricle of transgenic model compared to right ventricle of non-transgenic model (TgR-Vs-NonTg-R), left ventricle of transgenic model compared to left ventricle of non-transgenic model (TgL-Vs- NonTg-L) and right ventricle of transgenic model compared to left ventricle of transgenic model (TgR-Vs- TgL).

PROGRAMME
H2020

PROJECT ID
764738

PIC

Personalised In-silico Cardiology

PROF. FRITS PRINZEN

PIC focuses on the innovation and the clinical translation of emerging in-silico technologies. This requires the creation of a novel cross-disciplinary training programme, where fellows are equipped with solid mathematical and computational foundations together with a good understanding of human physiology, existing healthcare technologies and clinical needs.

The vision of a Personalised In-silico Cardiology is materialised in the definition of 15 inter-related projects for each of the fellows, setting the scope of the research into four main modelling aspects of the heart (anatomy, mechanics, electrophysiology - EP, and fluid dynamics) and four cardiac conditions (heart failure, cardiomyopathies, arrhythmias and flow obstructions).

WP1 focuses on the in-silico modelling technology. Its objectives are to develop the simulation methodologies, and to obtain robust biomarkers by cardiac model personalisation. Interpreting clinical data through biophysical models allows the extraction of the underlying physiological parameters that best explain the data. WP2 focuses on the data. Its objectives are to use in silico cardiac models to reduce errors in clinical data, reduce invasiveness, and to maximise its diagnostic and prognostic value. WP3 focuses on the technologies for therapy: clinical devices and cardiac drugs. Its objective is to personalize these technologies through the adoption of the in-silico methodology and its predictions. WP4 focuses on the clinical translation of the in-silico technology. Its objective is to evaluate in specific CVD problems the envisioned improved care through better data, diagnosis and therapies.

BENEFICIARIES
- King's College London UK (lead)
- Oslo Universitetssykehus Norway
- FEOPS NV Belgium
- The University of Oxford UK
- Universiteit Maastricht The Netherlands
- Universidad de Zaragoza Spain
- Université de Bordeaux France
- Consorci Institut d'Investigacions Biomediques August Pi i Sunyer Spain
- GE Vingmed Ultrasound AS Norway
- Medtronic Bakken Research Center B.V. The Netherlands

PROGRAMME
FP7

PROJECT ID
602904

Fibro-Targets

Targeting cardiac fibrosis for heart failure treatment

PROF. STEPHANE HEYMANS

The Fibro-Targets project is a multi-disciplinary program involving 11 partners ambitioning 'the identification, characterisation and validation of in vitro and in vivo models of novel therapeutically relevant targets' for myocardial interstitial fibrosis (MIF) in heart failure.

Heart failure is a serious disease since it is often irreversible. It is estimated that more than 6.5 million people suffer from heart failure in Europe. It is the leading cause of hospitalisation for patients over the age of 65. The incidence is increasing at an alarming rate because of an aging population and the burden of cardiovascular risk factors (diabetes, obesity and high blood pressure). Early interventions targeting key mechanisms, including myocardial interstitial fibrosis, could slow down progression to heart failure.

Fibro-targets ambition to identify biomarkers to predict, monitor and describe the response to myocardial interstitial fibrosis treatments in order to help resolve one of the 21st century's major health problems that affects elderly people in particular.

BENEFICIARIES
- Institut National de la Sante et de la Recherche Medicale France (lead)
- Fundacion Publica Miguel Servet Spain
- Medizinische Universität Wien Austria
- Medizinische Hochschule Hannover Germany
- Universiteit Maastricht The Netherlands
- INSERM Transfert SA France
- Innovative Technologies in Biological Systems Spain
- Greenpharma S.A.S. France
- University College Dublin, National University of Ireland
- Firalis France
- Fundacion para la Investigacion Medica Aplicada Fima Spain

PROGRAMME
H2020

PROJECT ID
633196

CATCH ME

Characterizing Atrial Fibrillation by Translating its Causes into Health Modifiers in the Elderly

PROF. ULI SCHOTTEN

PROF. HARRY CRIJNS

PROF. MONIKA STOLL

Atrial Fibrillation (AF) is a major threat to healthy ageing in Europe. AF affects 1.5-2% of the European population, and 12-15% of Europe's octogenarians. AF prevalence will double or triple in the next decades. Patients suffering from AF experience reduced life expectancy (with many premature deaths due to heart failure or sudden death) and quality of life, especially at older age. In addition, AF leads to stroke (often with major disability or fatal outcome), cognitive dysfunction, and dementia, and worsens heart failure. Thus, AF has immense detrimental effects on the well-being of elderly European citizens and burdens European health care systems and societies with considerable cost.

Prevention, diagnosis, and therapy of AF patients need to be informed by the causes of the arrhythmia. Preventing AF, timely detection of AF, and slowing of AF progression can alleviate this burden to elderly Europeans. Unfortunately, the current management of AF can only be tailored to individual patients on the basis of thrombo-embolic risk factors, symptoms, and AF pattern, rather than by exploiting existing knowledge on pathophysio-logical and molecular processes causing and maintaining AF. Thus, important components of AF management and AF prevention, are not guided by mechanistic insights, they lack standardisation, and often fail.

To bridge the disconnect between our understanding of the molecular and electrophysiological mechanisms of AF and the clinical management of AF patients, the CATCH ME consortium plans to characterise major health modifiers underlying AF by integrating information from human atrial tissue and clinical/population cohorts. The accrued information on the major drivers of AF will be validated in large, independent patient data sets and combined into a clinically useful set of markers informing on distinct types of AF (based on mechanisms rather than on AF pattern). Such strategy will underpin the development of evidence-based and personalised preventive, diagnostic, and ultimately therapeutic strategies for AF.

The CATCH ME consortium combines clinical, molecular, bio engineering, and biostatistical expertise, and has access to large sets of human biological material (atrial tissue and bloods samples) and carefully phenotyped patient populations. Together, we will identify and integrate the main drivers of prevalent and incident AF in patients, and validate new clinical, ECG- and blood based markers for the major drivers of AF in well-characterised cohorts. Validation will be performed in two large cohorts, including response to current treatment strategies and effect on AF-related complications. The results of CATCH ME will quantify the prevalence and impact of new and established risk factors and causes leading to AF in Europe ('health modifiers'), and uncover new targets and approaches for the prevention and treatment of AF patients.

In summary, CATCH ME will:
- Identify major health modifiers underlying AF in the elderly in Europe
- Develop clinical tools that have the potential of transforming the management of AF in individual patients
- Underpin and guide future personalised strategies to prevent and treat AF in Europe.

BENEFICIARIES
- The University of Birmingham UK (lead)
- Ludwig-Maximilians University Munich Germany
- Universiteit Maastricht The Netherlands
- Consorci Institut d'Investigacions Biomèdiques August Pi i Sunyer Spain
- Societé Europeenne de Cardiologie France
- Université Pierre et Marie Curie – Paris 6 France
- Kompetenznet Vorhofflimmern E.V. Germany
- The University of Oxford UK
- The UK Health & Environment Research Institute Limited UK

PROGRAMME
H2020

PROJECT ID
666881

SVDs@target

Small vessel diseases in a mechanistic perspective: Targets for Intervention Affected pathways and mechanistic exploitation for prevention of stroke and dementia

PROF. ROBERT VAN OOSTENBRUGGE

Cerebral small vessel diseases (SVDs) are a major cause of stroke and dementia, and yet there is no targeted treatment. Progress in understanding the mechanisms that drive microvascular dysfunction and brain damage in SVDs has been elusive, until now.

An international consortium has launched a major collaborative research program 'SVDs@target'. SVDs@target is an ambitious project which aims to elucidate key mechanisms common to multiple SVDs and to validate novel mechanisms through interventions, with the ultimate goal of reducing the burden of SVDs, stroke and dementia. The five-year program will combine pre-clinical with clinical research.

The SVDs@target investigators of Maastricht University lead the clinical part of work package 4 on immune-cell-driven mechanisms in SVDs. In this subproject, we aim to identify, localise and characterise immune cells and determine binding and transmigration of these cells in different SVDs. By combining experimental work with immune cell phenotyping in humans this work will reveal novel entry points for the development of therapeutic approaches.

BENEFICIARIES
- Ludwig-Maximilians-Universität München Germany (lead)
- Universitair Medisch Centrum Utrecht The Netherlands
- The University of Edinburgh UK
- Klinikum Rechts der Isar der Technischen Universität München Germany
- Westfalische Wilhelms-Universität Münster Germany
- Stroke Alliance for Europe Belgium
- Universiteit Maastricht The Netherlands
- University of Vermont and State Agricultural College USA
- ARTTIC France
- Kobenhavns Universitet Denmark
- Institut national de la santé et de la recherche médicale France
- The University of Oxford UK
- GABO:MI Gesellschaft für Ablauforganisation:Millarium MBH&C

PROGRAMME
FP7

PROJECT ID
294683

RadMed

Radical Medicine: Redefining Oxidative Stress

Personal Grant ERC
Advanced Grant

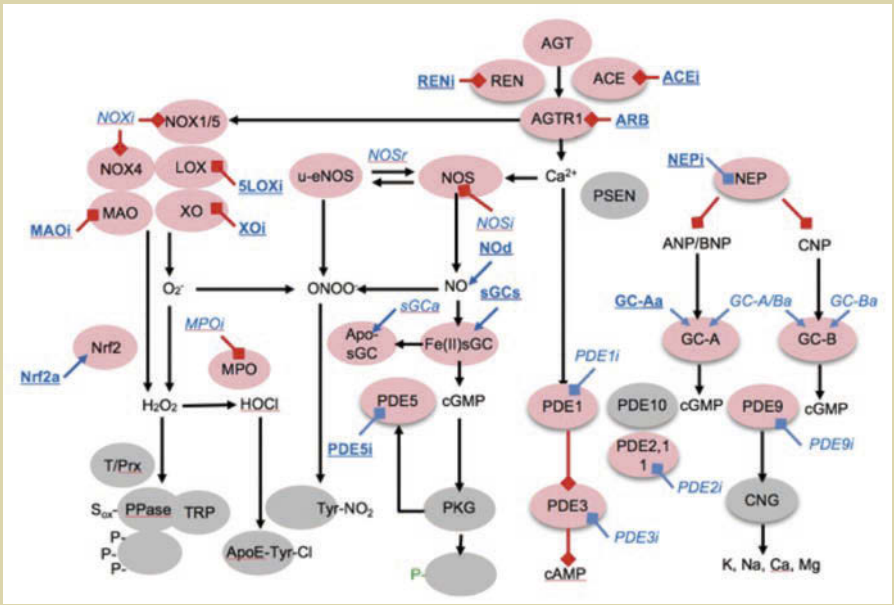
PROF. HARALD SCHMIDT

Oxidative stress, an excess of radicals and reactive oxygen species (ROS), has been suggested as a major disease mechanism. However, all major clinical trials using anti-oxidants have been failures, even suggesting serious side effects. In this grant, I proposed completely different approaches: First, instead of letting radicals form and then scavenge them we would identify their sources (shown in pink) and rather prevent their formation or specifically repair radical damage. Second, we would here from differentiate beneficial signalling roles of ROS.

In combination, this was predicted to result in unprecedented precision and molecular specificity. We achieved major breakthroughs by identifying a radical/ROS source as fundamental mechanism in stroke, the fastest growing and soon no. 1 cause of death. We also developed in phase II and now in phase III clinical development a radical synthesis inhibitor for neurotrauma. Moreover, our basic research facilitated the development of a class of drugs re-activating an oxidatively damaged signalling receptor, now in phase III, and continued as a multicentre trial.

A finding in diabetic nephropathy was picked up by a Swiss biotech company and is now developed in a phase III clinical trial with close Australian collaborators. We also identified protective roles of ROS in angiogenesis and diabetes accelerated atherosclerosis, i.e. potential side-effects of non-specific anti-oxidants. Our approach was disruptive for the field and in several additional landmark reviews all amongst the top 10 most influential papers on ROS in recent years and a book that will be released in 2018. I also coordinated the EU-ROS COST action which united all top scientist in the field of ROS in Europe to promote this change.

We also contribute to the improved diagnosis and earlier identification and stratification of patients at risk and to monitor their successful treatment, e.g. in a diagnostic development project together with Bayer and the implementation of new in vivo imaging methods for the field of ROS allowing the localization and monitoring of disease processes. A new generation of more effective, predictable, and mechanism-based drugs (shown in blue) is indeed replacing the failed antioxidant approach for a new class of radical-modulating medicines.



PROGRAMME
H2020

PROJECT ID
768657

SUMMA

Stimulating mir-106b expression to regenerate the myocardium

Personal Grant ERC

Proof of Concept

PROF. LEON DE WINDT

Most people who develop ischemic HF have (or had) an ischemic heart condition first (e.g. myocardial infarction, MI). Restoring damaged heart muscle tissue therefore represents a fundamental mechanistic strategy to treat HF. Cardiac regeneration after ischemic damage can be achieved by stimulating the proliferation of already existing (endogenous) cardiomyocytes rather than having to rely on the implantation of exogenous cells (i.e. stem cell therapy).

Compelling evidence supports that expanding the endogenous cardiomyocyte proliferation capacity by gene therapy appears to represent a promising approach to achieve endogenous cardiac regeneration. Species of non-coding RNA molecules, microRNAs, have been demonstrated to stimulate cardiomyocyte proliferation and the recognition of microRNAs as potential regenerative targets marks a major step towards fundamentally new therapeutic concepts that SUMMA addresses in ischemic heart disease.

In the context of the ERC-Starting Grant project CALMIRS, we identified the miR-106b~25 cluster with high potential as new target for therapy to stimulate regeneration of the heart by promoting cardiomyocyte proliferation. Within SUMMA, we aim to advance these valuable research results on microRNA cardiac gene therapy in mice towards commercial proof-of-concept.

During this project, proof-of-concept efficacy studies in a large animal (e.g. porcine) model of cardiac ischemia will be performed, while simultaneously market research, IP strategy development and business development activities take place to maximise the value of the project's results. Different business models will be studied in terms of market research, IP strategy and business development to eventually consolidate a commercial strategy and business case for presenting our business proposition to strategic partners or venture capitalists.

PROGRAMME
FP7

PROJECT ID
311549

CALMIRS

RNA-based regulation of signal transduction – Regulation of calcineurin/NFAT signaling by microRNA-based mechanisms

Personal Grant ERC
Starting Grant

PROF. LEON DE WINDT

Heart failure is a serious clinical disorder that represents the primary cause of hospitalisation and death in Europe and the United States. There is a dire need for new paradigms and therapeutic approaches for treatment of this devastating disease. The heart responds to mechanical load and various extracellular stimuli by hypertrophic growth and sustained pathological hypertrophy is a major clinical predictor of heart failure.

A variety of stress-responsive signaling pathways promote cardiac hypertrophy, but the precise mechanisms that link these pathways to cardiac disease are only beginning to be unveiled. Signal transduction is traditionally concentrated on the protein coding part of the genome, but it is now appreciated that the protein coding part of the genome only constitutes 1.5% of the genome. RNA based mechanisms may provide a more complete understanding of the fundamentals of cellular signalling.

As a proof-of-principle, we focus on a principal hypertrophic signalling cascade, cardiac calcineurin/NFAT signalling. Here we will establish that microRNAs are intimately interwoven with this signaling cascade, influence signaling strength by unexpected upstream mechanisms. Secondly, we will firmly establish that microRNA target genes critically contribute to genesis of heart failure. Third, the surprising stability of circulating microRNAs has opened the possibility to develop the next generation of biomarkers and provide unexpected mechanisms how genetic information is transported between cells in multicellular organs and facilitate inter-cellular communication.

Finally, microRNA-based therapeutic silencing is remarkably powerful and offers opportunities to specifically intervene in pathological signaling as the next generation heart failure therapeutics. CALMIRS aims to mine the wealth of these RNA mechanisms to enable the development of next generation RNA based signal transduction biology, with surprising new diagnostic and therapeutic opportunities.

PROGRAMME
H2020

PROJECT ID
722609

INTRICARE

International Network for Training on Risks of vascular Intimal Calcification And roads to Regression of cardiovascular disease

PROF. TILMAN HACKENG

PROF. THOMAS UNGER

DR LEON SCHURGERS

PROF. ERIK BIESSEN

DR RORY KOENEN

DR ELINE KOOI

DR SÉBASTIEN FOULQUIER

INTRICARE

Cardiovascular disease remains one of the major challenges of contemporary society, being responsible for a staggering 47% of deaths in Europe. Vascular calcification in particular requires immediate attention as it is strongly associated with increased cardiovascular mortality and morbidity, and is recognised as an important independent risk factor for cardiovascular death. Recent reports demonstrate that especially punctuated and spotty calcifications (microcalcifications) in the plaque are life-threatening. Microcalcifications are particularly prominent in the vulnerable atherosclerotic plaque that is at high risk of rupture, a cardinal event that can cause thrombosis, infarct, cardiac arrest, stroke and death. In fact, 20% of European deaths are directly attributable to thrombotic rupture of a vulnerable plaque; a clear indication that current treatments and preventive measures are insufficient.

Recent findings suggest a link between vascular smooth muscle cell phenotype mediated calcification and inflammation, which could underlie the plaque destabilising effects of microcalcification. However, a comprehensive view on what causes microcalcification and its impact on plaque stability remains elusive and there is an urgent need to translate experimental findings into adequate diagnostic, preventive and therapeutic solutions. INTRICARE is shaped to address the urgent unmet medical needs concerning calcification-induced vulnerable plaques and is guided by the academic and industrial demand for a new generation of entrepreneurial scientists that have the skills, expertise and know-how to expedite our understanding of vascular calcification and translation thereof into concrete, effective clinical solutions. The INTRICARE ESRs harbour ongoing vitamin K-supplementation trials that will be pivotal in the identification of selective biomarkers for microcalcification and subsequent development of strategies for prevention or amelioration of vulnerable plaque formation.

INTRICARE is organised around three pillars:
WP 1: Initiation of atherogenesis
WP 2: Vascular remodelling associated microcalcification
WP 3: Imaging of microcalcification and vulnerable plaque formation
Each of the three themes will incorporate both basic and translational science and education, supported by a strong network of academic and non-academic partner organisations.

BENEFICIARIES
- Universiteit Maastricht The Netherlands (lead)
- Universitätsklinikum Aachen Germany
- Karolinska Institutet Stockholm Sweden

PROGRAMME
H2020

PROJECT ID
737817

AXONE

Commercial multiple electrode lead technology for cardiac disease

PROF. FRITS PRINZEN

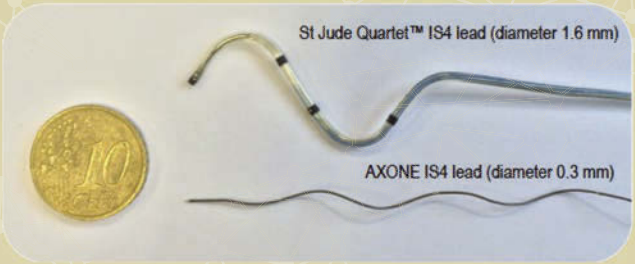
Heart failure affects more than 14 million people in Europe and is projected to affect about 30 million people by 2020. While the effects of Cardiac Resynchronisation Therapy (CRT) on the wider heart failure population are impressive, benefits at the individual level vary considerably. Depending on the definition, the responder rate CRT is positive in 50-70% of patients, leaving 30-50% without significant benefit. This project will finalise the development of a pacemaker cardiac lead that is 5 times smaller diameter than the state-of-the-art¨ and start the commercialisation of the product.

The project is expected to improve the efficiency of CRT by reducing the time required for the implantation procedure by 25%, and decrease the yearly healthcare costs by 82 M€/year in Europe. In addition, the project will help European companies to compete in the pacemaker market currently dominated by US companies. Axone IS4 lead combines the advantages of a single lead, which is easy to place in any coronary vein, with the capability to stimulate the left ventricle at 2 widely spaced sites for a more global resynchronisation – this has previously required 2 leads to be placed in the heart.

The objective of the AXONE project is to:
- Finalise product industrialization
- Confirm chronic pre-clinical performance with large scale studies
- Perform an acute clinical study and a chronic clinical validation
- Manufacture clinical and commercial products
- Build the marketing plan and prepare the product launch
- File CE marking of the class III medical device system
- Launch the commercialisation of AXONE system and start selling the system in Europe

This novel approach of multi-site pacing has the potential to become the next CRT therapy device generation, initiated in Europe.

BENEFICIARIES
- Sorin CRM SAS France (lead)
- Heraeus Deutschland Gmbh & Co KG Germany
- Universiteit Maastricht The Netherlands
- Centre Hospitalier Universitaire de Rouen France



PROGRAMME
FP7

PROJECT ID
316738

RADOX

RADical reduction of OXidative stress in cardiovascular diseases

PROF. ULI SCHOTTEN

Cardiovascular diseases (CVD) are the n°1 killer worldwide. They constitute a major and increasing health and ensuing economic burden in developed countries. The prediction is that the prevalence of these conditions will increase by ~60% over the next 20 years. Subsequently the development of novel treatments for patients with CVD becomes more and more urgent. Oxidative stress is a major molecular contributor to the pathogenesis of CVD; however, oxidative stress related therapeutic strategies are still missing. This ITN consortium links investigators highly active in the field of oxidative stress-signalling, and will strongly enhance collaborative research and integrate complementary interests to obtain innovative science and outstanding in- depth integrative multidisciplinary training possibilities.

The scientific aims of this ITN proposal entitled 'RADical reduction of OXidative stress in cardiovascular disease (RADOX)' are to characterise the specific sources of reactive oxygen species (ROS) and their interaction in cardiovascular disease and to use this knowledge to develop diagnostic tools for the detection and quantification of ROS and their subcellular targets. This will lead to new therapeutic strategies which modulate the activity of these specific sources of ROS. The project objectives also fit perfectly with the FP7 focus on identification and validation of novel, therapeutically relevant targets for the development of new medications for cardiovascular pathologies. This RADOX consortium, containing 9 full partners (8 academic and 1 private) and 7 associated partners will train 11 PhD- students (ESR, 396 research months =82.5%), and 4 junior post-doctoral fellows (ER, 84 research months =17.5%).

The mission of this ITN proposal is to create in a period of 4-years the future leaders in the field of redox and oxidative stress-biology and lay the foundation for a robust translational research and training programme in this field and contribute unambiguously to treatment and prevention of CVD. Our trainees will receive unequaled multidisciplinary scientific and transferable skills-training which will make them ready for leading positions in academia or industry and will develop new therapeutic approaches to tackle oxidative stress in the cardiovascular system. The training in this programme will be at 3 levels i.e. through research under supervision, transferable skills and secondments and will have an intersectoral, international and interdisciplinary character. Afterwards, the RADOX structure will serve as a European platform for outstanding doctoral training and oxidative stress research.

BENEFICIARIES
- Charité Universitätsmedizin Berlin Germany (lead)
- Universidad degli Studi di Padova Italy
- University of Glasgow UK
- Katholieke Universiteit Leuven Belgium
- Universiteit Maastricht The Netherlands
- Bayer Pharma AG Germany
- Universidad de Navarra Spain
- The University of Cambridge UK
- The University of Oxford UK

PROGRAMME
H2020

PROJECT ID
665647

SIRENE

Silencing miR-199b to attenuate the progression of heart failure

Personal Grant
Proof of Concept

PROF. LEON DE WINDT

Cardiac hypertrophy is the principal risk factor for the development of heart failure and lethal arrhythmias. A complex web of interconnected signalling pathways has been implicated in hypertrophy and species of non-coding RNA molecules, microRNAs, have been shown to regulate these pathways. The recognition of microRNAs as potential therapeutic targets marks the principal step towards new therapeutic concepts.

The SIRENE project represents the advancement of the therapeutic strength of miRNA silencing in clinically relevant heart failure models towards a valuable proposition for counteracting pathological hypertrophic signalling and heart failure development. In specific, during the related ERC CALMIRS project, it was found that sustained knockdown of endogenous miR-199b in the adult mouse heart in vivo leads to profound protective effects against symptoms of heart failure. Therefore, a new class of RNA antagonists, targeting miRNAs is powerful and holds great promise to become the next generation therapeutics. At this stage the newly developed antagonists are unique in their affinity and specificity for miR-199b and current data demonstrates a profound rescue by miR-199b antagonists on heart failure symptoms such as pressure overload induced cardiac morphological, histological, functional and molecular abnormalities in mice.

The challenge of the SIRENE project is to identify immediate and longer term opportunities for commercialisation with high clinical and commercial feasibility. Therefore different business models will be studied in terms of market research, IP strategy and business development to eventually consolidate a commercial strategy and business case for presenting our business proposition to strategic partners or venture capitalists. Simultaneously, dose-range finding and efficacy studies will be conducted in rats, a clinically relevant and larger animal model of heart failure, for further preclinical development.

PROGRAMME
H2020

PROJECT ID
675351

AFib-TrainNet

EU Training Network in Novel Targets and Methods in Atrial Fibrillation (AFib-TrainNet)

PROF. ULI SCHOTTEN

DR ARNE VAN HUNNIK

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in between 1 and 2% of the general population. More than 6 million Europeans suffer from this arrhythmia and its prevalence is expected to increase by more than 2-fold during the next 40 years due to increased life expectancy. Thus, AF is said to assume epidemic proportions. According to the European Society of Cardiology (ESC), at least 1% of the healthcare budget of European countries is currently spent on AF management. Despite improvements in healthcare, the prognosis related to AF has not improved and, if anything, mortality and hospitalizations related to AF are increasing. Current options for pharmacological therapy are limited by both low efficacy and side effects, including life-threatening ventricular arrhythmias and severe extra-cardiac toxicities. The 'Guidelines for the management of atrial fibrillation', as published by the ESC, call for an urgent need for development of safe antiarrhythmic drugs.

The AFib-TrainNet consortium is committed to training early stage researchers (ESRs) in a number of intersectoral, interdisciplinary and complementary skills. We will enable promising young scientists to become excellent research leaders of the future, capable of fighting the challenges that AF presents to the European population. Within this network, the contribution from multisectoral partners, spanning from basic research to drug development to clinical involvement, together with a highly ambitious research training programme, will ensure ground-breaking research results for the benefit of both AF basic research and pharmaceutical development. Importantly, the established consortium will further have the potential to form a European scaffold for an increased focus on AF research for many years to come.

The goals of AFib-TrainNet are achieved by the synergy and complementarity of i) 5 universities and 3 research institutes in 8 countries, each of which are well-recognised specialists within fields encompassing different aspects of AF; ii) the only 2 SMEs in Europe having drug development programmes towards treatment of AF; iii) 1 contract research organisation with a focus on cardiac screening models; iv) both a human and an equine hospital; v) Simula Research Laboratory, known internationally for their development of computer simulation models; and vi) Fondazione Cardiocentro Ticino, a state-of-the art university clinic, highly specialised in cardiology, cardiac surgery and cardiac anaesthesia.

We will exploit maximal benefit from this network by providing international and intersectoral secondments for all ESRs, by launching a very ambitious training and knowledge exchange programme, as well as establishing biannual meetings including all partners, which will provide an extensive network exchange platform for skills, information and knowledge.

BENEFICIARIES
- Kobenhavns Universitet Denmark
- University of Glasgow UK
- Acesion Pharma APS Denmark
- Universiteit Maastricht The Netherlands
- Universitätsklinikum Hamburg-Eppendorf Germany
- Simula Research Laboratory AS Norway
- Clyde Biosciences Limited UK

PROGRAMME
FP7

PROJECT ID
305507

HOMAGE

Heart OMics in AGEing

PROF. STEPHANE HEYMANS

DR BLANCHE SCHROEN

HOMAGE proposes to validate more specific and more sensitive biomarkers which should facilitate an early detection of the disease in patients at risk of Heart Failure.

HF affects more affects more than 6.5 million persons in Europe. Indeed, the prevalence of heart failure is increasing worldwide due to an ageing population as well as a rising trend of risk factors for heart disease such as diabetes, obesity and hypertension. Heart failure is a major cause of mortality and morbidity in the world and remains the most frequent cause of hospitalization for patients over 65 years old. HOMAGE is a translational project, which aims to fill the therapeutical void by delivering clinically relevant and industrially applicable clinically validated – 'omics based' biomarkers s that will quantify pathological activity in disease pathways that may lead to HF enabling early detection of risk and effective and efficient targeting of treatments at groups of patients that will have the largest net gain.

BENEFICARIES
- Institute National de la Santé et de la Recherche Médicale France (lead)
- Medizinische Universität Graz Austria
- University of Glasgow UK
- Emory University Non Profit Corp USA
- Fondation Transplantation France
- University of Hull Royal Charter UK
- Instituto di Ricerche Farmacologiche Mario Negri Italy
- The Research Foundation of State University of New York USA
- Randox Clinics Limited UK
- University of Keele UK
- Fundacion para la Investigacion Medica Aplicada Fima Spain
- Tataa Biocenter AB Sweden
- Katholieke Universiteit Leuven Belgium
- London School of Hygiene and Tropical Medicine UK
- Medizinische Hochschule Hannover Germany
- INSERM Transfert SA France
- Universiteit Maastricht The Netherlands
- Mosaiques Diagnostics GmbH Germany
- The University of Manchester UK
- Charité Universitätsmedizin Berlin Germany
- ACS Biomarker The Netherlands
- University College Dublin, National University of Ireland

PROGRAMME
H2020

PROJECT ID
733203

PAPA-ARTiS

Paraplegia Prevention in Aortic Aneurysm Repair by Thoracoabdominal Staging with 'Minimally-Invasive Segmental Artery Coil-Embolization': A Randomized Controlled Multicentre Trial

PROF. MICHAEL JACOBS

DR BAREND MEES

Chronic aortic aneurysms are permanent and localised dilations of the aorta that remain asymptomatic for long periods of time but continue to increase in diameter before they eventually rupture. Left untreated, the patients' prognosis is dismal, since the internal bleeding of the rupture brings about sudden death. Although successful treatment cures the disease, the risky procedures can result in paraplegia from spinal cord ischaemia or even death, particularly for aneurysms extending from the thoracic to the abdominal aorta and thus involving many segmental arteries to the spinal cord, i.e. thoracoabdominal aortic aneurysms of Crawford type II.

Although various strategies have achieved a remarkable decrease in the incidence of paraplegia, it is still no less than 10 to 20%. However, it has been found that the deliberate occlusion of the segmental arteries to the paraspinous collateral network finally supplying the spinal cord does not increase rates of permanent paraplegia. A therapeutic option, 'minimally invasive segmental artery coil embolisation' has been devised which proceeds in a 'staged' way to occlude groups of arteries under highly controlled conditions after which time must be allowed for arteriogenesis to build a robust collateral blood supply.

PAPA-ARTiS is a phase II trial to demonstrate that a staged treatment approach can reduce paraplegia and mortality dramatically. It can be expected to have both a dramatic impact on the individual patient's quality of life if saved from a wheelchair, and also upon financial systems through savings in; 1) lower costs in EU health care; 2) lower pay-outs in disability insurance (estimated at 500K€ in Year 1), and; 3) loss of economic output from unemployment. Approx. 2,500 patients a year in Europe undergo these high risk operations with a cumulative paraplegia rate of over 15%; therefore >100M per year in costs can be avoided and significantly more considering the additional expected elimination of type II endoleaks.

BENEFICIARIES
- Universitaet Leipzig Germany (lead)
- Orebro Lans Landsting Sweden
- Baylor College of Medicine USA
- Liverpool Heart and Chest Hospital NHS Foundation Trust UK
- Insel Gruppe AG Switzerland
- Universidad de Granada Spain
- Academisch Ziekenhuis Maastricht The Netherlands
- Université de Lille II - Droit et Santé France
- Kite Innovation (Europe) Limited UK
- Universitätsklinikum Freiburg Germany
- Ludwig-Maximilians-Universität München Germany
- Ecrin European Clinical Research Infrastructure Network France
- Slaskie Centrum Chorob Serca w Zabrzu Poland
- Ospedale San Raffaele SRL Italy
- Societé Europeenne de Cardiologie France
- Skane Lans Landsting Sweden
- Alma Mater Studiorum - Universita di Bologna Italy
- Universitätsklinikum Hamburg-Eppendorf Germany
- Warszawski Uniwersytet Medyczny Poland
- The trustees of the University of Pennsylvania Corp USA
- Region Hovedstaden Denmark
- CHU Hopitaux de Bordeaux France

PROGRAMME
H2020

PROJECT ID
737586

SAVEBRAIN

Innovation in modelling Placenta for Maternal and Fetal Health

Personal Grant ERC

Proof of Concept

PROF. HARALD SCHMIDT

This grant is a direct spin-off from the ERC Advanced Grant Radical Medicine: Redefining Oxidative Stress 'RadMed'. Stroke represents currently one of the largest – if not the largest - unmet medical need: It is the second leading cause of death and the leading cause of disability. In contrast to this high demand for effective treatments, there is only one drug available, a blood-clot dissolving agent. However, this drug is marginally effective has over 30 contraindications, and bears an extremely high risk of causing fatal bleeding that 85% of all stroke patients are not treated with it. Moreover, much time is lost before initiating therapy because before its application a rarer form of stroke (caused by a ruptured blood vessel) has to be excluded by sophisticated imaging technology that is only available in specialised hospitals.

The needed innovation would be a drug which is broadly applicable, i.e. has no contraindication, can be given in all forms of stroke and already in the ambulance, is safe, i.e. bears no risk to cause secondary bleeding, is effective, i.e. reduces the brain infarct, increases survival and improves neurological outcomes for patients, has a different mechanism of action, i.e. is directly neuroprotective. All attempts to develop such a drug have been unsuccessful. One reason being that the key mechanism causing the death of neurons has not been discovered.

Our therapeutic principle, discovered in the course of the ERC-AdG RadMed fulfils all above criteria and is also commercially an innovative approach because we reduce the risk by developing only a single compound by combining three compounds that target the same disease mechanism but at different points. We thereby expect to dramatically reduce the likelihood risk of failure in our post-proof of concept (PoC) clinical development and commercialisation process (in orange). Due to the nature of clinical drug repurposing (in green) and the previous failures in stroke, we decided to include a large animal confirmation section (in blue), despite target validation has already been successful in two rodent species and all drugs act synergistically.

PROGRAMME
H2020

PROJECT ID
777111

REPO-TRIAL

An in silico-based approach to improve the efficacy and precision of drug REPurpOsing TRIALs for a mechanism-based patient cohort with predominant cerebro-cardiovascular phenotypes

PROF. HARALD SCHMIDT

This programme is based on insights gained from the successful hypothesis-driven ERC AdG RadMed leading to new non-hypothesis, Systems medicine-based approaches and an entirely new approach on how we define disease and find effective drugs. Specifically, the REPO-TRIAL programme will develop an innovative in-silico based approach to improve the efficacy and precision of drug repurposing trials. We have chosen drug repurposing as it has the shortest time for clinical validation and translation. Validation of all putatively de novo discovered cases for drug repositioning within the time-frame of this programme would be unrealistic.

To improve efficacy and precision, and to adopt our computer simulation parameters and models, we choose a systems medicine based in-silico approach that identifies mechanistically related disease phenotypes and, as a result, a virtual patient cohort. We then validate this in-silico drug repurposing via high precision clinical trials in patients with cerebro-cardiovascular phenotypes stratified using an exclusive mechanistic biomarker panel. We thus innovate two biomedical product classes, drugs and diagnostics. With this we will establish generally applicable in silico trials for other mechanistically related or defined disease phenotypes, for which size, duration, and risks will be reduced and precision increased. This generates rapid patient benefit, reduces drug development costs as well as risks, and enhances industrial competitiveness.

Scientifically, we will contribute to reducing the uncertainty and vagueness of many of our current disease definitions that describe a symptom or apparent phenotype in an organ rather than defining diseases mechanistically as disturbance of self-regulation equilibria of biomolecular processes. Finally, we will reduce animal experimentation and animal numbers in general by applying a preclinical randomised confirmatory trial (pRCTs) concept and preclinical systematic reviews and meta-analyses facilitated by our open access pre-clinicaltrials.org platform, a pendant to clinicaltrials.gov. In the course of this I am also leading a COST action on Systems Medicine and in 2018 will start together with leading international colleagues the open access journal, Systems Medicine.

BENEFICIARIES
- Universiteit Maastricht The Netherlands (lead)
- Universitair Medisch Centrum Utrecht The Netherlands
- University of Newcastle upon Tyne UK
- Medizinische Hochschule Hannover Germany
- Hermann Mucke Pharma Consultancy e.U. Austria
- Concentris Research Management GmbH Germany
- Biocrates Life Sciences AG Austria
- Universitätsklinikum Essen Germany
- Somalogic Limited UK
- Syddansk Universitet Denmark

PROGRAMME
FP7

PROJECT ID
322070

MacObesity

The obesity-induced macrophage: a new player in atherosclerosis development

DR KRISTIAAN WOUTERS

MAC-Obesity

Obesity is reaching epidemic proportions and is an independent risk factor for cardiovascular disease development, in particular atherosclerosis. Obesity-induced atherosclerosis thus represents a new health care challenge in the EU. Current treatments focus mainly on lowering plasma cholesterol levels, but this turned out to be only partially successful. Therefore, the need for alternative treatments and the identification of novel mechanisms involved in the obesity-related cardiovascular risk is crucial.

Parallel to atherosclerosis, a key event in obesity is macrophage recruitment from the bone marrow to adipose tissue. These macrophages differ from resident adipose tissue macrophages (ATMs) and display a pro-inflammatory phenotype which is thought to contribute to the local and systemic inflammation during obesity. Whether these pro-inflammatory macrophages directly influence atherosclerosis has not yet been investigated. In addition, adipose tissue expansion leads to increased free fatty acid (FFA) levels, which are important modulators of mature macrophages. Increased basal lipolysis in adipocytes results in local increases in FFA within the adipose tissue, spilling over to the bloodstream, leading to increased plasma FFA levels.

However, it is unknown whether FFAs influence macrophage differentiation and how FFAs affect ATM function. Thus, although macrophage recruitment and differentiation are key events during obesity and atherosclerosis, the interaction between obesity-induced macrophages and atherosclerosis remains elusive.

Hypothesis: Obesity-induced macrophages, through interactions with FFAs, are important players in atherosclerosis development and represent the key link between obesity and cardiovascular disease.

RESEARCH GOALS
- To identify the contribution of obesity-induced macrophages on atherosclerosis risk using mouse models and innovative experimental techniques such as adipose tissue transplantation.
- To find new inflammatory biomarkers associated with atherosclerosis in experimental models of which the predictive value will be evaluated in human subjects using a large cohort (Maastricht Study).

KEY RESULTS
- Inflammatory adipose tissue macrophages secrete chemotactic factors leading to enhanced immune cell recruitment from bone marrow, worsening NASH in experimental mouse models
- Human inflammatory adipose tissue macrophages are associated with circulating classical monocytes
- NK cell accumulation in visceral adipose tissue is associated with inflammatory macrophage polarization and insulin resistance in humans

PROGRAMME
FP7

PROJECT ID
602156

HECATOS

Hepatic and Cardiac Toxicity Systems modelling

PROF. STEPHANE HEYMANS

The HeCaToS project (Hepatic and Cardiac Toxicity Systems modelling) aims at developing integrative in silico tools for predicting human liver and heart toxicity. The objective is to develop an integrated modeling framework, by combining advances in computational chemistry and systems toxicology, for modelling toxic perturbations in liver and heart across multiple scales.

This framework will include vertical integrations of representations from drug(metabolite)-target interactions, through macromolecules/proteins, to (sub-)cellular functionalities and organ physiologies, and even the human whole-body level.

BENEFICIARIES
- Universiteit Maastricht The Netherlands (lead)
- F. Hoffmann-La Roche AG Switzerland
- Insphero AG Switzerland
- Fundacion para la Investigacion del Hospital Universitario la Fe de la Comunidad Valencia Spain
- Eidgenoessische Technische Hochschule Zürich Switzerland
- Imperial Colelge of Science Technology and Medicine UK
- Luxcel Biosciences Ltd Ireland
- European Molecular Biology Laboratory Germany
- Genedata AG Switzerland
- Max-Planck-Gesellschaft zur Forderung der Wissenschaften EV Germany
- King's College London UK
- Rheinisch-Westfälische Technische Hochschule Aachen Germany
- Microdiscovery GMBH Germany
- Optibrium Limited UK

PROGRAMME
H2020

PROJECT ID
645782

SysAFib

Innovation in modelling Placenta for Maternal and Fetal Health

PROF. ULI SCHOTTEN

Atrial fibrillation (AF) is the most common cardiac arrhythmia, characterized by chaotic electrical activation of the atria, preventing synchronised contraction. More than 6 mm Europeans suffer from it and age is the most powerful predictor of risk. Life-threatening complications and fast progression to persistent or permanent forms call for as early as possible diagnosis and effective treatment of AF. AF is often treated with anti-arrhythmic drugs, with limited efficacy and safety. Atrial ablation, an invasive procedure, is more effective. This procedure is by no means optimised, however, and AF may reoccur. The efficacy of first time ablation may range from 30%-75% depending on the individual patient and disease, such that multiple ablation procedures may be recommended.

It is critical to understand whether an ablation procedure is likely to benefit a particular patient with AF, and whether the arrhythmia is likely to reoccur in this patient, to maximise positive patient outcomes and ensure judicious resource allocation in our healthcare systems. Currently, there are no decision support tools enabling clinicians to access integrated AF patient data together with predictive models to facilitate prognosis and treatment planning.

The aim of SysAFib is to integrate the existing sources of knowledge using systems medicine approach into a focused decision support system to determine which patients are good candidates for atrial ablation and which patients are at risk for arrhythmia recurrence. This would be impossible to develop to the stage of a demonstrator project without a strong partnership of individually world-leading scientific, clinical, and experimental competencies.

A key aspect of SysAFib concerns the development and pursuit of a comprehensive dissemination/ exploitation strategy, which will ensure that the multifaceted project outcomes impact all key stakeholders at the level of the clinic, the policy-makers, and, not least, the individual AF patient.

PARTICIPANTS
- Simula Research Laboratory AS Norway (lead)
- Helmholtz Zentrum München Germany
- Oslo University Hospital, Rikshospitalet Norway
- Maastricht University The Nehterlands
- INRIA France

European Research Area Network on Cardiovascular Diseases (ERA-CVD)

Among non-communicable diseases Cardiovascular diseases (CVD) are the major cause of death in Europe, claiming more than 4 million people per year in the 53 member states of the WHO European Region and around 2 million in the European Union. Recent data indicate that up to 80% of all healthcare expenditure in Europe is allocated to chronic diseases, with CVD alone being estimated to cost the EU economy more than 196 billion € every year.

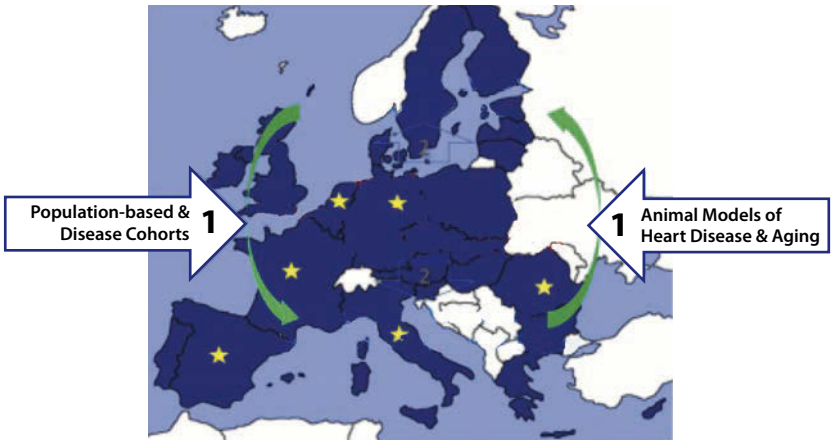
CVD research is not only a crucial area in health research overall, but could become an outstanding example of research driven innovation across Europe. An effective coordination of research at national and EU level, increased cross-disciplinary interaction and research advancements are urgently needed. By gathering their forces and funding capacities so far 18 countries aim at responding to this demand by setting up a new ERA-Net Cofund action (European Research Area Network co-funded by the European Commission, EC) dedicated to cardiovascular diseases (ERA-CVD) . ERA-CVD officially started in October 2015.

EXPERT

Exploring new pathways in age-related heart diseases

PROF. LEON DE WINDT

Exploring new pathways in age-related heart diseases- EXPERT
A European transnational project involving partners from Germany, The Netherlands, France, Romania, Spain and Italy



1. **EXPERT will perform population-based and disease cohort studies to identify theranostic biomarkers complemented by experimental studies in animal models of heart disease and accelerated ageing.**
2. **Identified novel ncRNA pathways will build the foundation for the development of innovative treatment strategies.**

EXPERT is aiming at the development of new strategies for the diagnostic and treatment of age-associated diseases such as heart failure, atherosclerosis and myocardial infarction by exploring non-coding RNA (ncRNA)-mediated regulatory pathways. For a long time regarded as evolutionary junk, ncRNAs are currently emerging as pivotal players in virtually all biological processes. As their levels fluctuate during ageing and disease, ncRNAs are believed to significantly contribute to biodiversity and disease susceptibility including cardiovascular disease. EXPERT will lay the foundation that will lead to novel diagnostic and therapeutic strategies for the treatment of heart failure and other cardiovascular alterations, such as atherosclerosis and myocardial infarction.

EXPERT CONSORTIUM

- Hannover Medical School, Institute of Molecular and Translational Therapeutic Strategies, Germany (lead)
- Universiteit Maastricht The Netherlands
- Humanities Research Hospital Milan Italy
- Centro Nacional de Investigacions Cardiovasculares Carlos III Madrid Spain
- University of Lorraine, INSERM-CHU of Nancy, France
- Institute of Cellular Biology and Pathology “Nicolae Simionescu” Bucharest Romania

LYMIT-DIS

Targeted LYmphatic and Microvessel Treatments in metabolic-DISease HFpEF

DR MARC VAN BILSEN

Heart Failure (HF) represents a serious health challenge, with the number of HF patients in the European Union estimated at 6.5 million, or equivalent to the combined current population of Brussels, Madrid, and Paris. Our research project, LYMIT-DYS, is aimed at developing new options for improved diagnosis, prognosis and treatment of patients suffering from HF, with the focus on HF with preserved Ejection Fraction (HFpEF). This type of HF, affecting more than 50% of HF patients, and notably women, is linked to the metabolic syndrome (MetS), an increasingly common condition characterised by insulin resistance, abdominal obesity, dyslipidemia, and hypertension.

The impact of metabolic syndrome on development of cardiac dysfunction and HFpEF will be evaluated, in a gender-dependent manner, using both experimental models and clinical cohorts. We will investigate if cardiac microvascular dysfunction and lymphatic vessel dysfunction, leads to cardiac edema formation, inflammation and oxygen supply/demand imbalance, and how this affects cardiac energy metabolism and fibrosis and impacts on the development of HFpEF. At the cellular level, we will determine how features of the metabolic syndrome alter paracrine signalling in endothelial cells, macrophages, and fibroblasts vs. cardiomyocytes in search for new molecular targets against diastolic dysfunction.

The overall objective of LYMIT-DIS is to forward our understanding of the mechanisms involved in the cardiac diastolic dysfunction in HFpEF, with the aim to identify and evaluate innovative treatments that could limit the cardiac impact of metabolic syndrome and prevent the transition from cardiac diastolic dysfunction to Heart Failure.

LYMIT-DIS CONSORTIUM
- INSERM Rouen Institute for Research and Innovation in Biomedicine France (lead)
- Universiteit Maastricht The Netherlands
- Medical University of Warsaw Poland
- KU Leuven Belgium
- Arantxa Gonzalez Mique Foundation for Applied Medical Research, Pamplona, Spain

MacroERA

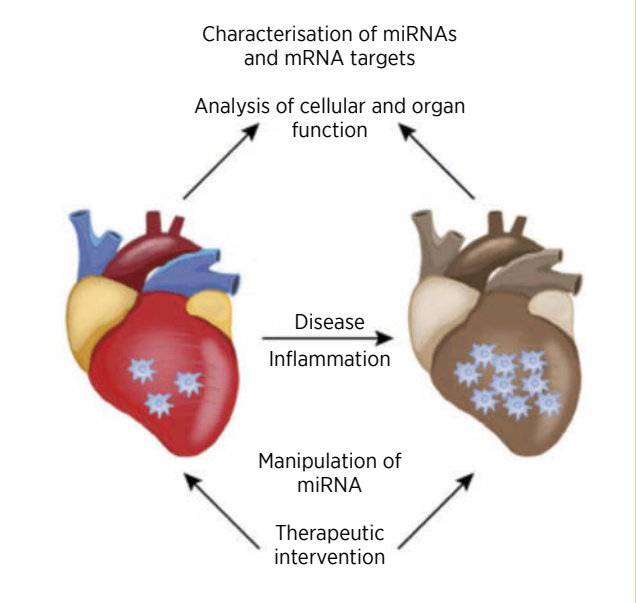
Non-coding RNAs in cardiac macrophages and their role in heart failure

PROF. LEON DE WINDT

PROF. STEPHANE HEYMANS

Long-term prognosis for patients suffering from acute heart failure is still poor. Immune cells in the myocardium are key players in heart failure development. The idea is that endogenous, non-coding microRNAs regulate essential functions in cardiac immune cells. The aim of MacroERA is thus to screen the microRNA portfolio of immune cells in disease models (e.g. chronic pressure overload of the left ventricle) and to characterise the function of candidate microRNAs. Given this, MacroERA will exploit the potential of immune cell microRNAs for heart failure therapy.

MACROERA CONSORTIUM
- Technische Universität München Germany (lead)
- Universiteit Maastricht The Netherlands
- Leuven University Belgium



EVENTS AND HIGHLIGHTS

04

SCIENTIFIC **HIGHLIGHTS**

In 2016, the hard work of our researchers was reflected in **577** scientific publications in peer refereed journals (**535** Wi-1 publications, excluding abstracts and **13** letters to the editor), **55** PhD theses, **2** patents and **1,3** M€ funding received in competition from national and international science foundations and **13,5** M€ funding from third money parties, charities, EU-framework programs, industry, etc. Due to the implementation of the FHML pure output assessment tool, the final data regarding the publications and average Impact Factor were not available at the time of print.

TOP PUBLICATIONS

WITH THE HIGHEST IMPACT FACTOR IN 2016 (with CARIM researcher as first and/or last author)

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The Quest for New Approaches in Myocarditis and Inflammatory Cardiomyopathy.
Journal of the American College of Cardiology 2016; 68: 2348-2364 IF 17.759

Mast TP, Teske AJ, **Walmsley J,** van der Heijden JF, van Es R, **Prinzen FW, Delhaas T,** van Veen TA, Loh P, Doevendans PA, Cramer MJ, **Lumens J -**
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Journal of the American College of Cardiology 2016; 68: 2185-2197 IF 17.759

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Wellens HJ, Lindemans FW, Houben RP, **Gorgels AP, Volders PG, Ter Bekke RM, Crijns HJ -**
Improving survival after out-of-hospital cardiac arrest requires new tools.
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TOP PUBLICATIONS

WITH THE HIGHEST IMPACT FACTOR IN 2016 (with CARIM researcher as first and/or last author)

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Blood 2016; 127: 487-95 IF 11.847

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WITH THE HIGHEST IMPACT FACTOR IN 2016 (with CARIM researcher as co-author)

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Lancet 2016; 388: 818-28 IF 44.002

Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, **Beumer D**, Stouch B, Brown S, Campbell BC, **van Oostenbrugge RJ**, Saver JL, Hill MD, Jovin TG; HERMES collaborators -
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Cell 2016; 167: 843-857.e14 IF 28.710

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Glioma-induced inhibition of caspase-3 in microglia promotes a tumor-supportive phenotype.
Nature Immunology 2016; 17: 1282-1290 IF 19.381

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Preclinical Development of a MicroRNA-Based Therapy for Elderly Patients With Myocardial Infarction.
Journal of the American College of Cardiology 2016; 68: 1557-71 IF 17.759

Joshi FR, Rajani NK, Abt M, Woodward M, **Bucerius J**, Mani V, Tawakol A, Kallend D, Fayad ZA, Rudd JH -
Does Vascular Calcification Accelerate Inflammation? A Substudy of the dal-PLAQUE Trial.
Journal of the American College of Cardiology 2016; 67(1): 69-8 IF 17.759

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WITH THE HIGHEST IMPACT FACTOR IN 2016 (with CARIM researcher as co-author)

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Ortega-Gomez A, Salvermoser M, Rossaint J, Pick R, Brauner J, Lemnitzer P, Tilgner J, de Jong RJ, **Megens RT**, Jamasbi J, Döring Y, Pham CT, Scheiermann C, Siess W, Drechsler M, **Weber C**, Grommes J, Zarbock A, Walzog B, Soehnlein O -
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Jeffcoate WJ, Bus SA, Game FL, Hinchliffe RJ, Price PE, **Schaper NC**; International Working Group on the Diabetic Foot and the European Wound Management Association -
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RESEARCHERS GRANTS AWARDED TO INDIVIDUALS

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

NWO TALENT SCHEME

Dr **Judith Cosemans** (Dept. of Biochemistry) has been awarded with a Vidi grant of 800 K€ and with an Aspasia grant of 100 K€ from NWO to launch an innovative research line and set up her own research group. Platelets play a key role in preventing excessive bleeding, but the inappropriate formation of platelet rich clots after rupture of an atherosclerotic plaque can lead to a myocardial or cerebral infarction. A first myocardial or cerebral infarction increases the chances of a second infarction. Preliminary data from her group suggest that the long-term release of platelet proteins can be involved in this – despite modern antiplatelet medication. The aim of her Vidi project is to disclose underlying mechanisms for the role of platelets in long-term vascular-directed thrombus activities and to effectively curtail the release of platelets proteins in order to find new reference points for medication.

NHS DR E. DEKKER PROGRAM

Dr **Judith Sluimer** (Dept. of Pathology) received one of the thirteen Dr E. Dekker personal fellowships awarded by the Dutch Heart Foundation for her proposal 'Chaperone-mediated autophagy: linking oxygen sensing to cholesterol and atherosclerosis'. She received 420 K€ to study the role of a new process in atherosclerosis and cholesterol metabolism: Chaperone-mediated autophagy (CMA). Her novel data indicate differential regulation of vascular CMA

in human plaque, and elevated plasma cholesterol in CMA-compromised, hepatic lysosomal-associated membrane protein 2A deficient (LAMP2Ako) mice. The latter may be related to CMA-dependent degradation of prolyl-hydroxylase (PHD) enzymes, which Judith recently uncovered as novel players in cholesterol metabolism. She will study the hypothesis that the role of vascular and extravascular CMA differentially modulate cholesterol metabolism and atherogenesis, through PHD dependent and independent mechanisms.

ERC ADVANCED GRANT FOR CHRISTIAN WEBER

Prof. **Christian Weber,** Professor at CARIM (Dept. of Biochemistry), Chair of Vascular Medicine and Director of the Institute for Cardiovascular Prevention at the LMU Medical Center, has been awarded his second ERC Advanced Grant. This ERC Grant entitled 'PROVASC' is an exceptional distinction for Christian, who is one of the few researchers to receive the honor of a second award in the course of his career to date. Atherosclerosis is a major cause of morbidity and premature death in modern societies, and the

principal goal of all of Christian's research is to contribute to our understanding of this condition and to identify new drug targets opening up new routes more effective and personalised treatment.

KOOTSTRA FELLOWSHIPS

Four Kootstra Talent Fellowships were granted to CARIM researchers in 2016. In the category 'Talented future Postdocs' the FHML Research Council rewarded three CARIM applications: **Bart Spronck** (applicant Prof. Tammo Delhaas, dept. of BME), **Elke Marsch** (applicant Dr Judith Sluimer, Dept. of Pathology) and **Romy Kremers** (applicant Dr Bas de Laat, Dept. of Biochemistry). In the category 'Talented student/future PhD student' the application of **Uyên Châu Nguyên** (applicant Prof. Frits Prinzen, Dept. of Physiology) was rewarded.

The Kootstra Talent Fellowships are granted to young scientific talents by the Board of MUMC+ with the aim to support developing their scientific career. The fellowship is meant to provide financial support for young researchers to bridge the time between graduation in Medicine, Health or Life Sciences and the start of a PhD, between the graduation of the PhD student and the start of an official contract as a postdoc or enable them to combine their studies in Medicine, Health or Life Sciences with an active involvement in scientific research.

OTHER AWARDS, PRIZES AND GRANTS

In 2016, many CARIM researchers were awarded with other grants, prizes and awards. Below, some of them are highlighted.

GRANT LANDSTEINER FOUNDATION FOR BLOOD TRANSFUSION

Dr **Rory Koenen** (Dept. of Biochemistry) received a research grant with the topic 'Intercellular communication and immunomodulatory activities of platelet microvesicles in vascular inflammation' from the Landsteiner Foundations. The granted 260 K€ covers the salary costs and bench fee of a PhD student, Alexandra Heinzmann, who will work on the possible risk of platelet-derived microvesicles that accumulate in platelet concentrates during storage using experimental models of vascular inflammation. The Landsteiner Foundation for Blood Transfusion Research (LSBR) supports clinical and experimental scientific research in the field of blood, blood-forming tissue, blood products, and blood (related) diseases, provided that the research bears a relationship to the field of transfusion or transplantation of blood cells.

GRANT NETHERLANDS THROMBOSIS FOUNDATION GERRY NICOLAES

The proposal 'Targeting of extracellular histones by rationally engineered proteases to prevent and treat immunothrombotic desease' of Dr **Gerry Nicolaes** and colleagues (Dept. of Biochemistry) at the Netherlands Thrombosis Foundation ('Trombosestichting Nederland') received a very positive response and was granted (178 K€). Funding will be provided for two years to support needed technical assistance and bench fee to study molecular mechanisms involved in NETosis and immunothrombosis and provide a proof-of-concept for novel sepsis therapeutics.

GRANTS DUTCH KIDNEY FOUNDATION

In collaboration with the Maastricht Multimodal Molecular Imaging Institute, Dr **Carine Peutz-Kootstra** and Prof. **Erik Biessen** (Dept. of Pathology) have been awarded an Innovation grant (100 K€) from the Dutch Kidney Foundation for the project 'Mass Spectrometry Imaging: an integrative molecular histology approach to assess severity of acute and chronic kidney injury'. In this new project the research group consisting of Prof. R. Heeren, Prof. S. Olde Damink, Prof. E. van Heurn, Prof. E. Biessen and Dr Carine Peutz-Kootstra will apply this novel and innovative technique on renal tissue. Using this approach their group ultimately aims to unravel the disturbed metabolic and molecular interactions between microvascular and renal cells in early stages of kidney disease, by integrating multimodal mass spectrometry imaging (MSI) and histopathology on affected renal tissue.

In collaboration with Dr P. Krediet (Nephrology, AMC Amsterdam) and Dr **Carine Peutz-Kootstra,** Dr **Ben Janssen** (Dept. of Pharmacology & Toxicology) has been awarded an Innovation grant (100 K€) for the project 'Opening a new window on the progression of chronic kidney disease: simultaneous long-term assessment of blood pressure and kidney oxygenation'. The grant allows the research group to conduct experiments to investigate if renal ischemia really precedes CKD or that renal hypoxia is rather a consequence of a disease process. By dual telemetric monitoring of blood pressure and renal cortical oxygen levels in rats that are known to develop CKD when the renin angiotensin system is chronically activated, experiments have been designed to explore how changes in oxygen delivery as well as how changes in oxygen use (for instance by diuretics) contribute to the induction and progression of CKD in this model. Results are expected to yield important information how to prevent renal damage in the future and may be helpful in how and when to raise oxygen levels in patients with CKD.

CVON YOUNG TALENT PROGRAM 'HBC OUT OF THE BOX IDEAS'

Dr **Sébastien Foulquier** (Dept. of Pharmacology-Toxicology) received a grant (50 K€) from the CVON Young Talent program 'HBC Out of the Box Ideas' for his project entitled: 'Cerebral hypoperfusion triggers microglia activation and subsequent neurodegeneration: direct evidence from a chronic in vivo imaging study'. Cerebral hypoperfusion is considered as a major trigger for the development of Vascular Cognitive Impairment. However the different key players involved in this pathological cascade and their involvement in a time-dependent manner remain elusive. This project will provide first insights into the dynamic contribu-

tion of microglia cells in the context of cerebral hypoperfusion, a non-neglectable key player of the CNS.

GRANT EUROPEAN FOUNDATION FOR THE STUDY OF DIABETES

Dr **Nordin Hanssen** and colleagues (Dept. of Internal Medicine) have been awarded a grant of 50 K€ by the European Foundation for the Study of Diabetes (EFSD) to investigate the association between plasma dicarbonyls, highly reactive glucose metabolites, and cardiovascular disease in people with diabetes. Funding was awarded to perform state-of-the-arts detection of these compounds in plasma samples in large cohort studies containing people with diabetes. Nordin and colleagues indeed found that plasma dicarbonyl levels are associated with cardiovascular disease in type 1 diabetes, and these results have recently been published in the prestigious journal *Diabetes*.

GRANT HEALTH FOUNDATION LIMBURG BLANCHE SCHROEN AND VANESSA VAN EMPEL

Cardiovascular diseases are still the number one cause of death in women. In recent years, diastolic heart failure has emerged as an important contributor to morbidity and mortality, and at the same time effective treatment options lack. The research by cardiologist Dr **Vanessa van Empel** and molecular biologist Dr **Blanche Schroen** addresses the high occurrence of diastolic heart failure in women. Patients are deep-phenotyped in the MUMC+ dedicated outpatient clinic, which includes the imaging of cardiac and systemic microvascular functions. The goal of this deep-phenotyping is to determine whether microvascular dysfunction correlates with heart failure severity, to ultimately stratify patients and adjust therapy accordingly.

HEART FAILURE RESEARCHERS RECEIVE CVON GRANT

The CARIM Heart Failure team of Prof. **Stephane Heymans** has received a million euro grant of the Dutch Heart Foundation. His team together with researchers of Amsterdam will look for early markers of heart failure with preserved ejection fraction. When the heart starts to lose its elasticity, the muscle has trouble relaxing, resulting in higher blood pressure in the heart and lungs. This can lead to shortness of breath and heart failure. This particular type of heart failure, known as HFPEF, is more common in women aged 65 and older and people with obesity, high blood pressure, diabetes and/or kidney failure. In many patients, this loss of elasticity has progressed for several years before symptoms occur. At the moment, the disease is untreatable and irreversible. Early detection is therefore important to prevent unnecessary suffering.

MARIE CURIE FELLOWSHIP FOR YANNICK DEBING

Yannick Debing (Dept. of Cardiology) received a Marie Skłodowska -Curie fellowship for his project 'Understanding parvovirus B19 myocarditis: the role of co-infections and development of the first mouse model'. The specific objectives of this project are to identify previously unknown viral co-infections in B19V-positive serum samples from myocarditis patients; confirm the pathogenic role of putative helperviruses in vitro; explore the underlying molecular biology of the helpereffect; and develop a relevant mouse model for B19V myocarditis.

CARIM TALENT FELLOWSHIP STIJN AGTEN

In 2016, CARIM introduced the CARIM Talent Fellowship, a grant to support a talented CARIM PhD student. The fellowship has been designed to fund an ambitious, innovative, and international one-year post-doctoral project. As part of the grant the postdoc is expected to go abroad to gain international experience with high-impact collaborators. Eventually the fellowship will support top CARIM talent and keep them connected to our institute.

The winner of the first CARIM Talent Fellowship is Dr **Stijn Agten** (Department of Biochemistry). He has started collaborating with Prof. Richard Payne at the University Sydney, School of Chemistry. The project will involve the synthesis of direct thrombin inhibitors isolated from ticks. New chemical ligation methods developed by Prof. Payne will be used to achieve this goal. See pages 108-111 for an interview with Stijn.

ALBERT FRANKEL AWARD FOR ULI SCHOTTEN

On 31 March 2016, Prof. **Uli Schotten** (Dept. of Physiology) was awarded the Albert Frankel Award of the German Society of Cardiology. He received the award for the discovery of cellular mechanisms underlying atrial fibrillation and the development of diagnostic methods and new therapeutic approaches for this arrhythmia. He received the award together with Prof. Jeanette Schulz-Menger (Charité, Berlin). Prof. A. Zeiher (Frankfurt, president of the annual congress of the society in 2016) and Prof. K.H. Kuck (Hamburg, president of the German Society of Cardiology).

ROGER PECORARO AWARD FOR NICOLAAS SCHAPER

Prof. **Nicolaas Schaper** (Dept. of Internal Medicine) has received the American Diabetes Association's 2016 Roger Pecoraro Award. This award recognizes a researcher who has made scientific contributions and demonstrates an untiring commitment to improving the understanding of the detection, treatment and prevention of diabetic foot complications. Schaper was recognized with this honor during the Association's 76th Scientific Sessions®, that took place from 10-14 June 2016, at the Ernest N. Morial Convention Center in New Orleans.

CAREER DEVELOPMENT AWARD THOMAS VAN SLOTEN

Dr **Thomas van Sloten** (Dept. of Internal Medicine and The Maastricht Study) received the Career Development Award at the annual Artery meeting of the Artery Society in Copenhagen on 13 October 2016.

W.H. HAUS PREIS FOR RORY KOENEN

On the 8th of April, Dr **Rory Koenen** (Dept. of Biochemistry) was awarded the W.H. Hauss prize 2016 of the German Atherosclerosis Society (DGAF) for the paper 'Hyperreactivity of Junctional Adhesion Molecule A-Deficient Platelets Accelerates Atherosclerosis in Hyperlipidemic Mice', which was published in Circulation Research in February 2015. The award consists of a certificate and a monetary award.

CLINICAL NEEDS TRANSLATION AWARD FOR MATTHIJS CLUITMANS AND COLLABORATORS

Dr **Matthijs Cluitmans** and his collaborators have been awarded the 'Clinical Needs Translational Award' by the ESC and CinC (Computing in Cardiology) for their work on advanced imaging methods to investigate cardiac arrhythmias. Electrocardiographic imaging (ECGI) allows medical doctors and scientists to noninvasively investigate a patient's electrical heart activity directly at the heart surface. The technique achieves this by employing mathematical formulations to reconstruct the electrical potentials at the level of the heart muscle, from extensive body-surface electrocardiograms and a digitized patient-specific body and heart geometry.

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

OTHER HIGHLIGHTS

APPOINTMENT ANTONIO ZAZA

Prof. **Antonio Zaza** was appointed on the Hein Wellens Wisselleerstoel 2016/2017. Prof. Zaza, from the University of Milano-Bicocca in Italy, is a basic scientist with a background in clinical cardiology, who has devoted the best of his professional life to the study of cellular mechanisms of arrhythmias and their pharmacological modulation. Prof. Zaza is also an academic teacher in cardiac physiology and pathophysiology, with experience at national and international levels. The longstanding scientific interaction between Prof. Zaza and members of CARIM, Prof. Paul Volders in particular, is supported by a common interest for the ionic mechanisms underlying ventricular repolarization and contributing to its intrinsic stability, or pathological instability. See a full interview with Prof. Zaza on pages 112-116.

BIOCHEMISTRY'S IRONMAN TEAM 4TH IN RELAY

On 31 July 2016, **Stijn Agten**, **Jelle Posthuma** and **Niko Deckers** (Dept. of Biochemistry) competed as a relay team named THE BIOCHEMICAL BROTHERS during the IRONMAN Maastricht (3.8 km swim, 180 km bike, 42 km run) and ended on a fourth position (out of 50 relay teams). The swim course was be completed by Stijn Agten (left), Jelle Posthuma (middle) completed the bike course and Niko Deckers (right) finished with a marathon.

CARIM COMMITMENT AWARD FRITS PRINZEN

Prof. **Frits Prinzen** (Dept. of Physiology) received the second CARIM Commitment Award. The CARIM Commitment Award is intended for any CARIM member who has devoted

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. "Frits has been an exceptional supervisor to all of us. He is easily approachable, patiently explains his ideas and stimulates us to find our own personal way in science. Even when research results are e-mailed late at night, comments and revisions can often be found in our inbox before midnight. Apart from being an excellent teacher and supervisor, Frits also looks at the person behind the researcher. He enjoys joining us for a casual drink during congresses and is always available to discuss the latest Tour de France or Olympic Games results. Furthermore, he is known for his comical presentations at the after-party after a dissertation about the 'real' person behind the researcher."

THOMAS UNGER ELECTED MEMBER ISH COUNCIL

Professor **Thomas Unger,** former Scientific Director of CARIM (until April 2017), was elected as member of the ISH Council during the 26th Meeting of the International Society of Hypertension (ISH) that was held in Seoul, Korea, from 24 until 29 September. Established in 1966, the ISH is committed to promoting and encouraging the advancement of scientific research and knowledge and its application to the prevention and management of heart disease and stroke in hypertension and related cardiovascular diseases around the world. Council members are responsible for furthering the aspirations and activities of the ISH, ensuring its efficient running and helping secure its continuity for the future.

JORDI HEIJMAN NOMINATED FOR THE NEW SCIENTIST SCIENCE TALENT 2016

Dr **Jordi Heijman** (Dept. of Cardiology) was one of the twenty-five nominees for the New Scientist 2016 Science Talent ('Wetenschapstalent') award. Jordi studies the mechanisms that cause cardiac arrhythmias. This knowledge can be used to more quickly determine which people have an increased risk for cardiac arrhythmias and can help researchers develop better treatment methods. In his research, Jordi uses so-called 'patch clamp' experiments to measure the electrical properties of heart muscle cells. He is also developing computer models that can analyse these data. This leads to the creation of 'virtual heart cells', which can foster our understanding of complex interactions and help us make accurate predictions about the effects of certain medications, for example.
Eighteen universities in Belgium and the Netherlands nominated young and talented candidates in recent months. New Scientist selected twenty-five candidates based on these nominees.

ACADEMY HONOURS PROGRAMME FOR YOUNG ARTISTS AND SCIENTISTS

In 2016 and 2017, **Noreen van der Linden** (Dept. of Clinical Chemistry, Central Diagnostic Laboratory) participated in the Academy Honours Programme for Young Artists and Scientists. Every year a group of talented young artists and scientists is selected for this program, initiated by the Royal Netherlands Academy of Arts and Sciences and the Society of Arts. During four meetings in the Trippenhuis, participants get the opportunity to discover each other's world, exchange experiences, explore possible collaborations and meet members of the three academies. This leads to vibrant and inspiring debates on topics that are relevant to both art and science.

UM MASTER THESIS PRIZE FOR MILOU MEEUSE

During the Dies Natalis 2016 on 11 January 2016, **Milou Meeuse,** intern at the Dept. of Molecular Genetics supervised by Willem Voncken and Dietbert Neumann, was presented a UM Best Master's Thesis Prize 2015. Title: 'MNK1a and AMPK: partners in metabolic adaptation?'

HIGHLIGHT THEME III

COEN STEHOUWER

DEPARTMENT OF INTERNAL MEDICINE

Harvesting he results of The Maastricht Study

Diabetes mellitus is a serious threat to health worldwide. The first WHO Global Report on diabetes demonstrates that the number of adults living with diabetes has almost quadrupled since 1980, to 422 million. This dramatic rise is largely due to the rise in type 2 diabetes, and factors driving it include overweight and obesity. Individuals with type 2 diabetes will lose 16-18 quality-adjusted life-years due to diabetes, and will die, on average, 6 years earlier than their peers. The dramatic loss in quality of life is not only due to the classic macro- and microvascular complications of diabetes, like myocardial infarction and stroke, retinopathy, nephropathy and neuropathy, but also to the high levels of chronic comorbidities like depression, dementia and chronic obstructive pulmonary disease. To turn around the diabetes epidemic, it is of crucial importance to increase our knowledge about the aetiology of type 2 diabetes, its complications and comorbidities. In 2010 CARIM took up this challenge by initiating the Maastricht Study within its theme III, Vascular Biology and Medicine.

THE MAASTRICHT STUDY

The Maastricht Study is an observational prospective population-based cohort study that focuses on the aetiology, pathophysiology, complications and comorbidities of type 2 diabetes mellitus (T2DM). Thanks to the comprehensive research questions of the study, the collected data can be used by a broad range of scientists from Maastricht University. The study is characterised by an extensive phenotyping approach, meaning that virtually every non-invasive test on risk factors and disease characteristics is performed, from basic measurements like blood pressure and biobanking of blood and urine samples, up to advanced imaging like CT-scans of the extremities and MR imaging of the brain and abdomen. Major outcomes of the study include important comorbidities like depression, cognitive decline and dementia, COPD and osteoporosis, which can be used to investigate their relation with diabetes, but also to study these phenomena independently of diabetes. To date, approximately 7,500 individuals aged 40-75 years, living in Maastricht and the surrounding area, have been included in the study. The inclusion will continue until 31 December 2018, and aims at 8,000 participants.

HIGHLIGHT THEME III

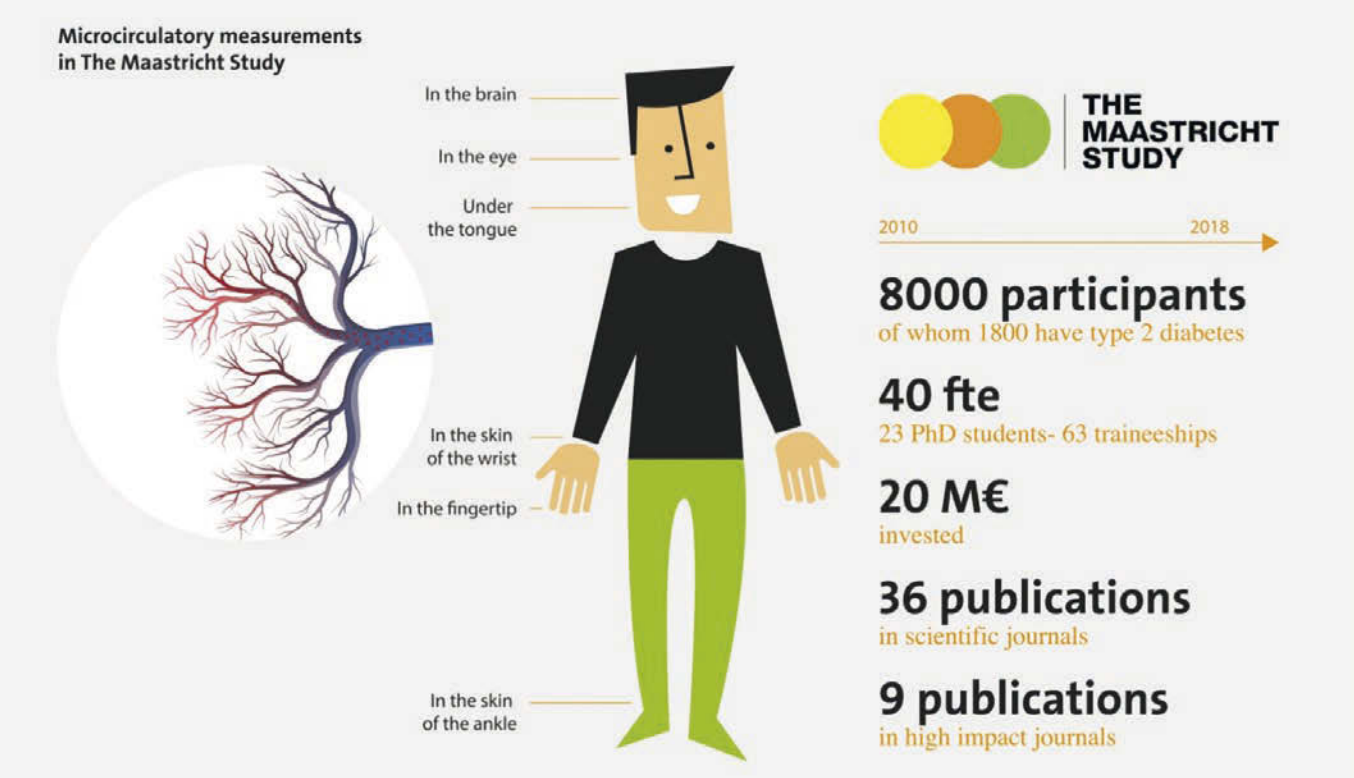


FIGURE 1

TINY VESSELS

One of the assets of the Maastricht Study is its in-depth assessment of microvascular function. The smallest vessels of the cardiovascular system are of crucial importance for the delivery of oxygen and nutrients to tissues and organs. However, the microvasculature is notoriously difficult to measure due to its small size. By using various non-invasive techniques, ranging from dynamic vessel analyses to diffusion tensor imaging using MRI (see Figure 1), the Maastricht Study generates important new knowledge about microvascular functioning and dysfunctioning.

Elaborating on the ticking clock hypothesis, which states that macrovascular disease develops even before the onset of type 2 diabetes, that is in the prediabetes phase, we were interested to see whether this hypothesis also holds true for the microcirculation. As we collected data on microvascular function in over 300 individuals with prediabetes and 600 with type 2 diabetes within the Maastricht Study, we chose

to compare these data with those of 1,200 individuals without diabetes. Interestingly, we found that individuals with prediabetes already had microvascular dysfunction, and their degree of dysfunction was approximately half that of individuals with type 2 diabetes (see Figure 2). Adjustment for potential confounding cardiovascular risk factors like hypertension, obesity and hyperlipidaemia did not materially change these results, nor did adjustment for the presence of cardiovascular disease or microvascular complications of diabetes. We therefore concluded that our findings support the concept that microvascular dysfunction precedes and thus may contribute to type 2 diabetes-associated cardiovascular disease. These results may even be extended to other diabetes complications with a presumed microvascular origin, such as impaired cognitive function, depression and heart failure. Results were presented at the annual conference of the European Association for the Study of Diabetes (EASD) in Munich in September 2016 and published in *Circulation* (Circulation. 2016 Nov 1;134(18):1339-1352).

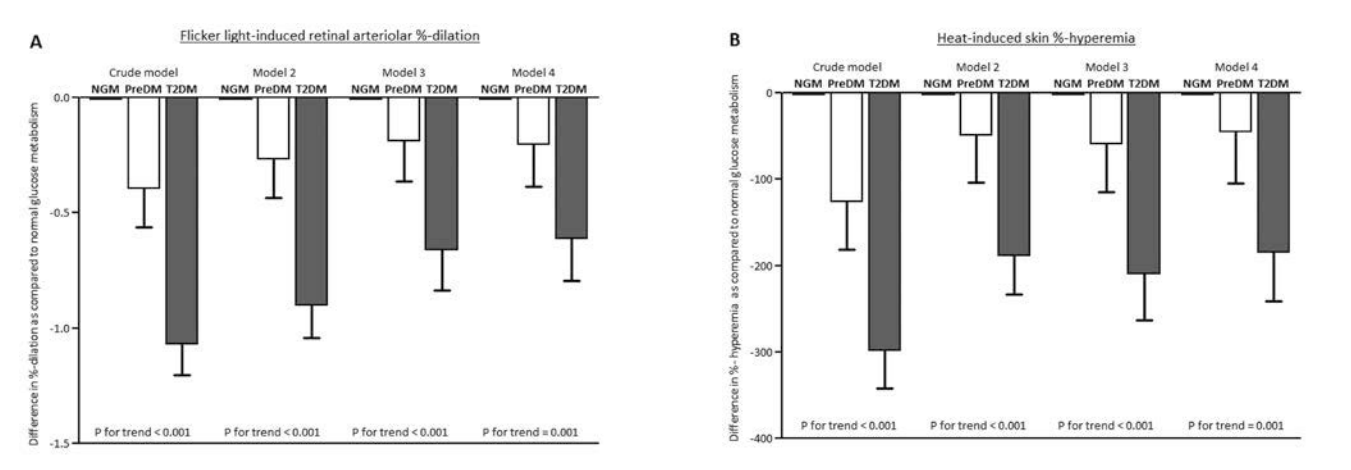


FIGURE 2

Multivariable adjusted differences in flicker light-induced retinal arteriolar %-dilation (A) and heat-induced skin %-hyperemia (B) between individuals with prediabetes (PreDM), and type 2 diabetes (T2DM) compared to normal glucose metabolism (NGM).

Bars represent the mean difference with standard error in retinal arteriolar %-dilation or heat-induced skin %-hyperemia for prediabetes and T2DM as compared to NGM. P-values indicate trend analyses among NGM, prediabetes and T2DM participants. NGM is the reference and is set to zero.

Model 2: adjusted for age, sex

Model 3: additionally adjusted for body mass index, triglyceride levels, total-to-HDL-cholesterol ratio, smoking status, systolic blood pressure, and use of antihypertensive and/or lipid-modifying drugs

Model 4: additionally adjusted for history of cardiovascular disease, retinopathy, estimated glomerular filtration rate and urinary albumin excretion.

HIGHLIGHT THEME III

IS SITTING THE NEW SMOKING?

The Maastricht Study also aims to prevent the development of type 2 diabetes. Given its high prevalence in Western society, sedentary behaviour may be a potential target for the prevention of type 2 diabetes. Using an advanced accelerometer, we were able to assess both the sedentary behaviour and physical activity of participants of the Maastricht Study. We conducted a study to examine associations between the total amount and patterns of sedentary behaviour and the metabolic syndrome and type 2 diabetes. Figure 3 shows the differences in activity patterns between individuals with normal glucose metabolism, with prediabetes and type 2 diabetes, where the diabetes group is seen to spend most time sedentary. In addition, larger amounts of sedentary time were associated with higher odds for the metabolic syndrome, as well as for type 2 diabetes. One extra hour of sedentary time was associated with 22% higher odds for type 2 diabetes and 39% higher odds for the metabolic syndrome. The patterns in which sedentary time was accumulated was weakly associated with the presence of the metabolic syndrome. These results suggest that sedentary behaviour may play a significant role in the development and thus potentially the prevention of type 2 diabetes. Therefore, we should consider including strategies to reduce the amount of sedentary time in diabetes prevention programmes. Results were published in *Diabetologia* (Diabetologia. 2016; 59: 709–718).

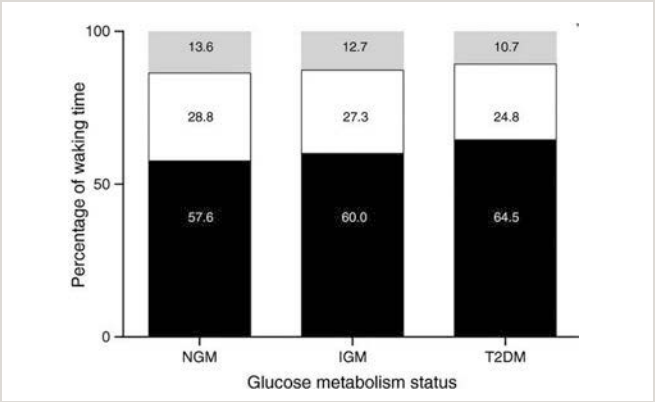


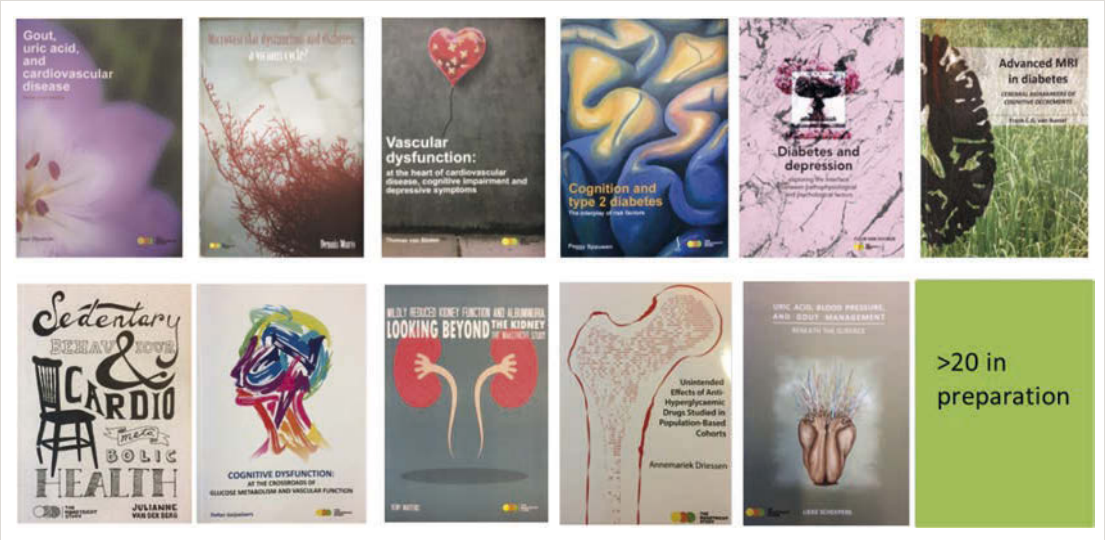
FIGURE 3

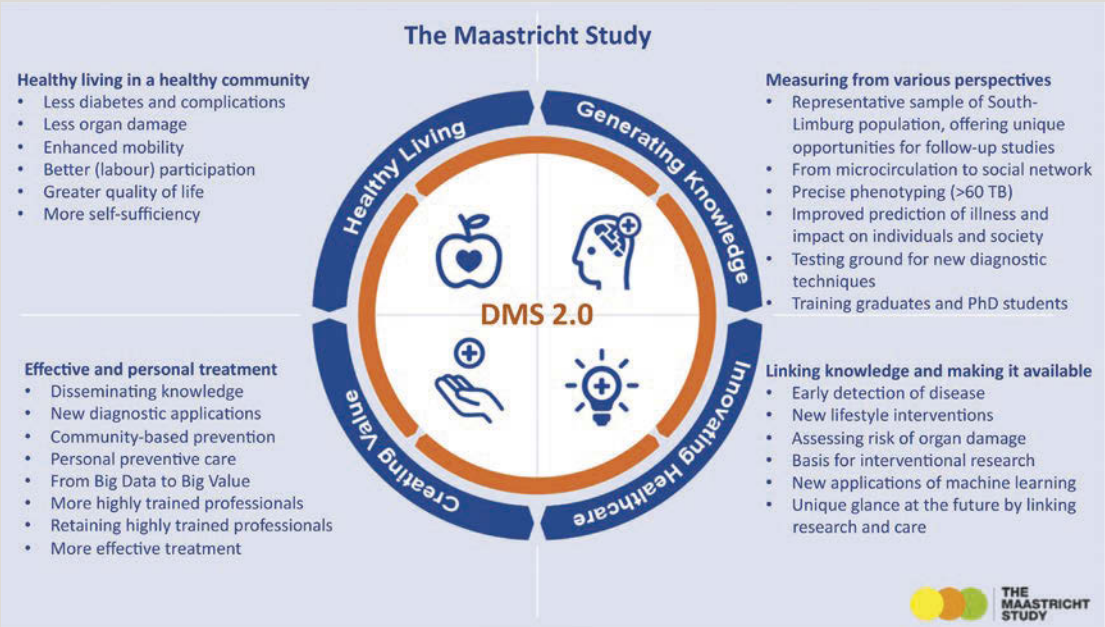
Percentages of waking time spent sedentary, standing and stepping according to glucose metabolism status.
NGM=normal glucose metabolism, IGM=impaired glucose metabolism (prediabetes), T2DM=type 2 diabetes mellitus. Black bars indicate sitting/lying; white bars indicate standing; grey bars indicate stepping.

BREEDING GROUNDS FOR FUTURE SCIENTISTS

In the end, what started as a rather unusual and highly ambitious project within CARIM turned out to offer good opportunities for multiple PhD students to acquire their doctorate. To date, 11 PhD students have defended their theses and over 20 PhD students are currently working on the Maastricht Study data. As depicted on page 91, these theses cover various areas of research, reflecting the multidisciplinary approach of the study. The Maastricht Study has truly become one that crosses the boundaries of research institutes.

HIGHLIGHT THEME III





INTERVIEW
AARON ISAACS

The return of family studies

Halfway through the interview, Aaron Isaacs says: “Everybody hates the statisticians.” He says it like he doesn’t really mind. As a genetic epidemiologist and statistical analyst, he knows what his added value is and how crucially important his work. “There’s only a limited number of ways to properly analyse something statistically. And if you don’t do that, the New England Journal of Medicine or Circulation isn’t going to give you a second look.” An interview with Aaron Isaacs about his reasons to come to Maastricht, the Worm Study, his allergy to mice and cooperation versus competition in science.

Was the leap from climatology to genetics a big one after obtaining your Bachelor's degree in the States?
"Not at all, actually. I studied climate and meteorology at Berkeley as an undergraduate, so I learned how to do a lot of computer modelling and handle 'big data'. At the point that I came to the Netherlands to do a Master's in Genetic Epidemiology in 2002, people had begun to realise that genetics was really data science on many levels."

Why did you want to come to the Netherlands?
"I was living in New York City, working on animal genetics in a mouse laboratory at Columbia University, where I discovered that I really liked genetics. Unfortunately, I also quickly learned that I'm allergic to mice. I took pills in the years that I worked there, but I realised I needed to change my work environment. On top of that, because New York is extremely expensive, I wanted to move somewhere where I might not have to struggle so hard to have a decent standard of living. One of my colleagues pointed out the option to do a Master's in the Netherlands, where she had studied many years before. So I came to Erasmus University for a year. Then they offered me another year. And a PhD position. And a postdoc. Somewhere along the way, I met a lovely Dutch woman and fifteen years later I'm still here."

But "here" is Maastricht, since 2015. Why this transfer?
"I had the opportunity to work in a truly multidisciplinary environment at CARIM, where you can find people from various biological and medical disciplines, who, together, can really move things forward. It gave me the opportunity to collaborate with people in wet labs and with clinicians and do things you could never do in an epidemiology only setting, like I had in Rotterdam. The RNA sequencing projects I'm working on here, for example, are being performed in heart tissue samples. That opens up whole new avenues for the research I'm interested in."

Can you describe your research?
"I have a lot of experience with family-based studies, which were very important at the beginning of the field of genetics. A lot of genetic loci were discovered that predisposed people to monogenetic diseases. Then, in the era of the genome-wide association study, or GWAS, we started to unravel the genetic causes of complex diseases, discovering a lot of common variants with small effects. However, these didn't explain overall disease risk very well. Nowadays, we're doing a lot of sequencing, looking at rarer genetic variants that have larger effects on disease risk. However, if you have a genetic variant that occurs in one in a hundred thousand people, it's very hard to study at the population level. So this has led to the return of families which may be enriched for rarer alleles, like the Worm Study, for which Paul Volders is the Principal Investigator. I have a lot of expertise in the math and statistics that you have to use in these family-based studies. Your sample is, by definition, very small, so you have to think of ways to utilise that data in the most efficient way to get interpretable results. It's quite a challenge and it's been fun."

How about the results so far?
"I can't tell you too much, I'm afraid, since we have generated several manuscripts on the Worm Study, which are in various stages of submission to journals. The first of these was published last July in *HeartRhythm*. As an example, though, we discovered that the mutation in this family that causes sudden cardiac death actually occurs on a haplotypic background with multiple other mutations. So we think that there is more than one thing happening in this family, and we're working on characterising this complex genetic architecture."

You're also involved in the CATCH ME project, funded by the European Union, where an international consortium is looking for ways to improve the diagnosis and care of patients with atrial fibrillation (AF).

"That's right and it's great! RACE V is another, related, project funded by the Hartstichting, and in both we do RNA sequencing on tissue biopsies from the atria of the heart. The transcriptome is a very dynamic system, compared to the genome, so that makes it extremely interesting to look at people with AF and see how genes are being translated towards protein in the relevant tissue. It's all about cutting edge technology and giant amounts of data! CATCH ME includes about 260 patients and the raw RNA sequencing data alone is over eight hundred gigabytes. After the first processing, it's another eight hundred, so you're already talking about more than 1,5 terabytes of data on 260 patients."

What does that exactly mean for your work?

"It requires a lot of experience to get the data analysis right. You can't check anything by hand anymore, so you have to be meticulous in how you approach these problems and minimise the chances of errors. You have to be really open and transparent with your collaborators, and, increasingly, with journals and funding agencies. A lot of data has to be made publicly available, too. When you write a script or generate results, you have to share them and subject them to intense scrutiny. The GWAS era brought this way of working to genetics earlier than to other fields. A decade ago, we started large consortia with groups that were cut-throat competitors. In the beginning, there was a lot of reticence, but, as time passed, people realised that this was the only way to move forward. Now it's becoming more widespread in other areas of science."

What are you most proud of?

"I've had some prominent authorships on important papers in *Nature Genetics*, including several large GWAS. But what I'm most proud of is that I've been able to collaborate successfully with many people from different fields of science on many different phenotypes. Although I've focussed on cardiovascular traits, I've also worked with, among others, neurologists, ophthalmologists, haematologists, and internal medicine people, and I've published on, for example, brain, eye, kidney and blood characteristics. I think it's increasingly important in modern science to work together with people from different backgrounds."

What does that require?

"Patience! Everybody has their egos and preferences for how things need to go. Sometimes it's about leading people towards your position, but without making them feel they're being led away from theirs. So compromise, but knowing when to stick firm to what you know, is important. Everybody hates the statisticians. They do a cell experiment and say: see, condition A is different from condition B. And we're the ones that say: you have to prove statistically that that difference is real, and there's only a limited number of ways to do so properly."

Why is your office not within CARIM, but at the MaCSBio institute?

"At MaCSBio, there are a lot of like-minded people who are also looking at how to deal with the computational problems that arise when you want to analyse hundreds of phenotypes with a million genotypes. That requires a lot of forethought, for instance, about how we can integrate data using computation. This environment gives me a sounding board. If you ask me, the smart use of statistics, data management and computational infrastructure is crucial to the research of the future."

TRAINING AND EDUCATION

05

INTRODUCTION

CARIM offers a flexible and integrated education and training program that suits the individual ambitions of our students. The education program consists of a specialisation within the FHML Master of Biomedical Sciences and a Physician-Clinical Investigator Program (MSc/MD) and a contiguous PhD (doctoral) training program. The content of the education program has been developed by CARIM'S top researchers, while its framework has been created by senior educators of Maastricht University, who have earned an excellent international reputation for their didactical system that is based on problem-based learning.

RESEARCH MASTER

In the Biomedical Sciences program, Master's students are informed about CARIM and the other FHML Research School programs during the start of the master. Students can attend School-specific lectures and parallel programs organised by School researchers. In the second semester, they may get acquainted in more detail with School-specific practical research. In this respect CARIM offers students the opportunity to do a junior research internship in the field of cardiovascular biology at one of CARIM's laboratories. In the second year, the students that are attracted to cardiovascular research can do their senior research internship and master thesis in CARIM. This will lead to a notification of cardiovascular specialisation on their Master's certificate.

PHD PROGRAM

Our PhD program is accessible for talented and motivated students graduated from national and international Medical and Biomedical Masters. At the end of 2016, 95 PhD students attended our PhD program. Almost 50% of our PhD candidates come from foreign countries, guaranteeing an international atmosphere. The principal goal of the 4-year PhD training program 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 a skilled and experienced supervisory team, thereby providing a stimulating and critical environment to further develop one's research skills. We also offer our PhD candidates a broad range of possibilities to attend general and school-specific courses, to attend seminars and master classes. PhD candidates are stimulated to visit symposia to present their own research on national and international podia.

NUMBER OF PHD STUDENTS
(date set 31-12-2016)

FUNDING SOURCE	2013	2014	2015	2016
UNIVERSITY	41	34	34	18
NWO	12	13	11	12
NON-PROFIT AND INDUSTRY	74	82	51	65
TOTAL	**127**	**129**	**96**	**95**

PHD DELIVERABLES

In 2016, 48 PhD students finished their theses within our institute and 5 theses were externally prepared. The table below illustrates the numbers of PhD students in the years 2008-2012, related to the period in which they obtained their degree. The table on page 26 present the number of PhD theses on the level of our research themes.

PHD STUDENT CAREERS
(date set 31-12-2016)

YEAR INTAKE	2008	2009	2010	2011	2012
COHORT VOLUME (annual intake)	20	34	31	38	28
MALE	10	18	12	20	12
FEMALE	10	16	19	18	16
PHD FROM ABROAD	6	12	14	15	11
DROP OUT	4	2	2	-	1
DROP OUT > 1 YEAR	1	4	1	1	3
THESIS COMPLETED	14	24	21	28	10
AVERAGE DURATION (in months)	67	62	59	57	46
ONGOING	1	4	14	9	14

CARIM THESES 2016

Strijkers R -
Title: 'Safety and Feasibility of Ultrasound Accelerated Catheter Directed Thrombolysis and the Postthrombotic Syndrome'
Promotors: Prof. C.H.A. Wittens; Prof. H. ten Cate
Co-promotor: Dr A.J. ten Cate-Hoek
13 January

Roest A -
Title: 'Emergency Care in Sepsis Patients'
Promotor: Prof. C.D.A. Stehouwer
Co-promotor: Dr P.M. Stassen
13 January

Nuzzo F -
Title: 'Coagulation factor V deficiency: From molecular diagnosis to molecular therapy'
Promotor: Prof. T.M. Hackeng
Co-promotor: Dr E. Castoldi
14 January

Ševerdija E -
Title: 'Cerebral circulation and metabolic properties in patients undergoing normothermic cardiopulmonary bypass'
Promotor: Prof. J.G. Maessen
Co-promotors: Dr P.W. Weerwind; Dr J.H. Heijmans
28 January

Mattheij N -
Title: 'Molecular mechanisms underlying the platelet procoagulant response: back to basics'
Promotor: Prof. J.W.M. Heemskerk
Co-promotor: Dr J.M.E.M. Cosemans
29 January

Klarenbeek P -
Title: 'Blood pressure and cerebral small vessel disease'
Promotor: Prof. R.J. van Oostenbrugge
Co-promotor: Dr J. Staals
29 January

Bouman A -
Title: 'Post thrombotic syndrome, exploring aspects of pathophysiology and personalized management'
Promotor: Prof. H. ten Cate
Co-promotors: Dr A.J. ten Cate-Hoek; Dr M.A. Joore
18 February

Truijman M -
Title: 'Plaque vulnerability in stroke patients: a multimodality imaging approach'
Promotors: Prof. W.H. Mess; Prof. J.E. Wildberger
Co-promotor: Dr M.E. Kooi
19 February

Rienks M -
Title: 'Secreted Glycoproteins and Proteoglycans Orchestrate Inflammation in Cardiac Disease'
Promotor: Prof. S. Heymans
Co-promotor: Dr A.P. Papageorgiou
26 February

Klinkenberg L -
Title: 'High-sensitivity cardiac troponins in health and disease'
Promotors: Prof. M.P. van Dieijen-Visser; Prof. L. v. Loon
Co-promotor: Dr S.J.R. Meex
4 March

Swieringa F -
Title: 'Platelets and Coagulation; Partners in haemostasis'
Promotor: Prof. J.W.M. Heemskerk
Co-promotor: Dr P.E.J. van der Meijden
31 March

Hertle E -
Title: 'The complement system and cardiovascular disease: The codam study'
Promotor: Prof. C.D.A. Stehouwer
Co-promotors: Dr M.M.J. van Greevenbroek; Prof. I.C.W. Arts
1 April

Gharaviri A -
Title: 'Computer models of endo-epicardial dissociation of electrical activity and transmural conduction'
Promotor: Prof. U. Schotten
Co-promotor: Dr S. Verheule
29 April

CARIM THESES 2016

Hermans K -
Title: 'Wnt/Frizzled Signaling in Myocardial Infarction; Characterization and Interventions with Peptide Fragments of Wnt'
Promotors: Prof. H. Struijker-Boudier; Prof. P. Timmerman
Co-promotor: Dr W. Blankesteijn
11 May

Loeffen R -
Title: 'Hypercoagulability in cardiovascular disease'
Promotor: Prof. H. ten Cate
Co-promotor: Dr H. Spronk
13 May

Marsch E -
Title: 'Hypoxia in Experimental Atherosclerosis - Linking Cellular Oxygen Sensors and Cholesterol Metabolism'
Promotors: Prof. M. Daemen; Prof. E. Biessen
Co-promotor: Dr J. Sluimer
18 May

Theelen Th -
Title: 'The Role of Hypoxia and Vascular Growth Factors in Experimental Atherosclerosis'
Promotors: Prof. M. Daemen; Prof. E. Biessen
Co-promotor: Dr J. Sluimer
20 May

Kremers R -
Title: 'Thrombin dynamics'
Promotors: Prof. H. ten Cate; Prof. H. Hemker
Co-promotors: Dr R. Wagenvoort; Dr H. de Laat
20 May

Peters T-
Title: 'Non-coding RNA species in heart failure; regulators of cardiac hypertrophy, fibrosis and inflammation'
Promotor: Prof. S. Heymans
Co-promotor: Dr B. Schroen
1 June

Derks W -
Title: 'Inflammation as orchestrator of cardiac disease progression'
Promotors: Prof. S. Heymans; Prof. E. Lutgens
Co-promotor: Dr M. van Bilsen
3 June

Van Anten M -
Title: 'Chlamydia Pneumophyla and the risk of cerebral ischemia'
Promotors: Prof. J. Lodder; Prof. C. Bruggeman
3 June

Chennupati R -
Title: 'Role of arginine metabolism in the production of endothelium- derived relaxing factors; effects of aging, hyperglycemia and hyperglycemia and hyperlipidemia'
Promotors: Prof. J.G.R. De Mey; Prof. W.H. Lamers.
Co-promotor: Dr S.E. Köhler
20 June

Legein B -
Title: 'Role of dendiritic cell subsets in hyperlipidemia and atherosclerosis'
Promotors: Prof. E. Biessen; Prof. E. Lutgens
Co-promotor: Dr L. Temmerman
23 June

Berendsen B -
Title: 'Measurement and promotion of physical activity; evaluation of activity monitors and a multidisciplinary lifestyle intervention in primary care'
Promotors: Prof. H. Savelberg; Prof. N. Schaper
Co-promotor: Dr M. Hendriks
24 June

Van Twist D -
Title: 'The renin-angiotensin system in the hypertensive kidney; clinical studies in patients with essential hypertension, fibromuscular dysplasia, and the atherosclerotic renal artery stenosis'
Promotors: Prof. P. de Leeuw; Prof. A. Kroon
Co-promotor: Dr A. Houben
29 June

CARIM THESES 2016

Vries M -
Title: 'Cytokines in arteriogenesis from a therapeutic perspective'
Promotor: Prof. M.J. Post
Co-promotor: Dr D.G.M. Molin
1 July

Van der Berg J -
Title: 'Sedentary behavior and cardio-metabolic health; a study into the hazards of sitting too much'
Promotors: Prof. C.D.A. Stehouwer; Prof. H. Bosma.
Co-promotor: Dr A. Koster
6 July

Magdelijns F -
Title: 'Health-care-related adverse events leading to (re)hospitalization; how much do we really know?'
Promotor: Prof. C.D.A. Stehouwer
Co-promotors: Dr P.M. Stassen; Dr E. Pijpers
7 July

Liu Y -
Title: 'v-ATPase is a key player in lipid-induced cardiomyopathy'
Promotor: Prof. J.F.C. Glatz
Co-promotors: Dr J.J.F.P. Luiken; Dr D. Neumann
13 September

Mafi Rad M -
Title: 'Mapping and prevention of cardiac dyssynchrony; Towards better substrate identification and lead implantation'
Promotors: Prof. H.J.G.M. Crijns; Prof. F.W. Prinzen
Co-promotor: Dr K. Vernooy
16 September

Vaidya A -
Title: 'Economic modelling in arterial vascular diseases; Studying the cost-effectiveness of various strategies for screening, diagnosis and treatment'
Promotors: Prof. J.L. Severens; Prof. H. ten Cate; Prof. M.A. Joore
16 September

Cluitmans M -
Title: 'Noninvasive reconstruction of cardiac electrical activity; Mathematical innovation, in vivo validation and human application'
Promotors: Prof. P. Volders; Prof. R. Peeters; Prof. R. Westra
29 September

Geijselaers S -
Title: 'Cognitive Dysfunction: At the crossroads of glucose metabolism and vascular function'
Promotors: Prof. C.D.A. Stehouwer; Prof. G.J. Biessels
Co-promotor: Dr S.J.S. Sep
5 October

Kleinegris M -
Title: 'Coagulation testing in atherosclerosis and liver disease'
Promotor: Prof. H. ten Cate
Co-promotors: Dr A.J. ten Cate-Hoek; Dr G.H. Koek; Dr B. de Laat
12 October

Daamen A -
Title: 'Heart failure in nursing home residents; Prevalence, Diagnosis and treatment'
Promotors: Prof. J.M.G.A. Schols; Prof. J.P.H. Hamers; Prof. H.P. Brunner-La Rocca
12 October

Engels E -
Title: 'Something old, something new: vectorcardiographic loop size and response to cardiac resynchronization therapy'
Promotor: Prof. F.W. Prinzen
Co-promotor: Dr K. Vernooy
19 October

Spronck B -
Title: 'Stiff vessels approached in a flexible way: Advancing quantification and interpretation of arterial stiffness'
Promotor: Prof. T. Delhaas.
Co-promotors: Dr K.D. Reesink; Dr R.T.A. Megens, Munich
19 October

CARIM THESES 2016

Zhu X -
Title: 'The AMPK-MNK1 signaling axis'
Promotor: Prof. J.F.C. Glatz
Co-promotors: Dr D. Neumann; Dr J.W. Voncken
20 October

Deckx S -
Title: 'Matrix Glycoproteins and Proteoglycans are Paramount in cardiac disease'
Promotor: Prof. S. Heymans
Co-promotor: Dr A. Papageorgiou
21 October

Mastenbroek T -
Title: 'Role of platelets in vascular remodeling: acute and persistent effects'
Promotor: Prof. J.W.M. Heemskerk
Co-promotor: Dr J.M.E.M. Cosemans
27 October

Burgmaier M -
Title: 'From bench to bedside: Tools to diagnose and treat atherosclerosis and heart failure'
Promotors: Prof. C.P.M. Reutelingsperger; Prof. N. Marx, Aachen
Co-promotor: Dr L. Schurgers
8 November

Lankveld T -
Title: 'Use of the electrocardiogram for prediction of arrhythmia outcome in atrial fibrillation'
Promotors: Prof. U. Schotten; Prof. H.J.G.M. Crijns
Co-promotor: Dr S. Zeemering
17 November

Mihl C -
Title: 'Decisive modification tools in coronary computed tomographic angiography; from phantom to patient'
Promotor: Prof. J.E. Wildberger
Co-promotors: Dr M. Das; Dr B.L.J.H. Kietselaer
18 November

Kok M -
Title: 'Individual Optimisation of Contrast Media Application and Radiation Dose in Computed Tomographic Angiography; from Phantom to Patient'
Promotor: Prof. J.E. Wildberger
Co-promotors: Dr M. Das; Dr B.L.J.H. Kietselaer
18 November

Philippen L -
Title: 'Non-coding RNAs in eccentric cardiac remodeling and heart failure'
Promotor: Prof. L.J. De Windt
Co-promotors: Dr P. Da Costa Martins; Dr E. Dirkx
23 November

Omarova F -
Title: 'Primed to act: the effect of fibrinogen 'Y' on thrombin functions'
Promotors: Prof. J. Rosing; Prof. R.M. Bertina, UL
Co-promotor: Dr E. Castoldi
24 November

Kurstjens R -
Title: 'Haemodynamics in Deep Venous Obstruction'
Promotors: Prof. C.H.A. Wittens; Prof. J.E. Wildberger
Co-promotor: Dr R. de Graaf
14 December

Karmann-Sailer A -
Title: 'Multimodel image fusion in endovascular complex aortic aneurysm repair'
Promotors: Prof. G.W.H. Schurink; Prof. M.W. de Haan
Co-promotor: Dr C. Jeukens
14 December

Agten S -
Title: 'Oximation optimization and applications in cardiovascular research'
Promotor: Prof. T.M. Hackeng
Co-promotor: Dr R. Koenen
15 December
CUM LAUDE

PHD THESES externally prepared

IJzerman R -
Title: 'Muscle strength, mobility and quality of life in patients with diabetic polyneuropathy; the influence of a functional strength and gait training'
Promotor: Prof. N.C. Schaper
Co-promotors: Dr H.H.C.M. Savelberg; Dr K. Meijer
5 February

Kaufmann B -
Title: 'Echocardiography – modern evaluation of cardiac structure and function'
Promotor: Prof. H. Brunner-La Rocca
Co-promotor: Dr V.P.M. van Empel
11 March

Knackstedt C -
Title: 'Improvement of Technical Options Regarding Imaging and Therapy of Heart Failure'
Promotor: Prof. H. Brunner-La Rocca
Co-promotor: Dr V.P.M. van Empel
11 March

Heggermont W -
Title: The role of micro-RNA -221 and -222 in the pathophysiology of viral myocarditis
Promotor: Prof. S. Heymans
Co-promotores: Prof. P. Carmeliet, Dr A. Papageorgiou
22 March

Vaes R -
Title: 'Long term complications following elbow-based autogenous haemodialysis access: studies on high flow and hand ischemia'
Promotor: Prof. J.A.W. Teijink
Co-promotors: Dr M.R.N. Scheltinga; Dr J.H. Tordoir
20 April

DISSERTATION PRIZES 2015

Martijn Chatrou and **Thomas van Sloten** received a CARIM Dissertation Award 2015 during the CARIM annual scientific symposium. Martijn received the award for his thesis 'Role of vascular smooth muscle cell mediated calcification in atherosclerosis' and Thomas for his thesis 'Vascular dysfunction: at the heart of cardiovascular disease, cognitive impairment and depressive symptoms'.

KNOWLEDGE TRANSFER

CARIM COURSE WEEK

From the 20th of June until the 24th of June, the annual CARIM Course week took place. The course week consisted of parallel courses, covering several aspects of CARIM's research, alternated with a combined scientific program and a social program organised by I'M CARIM, the organisation of CARIM's PhD's. In 2016, three courses were organised by CARIM researchers: 'Heart Failure Research: Getting to Excellence', 'Non-invasive Biomedical Imaging' and 'Advanced Microscopy and Vital Imaging'. Almost 50 PhD and Master's students participated.

CARDIOVASCULAR GRAND ROUNDS, CARIM SYMPOSIUM 2016 AND CARIM LECTURES

The Cardiovascular Grand Rounds Maastricht and the yearly CARIM Symposium are means to update the knowledge of our graduate students, our researchers and other external people with interest in the field of cardiovascular research. In the framework of the Cardiovascular Grand Round Maastricht, three successful lecture series were organised in 2016 by Dr **Blanche Schroen**, Dr **Paula da Costa Martins** and Dr **Jordi Heijman** (Dept. of Cardiology), with cardiovascular lectures given by national and international experts, on a weekly basis. For the current programs please visit www.carimmaastricht.nl, 'CARIM lectures' in the 'Education' section.

CARDIOVASCULAR GRAND ROUNDS MAASTRICHT

CARIM's annual scientific symposium was held in Maastricht on 2 November. As in previous years a substantial part of the program was the poster session, in which scientists of the institute presented their recent research findings. During the morning program, the 2015 Dekker Laureates discussed their research projects and in the afternoon, a session on the Maastricht Study took please and two 'duo lectures' were presented by Vanessa van Empel/Matthijs Blankesteijn and Bram Kroon/Koen Reesink. The traditional Robert Reneman lecture was presented by Professor Stéphane Laurent, Professor of Pharmacology at the Paris Descartes Medical Schools. His research interests concern arterial hypertension and cardiovascular diseases, clinical investigation and pharmacology of large arteries (arterial stiffness, central pulse pressure, carotid intima-media thickness, and endothelial dysfunction.

During the evening program, the CARIM Award (see page 84), Dissertation prizes (see page 104) and the poster prizes were awarded. The following posters that were presented during the poster session were awarded with a prize:

- 'Targeting coagulation factor Xa with rivaoxaban reduces the onset and progression of atherosclerosis and enhances plaque stability in apoE null mice' by Postma J, Posthuma JJ, Van Oerle R, Schurgers LJ, Heitmeier S, Ten Cate H, Spronk HMH (Dept. of Biochemistry)
- 'Towards an in vitro model for preeclampsia' by Vangrieken P, Schiffers P, Weseler A, Haenen G, Blankesteijn M, Rango U, Al-Nasiry S, Spaanderman M (Dept. of Toxicology & Pharmacology)
- 'Early loss of peritubular capillaries after kidney transplantation is associated with later renal function decline: a validation study in 121 patients' by Keijbeck A, Steegh FMEG, Gelens MACJ, Van Heurn ELW, Christiaans MHL, Peutz-Kootstra CJ (Dept. of Pathology)

In 2016, the **second CARIM lecture session** was organised. The scope of the CARIM lectures is to stimulate interaction between the themes and by focussing on cellular processes and techniques that may benefit science across CARIM's themes. On the 20th of April the seminar was focused on: 'Advanced imaging: visions of a future for CARIMs cross-theme interactions'. This included lectures of imaging experts: Prof. **Peter Peters** (M4I nanoscopy); 'A revolution in Cryo-EM; beauty and benefits of nanobiology in life science with a focus on inherited cardiomyopathies' and Dr **Eline Kooi** (Dept of Radiology): 'Noninvasive imaging of the hallmarks of plaque vulnerability'. Future meetings will centre around e.g. tissue regeneration, crispr-cas, single cell sequencing, energy metabolism, autophagy.

OTHER CARIM LECTURES, SEMINARS AND SYMPOSIA 2016

Complementary to the regular lecture series and CARIM symposium, several lectures, seminars and conferences were been organised by our research staff in 2016. Some of them are presented below.

Since 2015, CARIM and the Institute of Cardiovascular Research (IMCAR) of the University Hospital RWTH Aachen (headed by Prof. **Joachim Jankowski**) organises joint Cardiovascular Seminars. In 2016 five keynote lectures were given by Prof. Angel Argilés (University of Montpellier, France; 28 January), Prof. Joachim Schultze (LIMES Institute Bonn; 25 February), Dr Anton Jan van Zonneveld (LUMC, Leiden; 30 June), Prof. Walter Kolch (University College Dublin, Ireland, 25 August), Dr Nicola Wick (Max-Delbrück-Centrum für Molekulare Medizin, Berlin, 27 October). The IMCARIM lecture series, which is alternately held in Aachen and Maastricht, offers a platform for international top scientists in the field of vascular biology and nephrology to present their recent work.

The **Maastricht Systems Biology Forum** held three meetings in 2016, covering Systems Approaches to Atrial Fibrillation, Bioinformatics and Systems Biology Approaches to Heart Failure with Preserved Ejection Fraction, and Modelling Variability in Cardiac Electrophysiology. This working group brings together researchers in the Maastricht area who are interested in the development and application of systems biology approaches. The main aim is to share research, experience and, through this exchange, inspire and initiate new research directions and collaborations. The Forum is organised by Michiel Adriaens (MaCSBio), Pietro Bonizzi (DKE), Mike Gerards (NeuGenNet), **Jordi Heijman** (Dept. of Cardiology), Martina Kutmon (BiGCaT & MaCSBio), **Joost Lumens** (Dept. of BME), **John Walmsley** (Dept. of BME) and **Stef Zeemering** (Dept. of Physiology).

The **Vascular Network Group (VNG)**, formed in 2013 and led by Dr **Koen Reesink** and Prof. **Chris Reutelingsperger,** facilitates interdisciplinary exchange between basic and clinical researchers and joint research initiatives, across schools and themes.

In 2016, the VNG has taken up the task as set by Daily Board of CARIM (Prof. Coen Stehouwer and Prof. Harry Struijker-Boudier) to develop the Vascular Biology & Medicine research programmes from a botom-up approach. Focus topics included atherosclerosis, arterial stiffening and hypertension, diabetic vascular complications, neurovascular disease, regenerative and reconstructive vascular medicine, and venous thrombosis and insufficiency. The incorporation of these topics within CARIM Themes will be further discussed.

'Bright of mind' was the topic of the annual Scientific Meeting of the **Maastricht Study**, on the 8th of April. The key note lecture from Prof. Geert Jan Biessels (UMC Utrecht), taught us that type 2 diabetes patients are 3-5 year ahead in cognitive decline as compared to their peers without diabetes. Results from the Maastricht Study indicate that damage to small vessels in the brain and kidney is related to cognitive decline and depression, as was presented by diverse PhD students. The aim of the scientific meeting is to present recent results from the Maastricht Study, in order to facilitate discussions between UM scientists from a broad range of disciplines and to strengthen collaborations.

CARIM, in collaboration with Synapse BV, organised the **3rd Maastricht Thrombin Summer School** on 16 and 17 June. This 2-day symposium comprised lectures on thrombin generation by established researchers, presentations from selected abstracts and an exposition of state of the art thrombin generation equipment.

On 29 and 30 September, the workshop **'Frontiers in Computational Electrocardiology 2016: Electrocardiographic Imaging and Image Integration'** took place in Maastricht. The workshop was jointly organized by the Department of Cardiology and the Department of Data Science & Knowledge Engineering and brought together national and international experts and stimulate a productive discussion about a number of open questions related to the methodology, validation and clinical application of ECGI. Renowned experts such as Dr Yoram Rudy (Washington University in St. Louis, USA), Dr Rob MacLeod (University of Utah, USA), and Dr Phillip Cuculich (Barnes-Jewish Hospital in St. Louis, USA were part of the program.

The **second International Scientific Conference on Cultured Meat** was held in Maastricht from 9 until 11 October. As the previous edition in 2015, it aimed to broaden the scientific base of this exciting application of tissue engineering. The conference hosted over 100 scientists, journalists and investors from 18 different countries. The opening keynote was presented by the renowned Prof. Matthias Lutolf from EPFL on his biosynthesis/bioinformatics toolbox approach for soft biomaterials with high throughput screening. State of the art for large volume mammalian cell culture was covered by Dr Rafiq Qasim from UCL. Prof. Allesandro Sacco from La Jolla elaborated on fundamental skeletal muscle stem cell biology. In addition, there were numerous presentations from young scientist in the field of cellular agriculture. The societal role of meat eating over the ages was discussed by Martha Zaraska, author of the book 'Meat hooked'. The social event was held at the opening of the exhibition on cultured meat at the Cube design museum in Kerkrade.

On 24 and 25 November, the **Dutch Physiology Days (DPD-2016)** were organized in Maastricht by Dr **Frans van Nieuwenhoven** and **Rick Schreurs** (Dept. of Physiology) and Dr Marcel van der Heyden (UMC Utrecht). The theme of DPD-2016 was 'Nutrition and Metabolism', and the programme consisted of five lectures from internationally renowned experts, 16 selected oral presentations and eight posters. The keynote lecture 'Normal and abnormal gastrointestinal conduction: From the slow wave to the magenstrasse' was presented by Prof. Wim Lammers from Unit Arab. Emirates University. During the meeting the Hamburger Award (named after the famous Dutch physiologist) for the best Dutch PhD thesis in the area of physiology was awarded to Dr Vasco Sequeira (VUmc, Amsterdam) for his thesis 'Cross-bridging the gap between energetics, calcium, sarcomere length and diastolic dysfunction'. Prices for best oral and poster presentations were awarded to Alexander Turaihi (VUmc, Amsterdam) and Hugo Hulshof (Radboud UMC, Nijmegen) respectively.

INTERVIEW
STIJN AGTEN

Stijn's Triathlon

Stijn Agten had an eventful year in 2016, for three reasons. To begin with, he joined the Iron Man triathlon in Maastricht, in a relay team with two of his colleagues. Then he got his doctorate with full honours, to his parents' great surprise. And finally he was awarded the first CARIM Fellowship grant, enabling him to work abroad for a year. On Skype from Sydney, he talks about his experiences. "At some stage, I'm hoping to complete the triathlon on my own, just as I like looking at the entire chain of scientific research, from basic protein chemistry to clinical application."

Stijn Agten's PhD project focused on chemokines, the small proteins that play a role in atherosclerosis. Working in the chemistry group led by Prof. Tilman Hackeng, he developed a chemical method to link two specific chemokines, whose linkage had for some time been thought to increase the risk of atherosclerosis. "Our research proved once and for all that the interaction between these two chemokines does indeed induce and worsen this disorder." This does not mean that a medicine to treat it is now within easy reach, but it helps to understand the mechanisms underlying atherosclerosis.

That he should get his doctorate with full honours was a bit of a surprise to him, but his parents were actually rather flabbergasted. "I greatly enjoyed my PhD project, and didn't run up against any of the kind of setbacks that can make PhD students lose heart. My parents had heard those kinds of stories about children of friends of theirs who were doing a PhD, and since they didn't hear them from me, they thought, well, Stijn is probably just doing the bare minimum and not going all-out. So they were highly surprised when I got my degree with full honours." In fact, it was a kind of running gag among his colleagues that Stijn often went home from work early as he had to go swimming in the evening and wanted to have had his dinner before that. "They pretended to be baffled that I worked six-hour days and still managed to get everything done."

IRON MAN

Swimming has been his passion ever since his childhood. And when he found out that one of his colleagues at the Department of Biochemistry was a good cyclist and another was a good runner, they quickly decided that they would join the 2016 Iron Man triathlon in Maastricht. This triathlon can be done not only by individuals but also by relay teams, and Stijn was going to take care of the swimming part. He was the first of the three to start, at seven in the morning, by swimming four kilometres in the river Maas. "Triathletes are usually not known for their swimming capacities, and since the relay participants had to start last, it meant I spent the first half of the race having to pass about five hundred other swimmers, finding my way around, underneath and over them. Our cyclist, Jelle Postma, was very good, so I knew that if I managed to give him a good head start, we had a chance of making the podium."

After swimming for 48 minutes, Stijn climbed ashore in joint second place among the relay swimmers, and eleventh of all two thousand swimmers who had taken part. "Which wasn't all that bad really. Unfortunately we ended up fourth overall, so no prize, which was a disappointment. If you join a race, you want to win." In any case, he has been bitten by the Iron Man bug: at some stage he is hoping to complete the entire triathlon on his own. "That's very special. It's a bit like a PhD project: you don't want to do only a part of it."

TO SYDNEY

And that brings us to Australia. Whereas during his four years at CARIM, he saw how inspiring it can be to work on a research project all the way from the basic science up to the clinical applications, now at Richard Payne's lab in Sydney, he is fully concentrating on the very fundamentals. "I'm now learning the basic organic chemistry that enables me to make molecules. At Maastricht we used to buy the building blocks of proteins ready-made, and if we couldn't buy something, we were unable to make it. Now I can produce these specialised building blocks myself. And I've also learned selenium chemistry here."

He will return to Maastricht in December, taking all this new knowledge home with him. That is exactly the purpose of the

CARIM Fellowship grant, which offers a one-year contract, at least nine months of which have to be spent abroad. Stijn was fascinated by Prof. Payne's research, and he also wanted to go to a warm country, as he needed to keep up his swimming. He has joined the Sydney Lifeguards, as this enabled him to join in sea swimming events. He is on guard duty on the beach once every four weeks. Initially, he also had to work at the lab through the weekend.
"Professor Payne is extremely competitive, and his own life is one hundred percent devoted to his work. And he expects the same from his team. Each subgroup has to report to him weekly, and he makes it very clear if he thinks you haven't achieved enough. That does put a bit of pressure on you, as he basically only wants to hear positive results, whereas a reaction may sometimes not go exactly as planned. So if you've had the kind of week where nothing went right, you feel under pressure to work through the weekend. That's considered normal here. I found that a bit awkward at first, but by now my research is going well and I no longer have to work weekends." Things in Sydney are different from what he had expected. "I've landed in the only research group in Australia which doesn't have a laid-back culture. But then I think the Department of Biochemistry in Maastricht is a bit special. It's apparently widely known for its Friday afternoon get-togethers and other social activities."

PLANS FOR THE FUTURE

So the experience of working abroad is not only highly instructive from the point of view of scientific research, but also helps Stijn decide what would be the most suitable career options for him. "Although I haven't quite figured that out yet. If I want to continue working as a scientist, the obvious thing to do would be another post-doc project, but I'm not sure I want to spend so much time abroad. And I'm also not sure whether I want to work in such a competitive environment as this one again." What he does know is that the advantages of an institute like CARIM in terms of scientific research have become even clearer to him. "Here in Sydney, they're extremely good at the early stages of research, but they leave all the research that comes further down the line to institutions they have collaborations with. If those partners are just two doors down the corridor from your own room, as is the case at Maastricht, that makes things so much easier. I think it's fantastic the way Professor Tilman Hackeng involved me in literally every step of my PhD research project."

"IT'S A BIT LIKE A PHD PROJECT: YOU DON'T WANT TO DO ONLY A PART OF IT"

INTERVIEW
ANTONIO ZAZA

A year amongst peers

"I would really like to take a year off", Antonio Zaza sighed at a meeting with foreign colleagues some years ago. Just take a break from his regular work environment at the University of Milano-Bicocca. To his surprise he received three invitations from abroad within a few weeks: California, Oxford and Maastricht. We interviewed Professor Antonio Zaza about his year on the Hein Wellens Wisselleerstoel: a year to transfer some of his extensive knowledge on electrophysiology and calcium dynamics and hopefully to form the basis for intensified collaboration in the future.

The reason Zaza opted for CARIM was twofold, he explains. Of course it starts with a scientific match: “I see CARIM as an incubator for scientific development in my field. It’s a very well-known institute in this discipline, and this environment offers me many opportunities for close contacts with people who are interested in arrhythmias and cardiovascular diseases in general, whereas in Milan I’m the only professor working on my specific topic.” And the second reason? “That is a personal relationship I’ve had for over fifteen years with professor Paul Volders, whose research is very relevant to mine. Plus my contacts with Dutch people in general. They’re a civilised and open-minded people, both qualities that rank very highly for me. I like the Dutch.”

Are they not too direct, or even rude sometimes?
“I’m heavily criticised for being too direct myself. If it’s black I say black, not white. That’s not the case in many countries. So here I’m amongst my peers, both in Maastricht and in the Netherlands.”

You arrived in October 2016. How do you value your experiences here so far?
“Being a guest is a very nice position, since I don’t have any administrative or educational obligations, and can completely focus on research. I would love to stay longer, but my university wants me back at work by October 2017. Close contact with peers is essential to nurture scientific development, in any discipline, so I think this environment is very profitable for my research.”

What exactly have you been doing so far in Maastricht?
“Paul Volder’s group was interested in setting up a laboratory for the measurement of calcium dynamics inside the cell, a subject in which I’m an expert. So together with Beatrice, a PhD student of mine, we’ve set up the equipment in Paul Volders’ lab and started running the experiments. I hope someone will continue this after we leave. And I helped to set up a hybrid experimental-computational technique, called ‘dynamic clamp’. More generally, I also tried to set up structures for further collaboration in the coming years, to intensify the cooperation between our labs. The biggest element is a study we try to organise on people with phospholamban mutations.”

Can you tell us something more about that?
“In 2005 my group discovered a drug for cardiac diseases, which we expect to be most beneficial for a group of patients who carry a mutation of the protein

I SEE CARIM AS AN INCUBATOR FOR SCIENTIFIC DEVELOPMENT IN MY FIELD

phospholamban, causing cardiac disease. The largest population of these patients in the world lives in the Netherlands, around Groningen. So we are trying to set up a study at the Groningen clinic, and collaborate on the issue with other groups within CVON, a network of the Netherlands Heart Foundation; of course my own laboratory in Milan will be willing to enter into such a collaboration. If we manage to get the clinical study started, it will be a success: if the drug works, the study will provide proof of concept for a novel treatment strategy for this devastating disease; if it doesn't, we'll at least gain new insights into the mechanism of the disease."

What exactly does the drug do?

"While current therapies address secondary effects of the abnormality induced by the mutation, the molecule we discovered has the potential of targeting the mechanism that is likely to initiate the disease. In a nutshell: at rest, the protein SERCA, which is crucial to the processes supporting cardiac contraction, is partially inhibited by its interaction with phospholamban. When the patient needs to exercise, phospholamban is physiologically dissociated from SERCA by activation of sympathetic nerves. But this cannot happen in these patients, because the mutation makes phospholamban stick to SERCA in spite of sympathetic activation. So these patients cannot recruit their SERCA when they need it and, in the long run, this is thought to be responsible for cell damage and the development of symptoms. Our drug prevents the SERCA-phospholamban interaction; hence, if abnormal SERCA inhibition by phospholamban is the disease mechanism, it is going to fix it"

You were trained as a cardiologist. Did you ever regret your decision to exchange the clinic for science?

"Never. My wife is a clinical cardiologist, we graduated together, and I am professionally much happier than she is. She also had an interest in basic research, but at one point we had to decide who would make money for the family and who would play and have fun. My wife gave me the opportunity to play. Academic researchers are privileged people: who else is paid to follow their own curiosity? However, I have to admit that there are also tough times. Science is, in a way, similar to art; since you invest a lot of yourself and your own ideas in it, both excitement and disappointment are more extreme than in other jobs."

What do you consider one of your most exciting moments in science?

"I've had several ups in my career, but they are a bit difficult to explain to a lay person..."

Try me.

"OK, if you insist.... One is about the 'reverse rate-dependency' of action potential duration modulation by drugs. The electrical signal that excites the cardiac muscle, called 'action potential', is a change in membrane voltage over time, with a depolarisation phase followed by repolarisation. The duration of the action potential is a very important parameter, as it sets the refractory period of the heart, which is important in relation to the way arrhythmias arise. Thus, the duration of repolarisation is something researchers are very interested in, but for many years there was a puzzling observation about it. Whatever drug you apply to change the duration of repolarisation, its effect is

always smaller at faster heart rates, which is therapeutically inconvenient. And there's been a lot of investigation into this mystery, which however has a very simple explanation. It's alarmingly simple, which makes me proud of having provided it.

The explanation is that whenever you modulate an ion channel, you change the steepness of repolarisation, which is dimensionally a 'velocity'. Instead, the duration of the action potential is a 'time'. If you look at the mathematical relationship between these two dimensions you find that it is non-linear, which explains why the effect of changing the steepness of repolarisation on action potential duration is larger when the action potential is longer, as occurs at slow heart rates. Thus, while everyone was looking for a complex biological explanation, the phenomenon can be easily explained by a numerical relationship. It is a simple explanation, but it has a significant impact on our understanding of how drugs may act on cardiac arrhythmias."

Will you be back in Maastricht sometime?

"I hope I will; it is not a big distance, as I experienced this past year when I visited Milan once a month. After all, the need to pursue all the plans I have initiated during my stay provides a good excuse for coming back, and as I said, I like Maastricht a lot".

COLOPHON

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