ACS 2018

JULY 2018

Officially united: one university medical center in Amsterdam

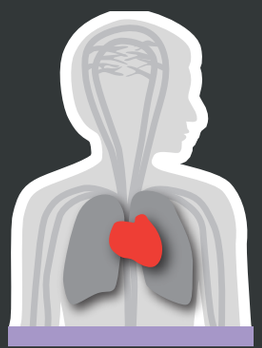
Meet our new professors

3 VICIs for ACS scientists

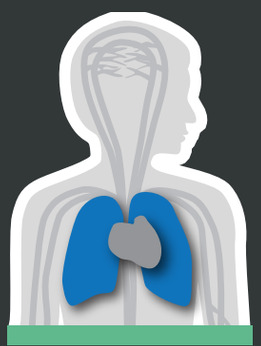
Advanced Imaging at Microscopy Core Facilities

Mission To design knowledge-based treatment strategies to prevent and cure cardiovascular disease.

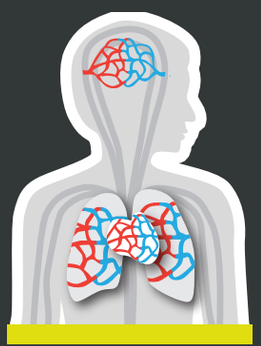
Vision To build one of the top European Cardiovascular Research Institutes by organizing education, research and clinical activities within 5 Research Themes to strengthen our position within Europe.



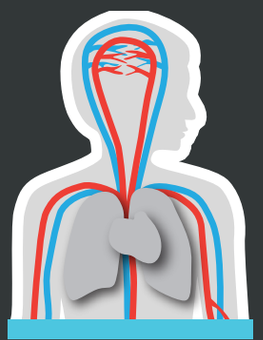
heart failure & arrhythmias



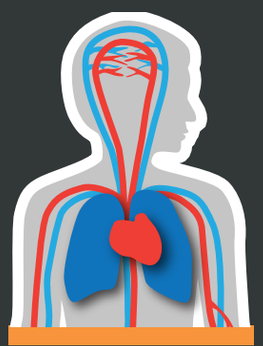
pulmonary hypertension & thrombosis



microcirculation



atherosclerosis & ischemic syndromes



diabetes & metabolism

Amsterdam Cardiovascular Sciences integrated in Amsterdam UMC

Jolanda van der Velden & Bert Groen
Directors of the ACS

At last, after many years of discussions and preparation, we are officially united into one Amsterdam University Medical Center (Amsterdam UMC). While many still have to get used to the idea that VUmc and AMC are history, collaborative research bridging the Amstel in the Amsterdam Cardiovascular Sciences institute (ACS) is swiftly moving forward. The monthly ACS symposia are well attended, stimulating discussion and inspiring new research ideas. Our Out of the Box grants have initiated new collaborations, which have led to joint publications and grant applications for external research funding. We hope that you share our enthusiasm for this marriage and will promote ACS research by using our new name and logo.

We can look back on a successful research year including: one NHS Dekker senior postdoc, two Rubicons, three Vici awards, two CVONs, and two Fondation Leducq awards.

Unfortunately, we also experienced the loss of, the chair of our advisory board, Professor Pim van Aken after a brief period of illness. Pim was of great value for the initiation of ACS providing constructive feedback on our initiatives and stimulating discussions. In addition to this, he was chair of the external review board of MD-PhD and postdoc grants, where young scientists presented and discussed their research applications. Pim was a master at guiding these sessions in a pleasant and objective manner. He will be missed.

In this second issue of the ACS magazine we highlight the research of our five Research programs, introduce the state-of-the-art microscopy imaging platforms and the PhD education committees. We also highlight the three Vici awards. In addition to this, our former director Mat Daemen tells us about the connections between the heart and the brain, which he is trying to unravel in the CVON-funded 'Heart-Brain connection' consortium.

We would like to take this opportunity to say thank you to Mat, for his central role in the development of ACS, and to wish him all the best in his new 'job' as chair of the Research Council.

Finally, we would like to welcome Bert Groen the new ACS director, and our new ACS directorate advisor Anne-Lieke van Deijk. We wish everyone a successful scientific year at Amsterdam UMC

Bert Groen & Jolanda van der Velden

CONTENTS

Colophon:

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Bert Groen
Anne-Lieke van Deijk
Isabelle Vergroesen

Website: https://www.amsterdamresearch.org/web/cardiovascular-–sciences/home-4.htm

Directorate advisors Anne-Lieke van Deijk en Isabelle Vergroesen

For the last six months, Anne-Lieke van Deijk and Isabelle Vergroesen have been working together as directorate advisors for the ACS. We support all internal committees, such as the Educational committee and the Science committee.

We organize and support events, including the monthly ACS symposia where a buffet is served followed by talks from ACS researchers on a specific Research Program. Together with YoungACS, we organize the annual ACS symposium in the Oosterkerk, an inspiring meeting where ACS researchers share their latest results.
We are involved in the creation of the annual ACS magazine and we are proud to be the first research institute to have its own glossy.

Each year, the ACS organizes several grant rounds that require coordination between referees, applicants and external jury members. After the money has been granted, we monitor the money flow within ACS and take care of questions regarding finances.

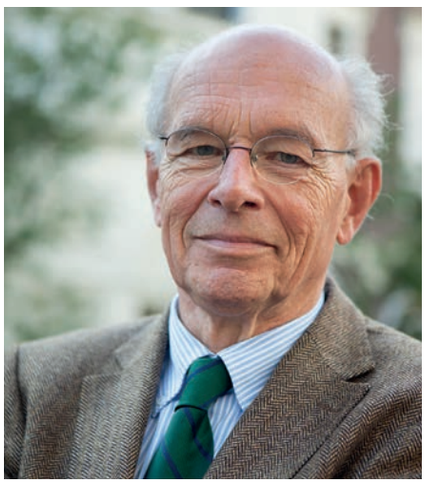
Anne-Lieke van Deijk (l) and **Isabelle Vergroesen** (r)

In addition to the annual ACS magazine, every two weeks we publish a newsletter and regularly update our ACS website with internal and external events, news items, vacancies, grant round announcements and information about the Research Programs. If you want to share news, events (symposia, workshops, PhD defenses) or vacancies with your ACS colleagues, send an email to a.f.vandeijk@amc.uva.nl. These events are examples of ways to stimulate collaboration between researchers from both sides of the Amstel.

IN MEMORIAM

Pim van Aken

Professor Pim van Aken died on the 6th of March after a brief period of illness. Pim was a dedicated member and chair of the Scientific Advisory board of the Cardiovascular Research Institute ICAR-VU for many years. His input on scientific and organizational matters was of great value for ICaR-VU, and for the initiation of the Amsterdam Cardiovascular Sciences Institute. Pim was able to translate his knowledge and experience as a medical doctor, scientist and department chair into constructive and visionary advice for our research institute. He very much enjoyed the interviews with the young scientists during the ACS grant rounds, and was impressed by the quality and dedication of AMC and VUmc scientists coming together to find treatment options for cardiovascular disease. We will remember Pim as a passionate and very kind person.



Cardiovascular imaging at the Amsterdam UMC microscopy core facilities

Eric Reits and René Musters

The Cellular Imaging and AO|2M core facilities of the Amsterdam UMC include a large variety of advanced microscopic imaging technologies including: super resolution microscopy, light sheet microscopy, correlative light and electron microscopy. These are used to visualize physiological and pathophysiological processes in heart and blood vessels in small animal models, as well as human and animal tissues and single cells and their organelles. This can be done using fluorescent tags such as GFP, fluorescently labeled antibodies and fluorescent probes, for example to measure calcium fluxes in living cells. Importantly, both core facilities work closely together using a variety of complementary techniques. Dedicated and experienced operators train researchers how to operate the different microscope systems, and together they share their experiences and experimental findings in regular user meetings.

With over 600 active users, the two microscope facilities support many researchers

The embedding of these core facilities in research departments is crucial, as the shared research progress feeds the facilities and their users directly leading to new developments. Supervised by Eric Reits (AMC) and René Musters (VUmc), the facilities are also involved in a variety of courses and teaching programs for PhD students and master students in the greater Amsterdam area.

Below are a few of the specialized techniques of the microscopy cores:

SUPER RESOLUTION MICROSCOPY

While electron microscopy at the EM center Amsterdam can still reach the highest magnification of up to 400,000 times, recent developments in super resolution microscopy allow fluorescent imaging of small details in cells and tissues that gets very close to EM. The AO|2M core facility at VUmc has a high-end confocal microscope equipped with multiple 3D STED lasers, which allows imaging of 3D structures in living cells at higher resolution than is possible with the standard confocal systems. At the Cellular Imaging core at AMC even higher resolution can be obtained by GSDIM/pSTORM, which requires blinking fluorophores coupled to antibodies.

LIGHT SHEET MICROSCOPY

To visualize larger tissues, including the beating heart of living small animal models, the core facilities are equipped with two types of light sheet microscopes. The Meibergdreef (Cellular Imaging) has recently acquired the Leica SP8 DLS (digital light sheet) allowing visualization of e.g., the heart in the living zebra fish animal model. The Boelelaan (AO|2M) has a LaVision light sheet microscope to visualize larger tissues, and when needed, surrounding tissues can be made transparent with clarity protocols.

ELECTRON MICROSCOPY

The AMC and VUmc have combined their EM experience to create the EM center Amsterdam (EMCA) as part of the Cellular Imaging unit at the Meibergdreef, with three transmission EM microscopes and one scanning EM microscope and a variety of techniques including immune-EM and tomography. The developments in correlative microscopy are new and allow fluorescence imaging of a protein of interest in combination with the high resolution structural information provided by electron microscopy.

With over 600 active users, the two collaborating microscope facilities directly support many researchers. ACS research topics include: heart development, angiogenesis, vascular immunology and atherosclerosis. New researchers can always drop by to present and discuss data and ideas for input and scientific advice, as well as for additional individual training. Please contact **Eric Reits** (e.a.reits@amc.uva.nl) or **René Musters** (r.musters@vumc.nl) or visit the core websites at **www.cellularimaging.nl** and **www.ao2m.amsterdam**.

→ *See page 23 for typical image of the heart with vessels.*

Jeroen Kole (l) and **René Musters** (r)

Jessica Meulmeester (l) and **Eric Reits** (r)

Numbers & Facts

From July 2017 to July 2018

- 2 annual meetings: Rembrandt meeting and Annual ACS meeting
- 9 monthly symposia at the AMC
- 9 different buffets before the symposia
- 550 scientist and students attended the symposia
- 50 educational lectures and discussions at these symposia

Grant rounds organized

- 1 OIO competition resulting in 3 ACS OIOs
- 1 OOTB call resulting in 7 grants of 25,000 euro
- 1 Postdoc call resulting in 3 Postdoc positions of 70,000 euro
- 1 MD/PhD call resulting in 4 MD in training for specialist with one day a week for research
- 2 Equipment calls resulting in 7 grants

ACS published in 2017

- 1 ACS glossy
- 18 ACS newsletters
- 11 ACS posters

ACS members in 2018

- 500 PhD students
- 62 Postdocs
- 140 Principal Investigators
- 80 Staff Members
- 19 Guests (senior and junior)
- 30 Students master Cardiovascular Research

ACS PhD defenses and inaugural lectures in 2017

- 80 PhD defenses
- 7 Inaugural lectures

The Heart Brain connection

MAT DAEMEN

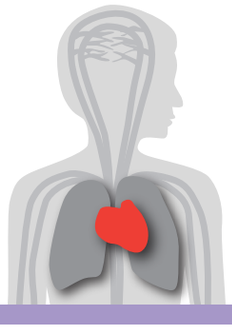
Professor Mat Daemen was involved in Amsterdam Cardiovascular Sciences from the start, and has now moved on to become Director of the Research Council and Chair of the board of Research Support+ at the AMC. In addition to being research council director and a pathologist, Mat Daemen coordinates the national research on the Heart Brain connection. His strength is in developing collaborations among various academic centers including the AMC and VUmc. This has led his research team to not only bridge the Amstel, but to also connect ACS and Amsterdam Neurosciences research institutes.

Mat Daemen

There is increasing, yet still underestimated, evidence that cardiovascular diseases do affect the structure and function of the brain. One of the ways through which heart and brain may be connected is a reduced cerebral blood flow and cerebral perfusion caused by for instance; cardiac failure, carotid occlusive disease and/or microvascular diseases of the brain. The goal of the Heart Brain Connection program, which started at the end of 2012, and is sponsored by CVON-NHS, is to test the hypothesis that cerebral hypoperfusion is the main cause of cognitive dysfunction in patients with cardiovascular diseases.

Cerebral hypoperfusion as main cause of cognitive dysfunction

To investigate this we measured the same series of parameters in the Rotterdam study as well as in a cohort of more than 500 patients with chronic heart failure, bilateral occlusive carotid disease or vascular cognitive impairment. These parameters included circulating biomarkers, relatively simple medical measurements, such as blood pressure and cognitive function and attention, as well as the structure and function of the heart, large vessels and the brain. The latter was done by 3T MRI protocols. A very special feature of the Heart Brain connection program is the involvement and collaboration of 6 UMCs, including AMC and VUmc, and many disciplines, such as cardiology, neurology, radiology, epidemiology, neuropsychology and pathology. The main investigators from AMC and VUMC include Professors Bert van Rossum and Wiesje van der Flier from VUmc and Professors Mat Daemen and Jan Piek from AMC. The first results show that there is indeed a heart brain connection and that almost one fifth of patients with chronic heart failure do show symptoms of cognitive dysfunction. The data also suggest that cerebral hypoperfusion is an important factor, but not the only one, that determines cognitive function in patients with cerebrovascular disease. In subsequent studies, the contribution of vulnerability factors, such as atrial fibrillation, old age and hemodynamics will be investigated.



Unraveling mechanisms underlying cardiac arrhythmias: synergy between AMC and VUmc

Cardiac arrhythmias, including ventricular arrhythmias and atrial fibrillation, are a major cause of morbidity and mortality worldwide. Ventricular arrhythmias can cause sudden cardiac death, whereas atrial fibrillation is strongly associated with higher risk for development of stroke and heart failure. There is often a genetic cause for these arrhythmias, especially in the younger patient population. Many mutations underlying arrhythmia syndromes encode genes for cardiac ion channels. However, there is a large variation in phenotypic symptoms within families carrying the same mutation, suggesting the influence of modifier genes for disease outcome.

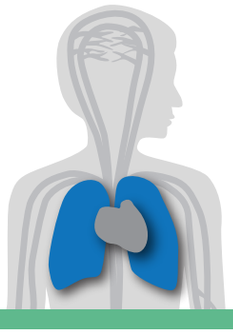
The research group of De Waard has studied the function of transcription factor Nur77 in a number of different cell types over the last decade and recently discovered that Nur77 plays a key role in cardiomyocyte contractility. Cardiomyocytes from Nur77-deficient mice exhibit elevated intracellular calcium levels, leading to enhanced arrhythmogenic potential. While the Nur77-deficient mice show normal heart development, they experience enhanced hypertrophy and an increased risk for sudden death upon chronic beta-adrenergic stimulation, presumably caused by arrhythmias. Since it is hard to catch an arrhythmia in the act, we set out to study cardiac arrhythmia susceptibility live in transparent Nur77-deficient Drosophila melanogaster prepupae in collaboration with Professor Bianca Brundel (Dept. of Physiology, VUmc). For human relevance we are studying the effect of known Nur77 polymorphisms on arrhythmogenic potential in human iPSC-derived cardiomyocytes together with Dr. Carol Ann Remme (Dept. Experimental Cardiology, AMC) and Dr. Phil Barnett (Dept. Medical Biology, AMC). So far, the findings indicate that Nur77 may be an important modifier gene for cardiac arrhythmias.

The research group of Brundel focuses on the molecular mechanisms driving proteostasis derailment and pathophysiology of cardiac diseases, especially atrial fibrillation and cardiomyopathies. The group previously found proof for a key role of cardioprotective heat shock protein exhaustion, excessive autophagic protein degradation and activation of epigenetics to underlie disease progression. Molecular findings are used to identify novel druggable targets. The group utilizes experimental cardiomyocyte and Drosophila cardiac disease models in combination with genetic and pharmacological manipulations. Various potential drugs against atrial fibrillation have been identified and the findings are communicated via the Atrial Fibrillation Innovation Platform (www.AFIPonline.org) to promote translational studies in collaboration with patients. As such, the group aims to move forward on getting candidate drugs into preclinical and clinical proof-of-principle studies.

The research group of Allaart focuses on assessment of substrate for arrhythmias using advanced imaging techniques such as nuclear imaging and cardiac magnetic resonance imaging, aiming to identify patients at increased risk for sudden cardiac death. Typical anatomical substrates that can be evaluated by multiple advanced imaging techniques include perfusion abnormalities, scar and its border zone, and sympathetic denervation. These imaging modalities have emerged as a promising clinical approach to guide patient treatment for ventricular arrhythmias such as ICD placement or ablation therapy. Presently, initial efforts are being undertaken to assess arrhythmic substrate in the challenging thin walled atrium, as a tool for risk stratification in atrial fibrillation. This might eventually aid in patient selection for new translational treatment strategies.

Bench to bedside research on cardiac arrhythmias: “Human iPSC-derived cardiomyocytes, Drosophila and in vivo imaging in patients”

left to right: **Cor Allaart, Vivian de Waard, Bianca Brundel**



CVON-Dolphin-Genesis

Pulmonary arterial hypertension (PAH) is a lung vascular disease with a poor prognosis. The majority of patients are diagnosed only after the development of right heart failure, which is at a time when the expected survival is less than 3.5 years. In just a minority of patients, early diagnosis and treatment make it possible to stabilize the disease. In these patients, outcomes are excellent. Recent studies have shown that in about 20% of patients, the cause of PAH is a genetic mutation, usually in the type 2-bone morphogenic protein receptor. So far, we have identified 29 families in the Netherlands with hereditary PAH (HPAH). Of these families, we are aware of 40 affected members and 23 healthy carriers of the mutated gene. International epidemiological data suggest that the true numbers of hereditary PAH patients and healthy mutation carriers in the Netherlands should be several fold higher. DOLPHIN-GENESIS aims to firstly, identify these patients and carriers, and secondly, to recognize the development of pulmonary vascular disease in mutation carriers before the onset of right heart failure. We expect that the number of referrals of PAH patients for genetic testing will increase following campaigns. In addition, a website and an app facilitating information transfer has resulted in increased awareness among physicians taking care of PAH patients. We also expect that more active, tailored and gender-specific approaches of providing information for HPAH patients and their family members will result in an increase in genetic counseling. Furthermore, we expect that innovative imaging and liquid biopsy methods will allow identification of vascular vulnerability and early detection of pulmonary vascular disease in healthy mutation carriers and other subjects at risk for developing PAH. An integrated strategy of longitudinal biomarker collection (including, but not limited to, positron emission tomography, magnetic resonance imaging, platelet transcriptome screens and metabolomics) will be used to enable early diagnosis of PAH. Finally, DOLPHIN-GENESIS will educate a new generation of cardiovascular scientists to be equipped with skills and knowledge to perform state-of-the-art data management and research into cardiogenetics and biomarkers.

Aim to educate a new generation of cardiovascular scientists'

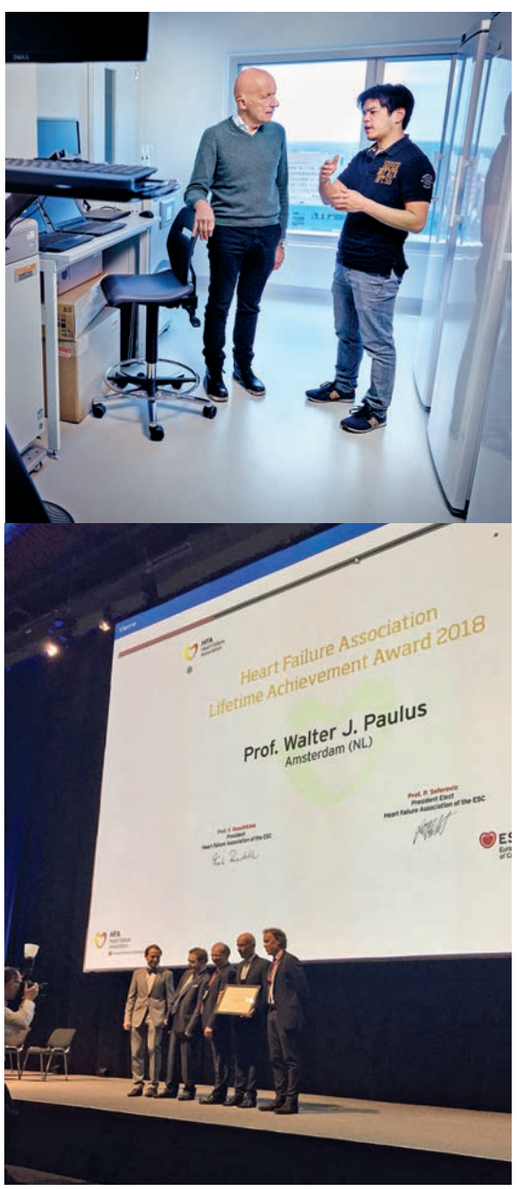
left to right: **Samara Jansen, Frances de Man, Berend Westerhof, Harm Jan Bogaard, Xiaoqing Sun, Joanne Groeneveldt**

The old & the young

LIFETIME ACHIEVEMENT AWARD WALTER PAULUS & RESEARCH LOUIS HANDOKO

Heart failure (HF) with preserved ejection fraction (EF; HFpEF) currently accounts for >50% of all HF cases and its prevalence relative to HF with reduced EF (HFrEF) continues to rise at a rate of 1% per year. Outcomes in patients with HFpEF and HFrEF are equally poor with 5-year mortality rates up to 75% in both HF phenotypes. In contrast to HFrEF, modern HF pharmacotherapy has not improved outcomes in HFpEF: evaluation over the entire EF spectrum of neurohumoral inhibition, the cornerstone of HFrEF therapy, revealed its inefficacy once EF exceeds 50%. Patients with HFpEF are frequently female and have a high prevalence of non-cardiac comorbidities especially metabolic comorbidities such as obesity, metabolic syndrome and type 2 diabetes. Although diastolic left ventricular (LV) dysfunction remains the main culprit for symptoms in HFpEF, numerous ancillary mechanisms such as reduced chronotropic reserve, impaired systemic vasodilation and skeletal muscle wasting are frequently present, which also contribute to early exhaustion during exercise.

Over the past decade, deep clinical phenotyping and translational research using endomyocardial biopsies have improved insights into HFpEF pathophysiology and the importance of comorbidities-induced systemic inflammation. A novel paradigm for HFpEF as postulated by Professor Walter Paulus (Department of Physiology at VUmc) suggests that comorbidities actually drive myocardial dysfunction and remodeling through coronary microvascular inflammation1. This new conceptual framework has been supported by numerous recent observations such as: a specific biomarker profile with inflammatory markers prominent in HFpEF and markers of myocardial injury or wall stress prominent in HFrEF; reduced coronary flow reserve with myocardial microvascular rarefaction in HFpEF and an upregulation of free radical-producing enzymes in endothelial cells in HFpEF and in cardiomyocytes in HFrEF.2 In accordance with this new conceptual framework, treatment strategies will shift towards control of comorbidities, anti-inflammatory therapy and replenishment of myocardial nitric oxide and cyclic guanosine monophosphate. Furthermore, a “one size fits all” strategy will be replaced by an individualized approach based on improved phenotypic patient characterization and pathophysiological stratification reflecting the relative importance of cardiomyocytes and extracellular matrix for diastolic LV dysfunction3. Currently, Louis Handoko (Cardiology at VUmc) is building on the foundation laid by his mentor. The VUmc now has a uniquely equipped clinical pathway for unexplained dyspnea and HFpEF,4 which greatly facilitates clinical research to improve the diagnostic work-up5 and to develop novel treatment strategies in HFpEF.6 Joint expertise in clinical phenotyping and basic experimental studies combining studies in endothelial and cardiac muscle cells (performed within CVON-ReConnect) will aid in identification of novel drug targets.



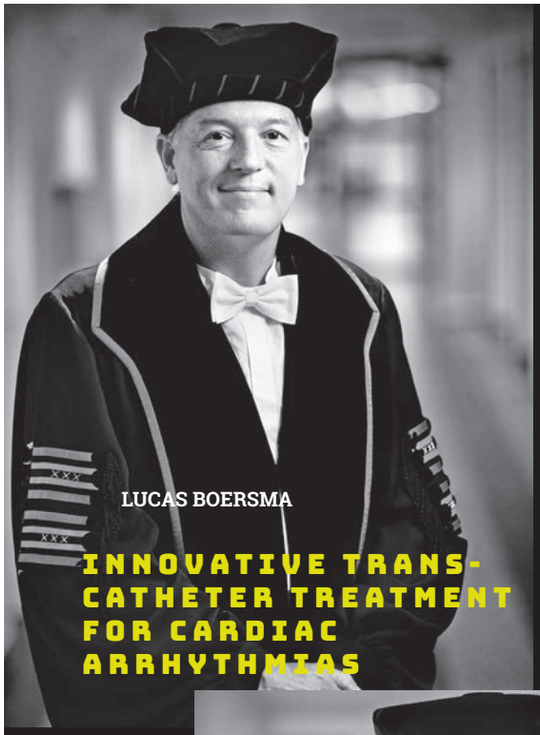
top:**Walter Paulus** (l), **Louis Handoko** (r)
bottom: **life time achievement award**
photo: Walter Paulus

amc

MEET OUR NEW PROFESSORS

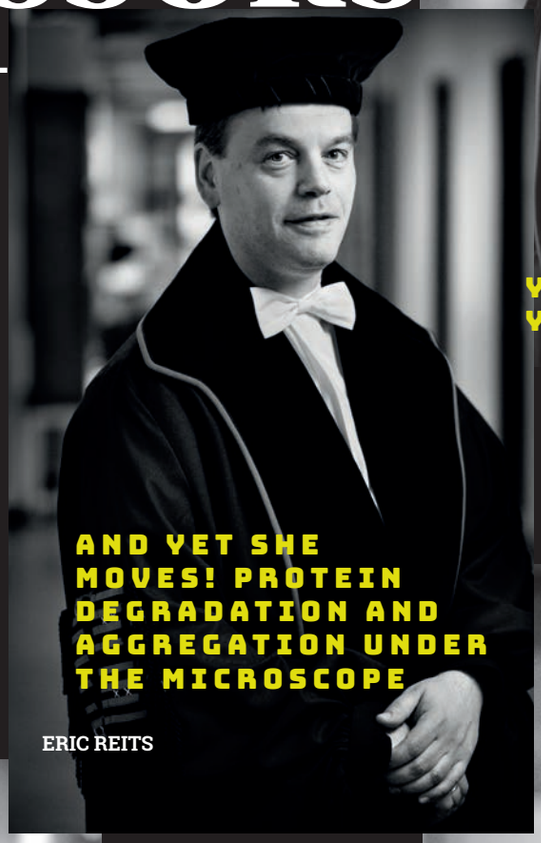
AART NEDERVEEN

YOU CAN'T SEE, WHAT YOU DON'T SEE



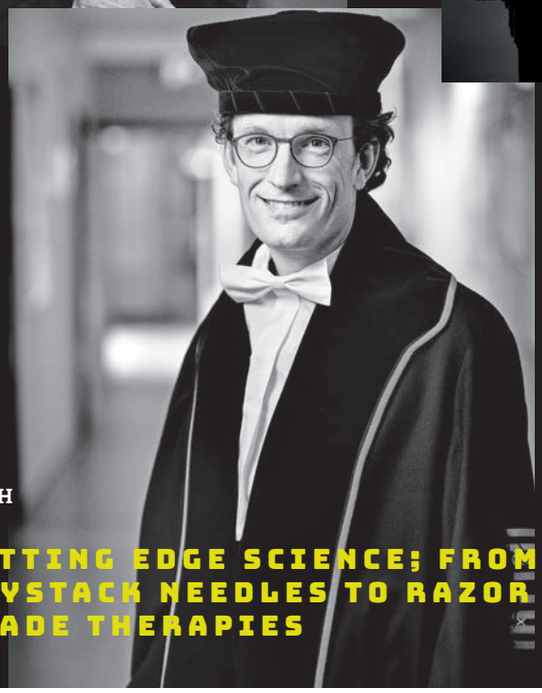
LUCAS BOERSMA

INNOVATIVE TRANS-CATHETER TREATMENT FOR CARDIAC ARRHYTHMIAS



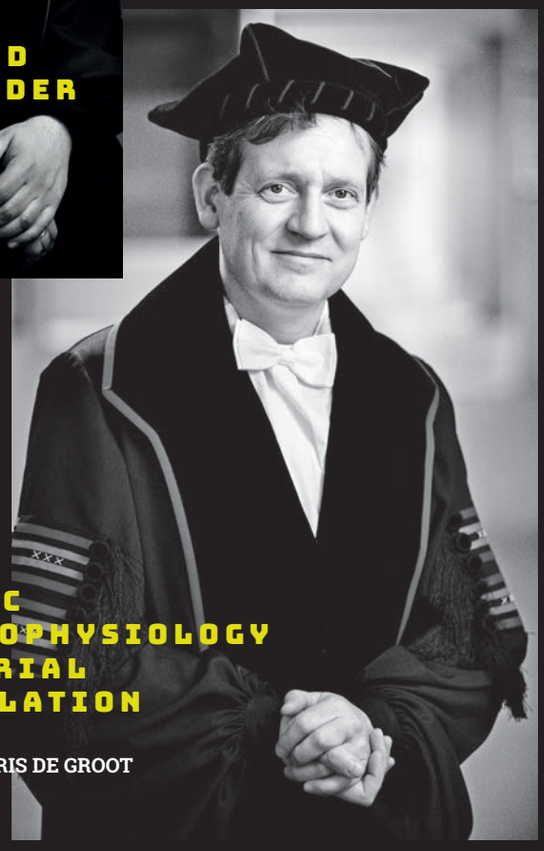
AND YET SHE MOVES! PROTEIN DEGRADATION AND AGGREGATION UNDER THE MICROSCOPE

ERIC REITS



KEES HOVINGH

CUTTING EDGE SCIENCE; FROM HAYSTACK NEEDLES TO RAZOR BLADE THERAPIES



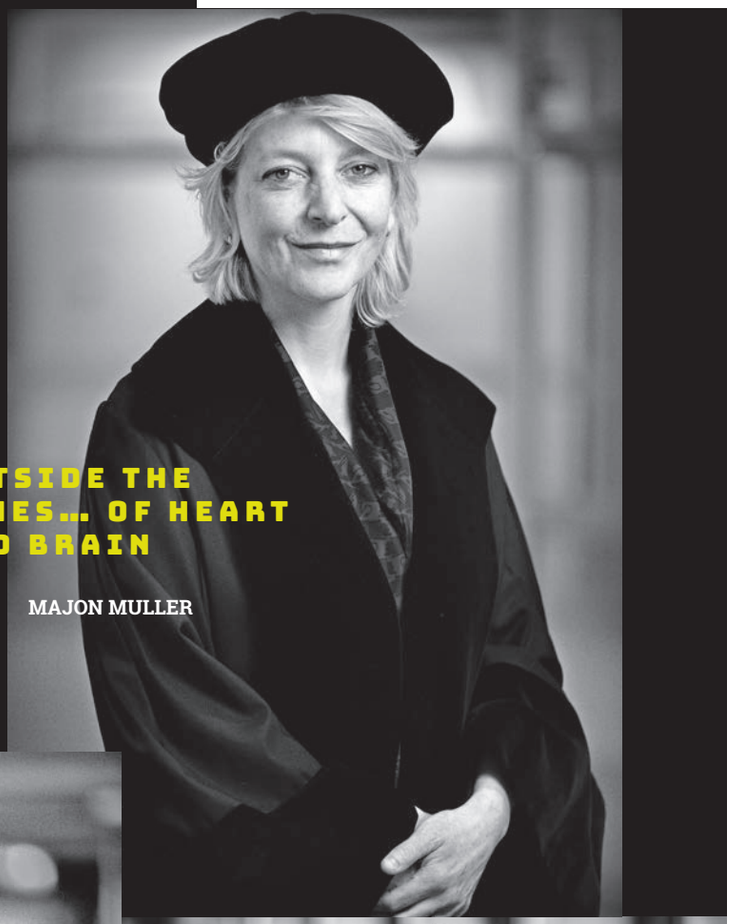
CARDIAC ELECTROPHYSIOLOGY AND ATRIAL FIBRILLATION

JORIS DE GROOT

VUmc

HARM JAN BOGAARD

MET HARTSTOCHT ELKE ADEMTOCHT. VOOR EEN LEVEN LANG LONGEN MET DE PERFECTE MATCH

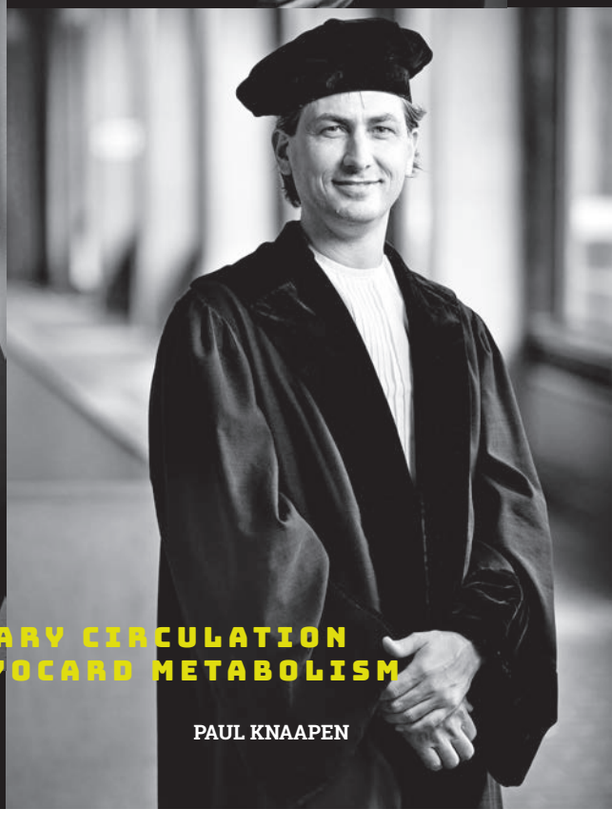


OUTSIDE THE LINES... OF HEART AND BRAIN

MAJON MULLER

THE VULNERABLE NEWBORN, TO WHAT EXTENT CAN WE ENSURE A HEALTHY ADULT LIFE?

MIRJAM VAN WEISSENBRUCH



CORONARY CIRCULATION AND MYOCARD METABOLISM

PAUL KNAAPEN

Personal Grants

Jolanda van der Velden, Physiology, Vici 2017: *Battling toxic protein in inherited cardiac disease*
A toxic protein causes inherited cardiac disease. We have strong indications that the toxic protein triggers an energy deficit in the heart that causes cardiac disease and sudden death. This project will establish key pathomechanisms triggered by the energy deficit leading to novel therapeutic approaches to treat disease.

Noam Zelcer, Medical Biochemistry, Vici 2017: *SPRING and a RING in lipid metabolism*
Our body needs cholesterol and fat, but in excess these are harmful and cause metabolic and cardiovascular disease. In this project, the scientists study the genes they found, SPRING and RING-finger-145 that regulate cholesterol and fat production. With these studies the researchers aim to develop new treatments for lipid-related diseases.

Willem Mulder, Medical Biochemistry, Vici 2017: *Nanobiologic training of innate immunity to treat disease*
Immunotherapy aims to empower the immune system to perform its natural role, to fight disease. In this project nanobiologics will be developed that reprogram a recently discovered innate immune memory – known as 'trained immunity' – to either induce immune tolerance and prevent transplant rejection, or provoke immunity to treat cancer.

Josine de Winter, Physiology, Rubicon 2017: *Energy for molecular dance*
The goal of this Rubicon project is to unravel how mitochondrial dysfunction contributes to contractile dysfunction in NEM6 myopathy, a disease that compromises muscle function. At Harvard Medical School (Boston, USA) I will use transgenic zebrafish to develop an assay to screen for compounds that improve mitochondrial function to restore contractile function in NEM6.

Ralf Harskamp, General Medicine, Rubicon 2017: *Influence of comedication on risk of bleeding with new anticoagulants*
This Rubicon grant allows for the investigation of the interaction and bleeding profiles of new anticoagulants in patients using multiple medications. The various projects that will fall under the grant are intended to strengthen the collaborative ties with an important international partner, the Duke Clinical Research Institute, one of the frontrunners in the field of cardiovascular research.

Jan van den Bossche, Molecular Cell Biology and Immunology, NHS Dekker senior postdoc 2017: *Targeting immunometabolic circuits in atherosclerotic plaque macrophages to improve their function and disease outcome*
Supported by a Netherlands Heart foundation senior research fellowship, we aim to understand the role of immunometabolic reprogramming in distinct macrophage subsets in human atherosclerotic plaques. By targeting specific metabolic pathways, the goal of our research group at the Department of Molecular Cell Biology and Immunology at VUmc is to improve macrophage function and atherosclerosis outcome.

ALL CANDIDATES

1 Vici candidates: **Jolanda van der Velden & Noam Zelcer**

2 Rubicon: **Ralf Harskamp**

3 NHS Dekker senior postdoc: **Jan van den Bossche**

4 Vici candidate: **Willem Mulder**

5 Rubicon: **Josine de Winter**

AMC GRADUATE SCHOOL

Marlies Stouthard (Director AMC Graduate School)

The AMC Graduate School organizes the doctorate level academic training for AMC PhD candidates. We register all AMC PhD candidates, provide a comprehensive PhD course program, monitor the PhD tracks and offer individual support. There are almost 1,650 active PhD candidates registered at the AMC. In 2017, 231 AMC PhD candidates successfully defended their theses. The PhD course program offers around 50 different courses to develop scientific skills, acquire transferable skills, and broaden and deepen scientific understanding. Each AMC PhD candidate follows an individual training program. A portfolio as part of the PhD thesis shows the acquired competences.

A standardized monitoring procedure strengthens the doctorate training. The individual Training and Supervision Agreement (to be submitted within the first three months) and the PhD Track Support (midterm monitoring) provide information and feedback on the process and progress of the AMC PhD projects. The AMC PhD Candidate Advisor offers support and advice to individual AMC PhD candidates upon their request, or in relation to the monitoring procedure. Supervisor support focuses on creating excellent supervisory arrangements aimed at optimal training of PhD candidates to become independent scientific researchers and highly qualified future professionals in an international environment.

Training PhD candidates to become independent researchers

Bettina Batista (l), **Marlies Stouthard** (r)

left to right: **Alexandra van Dissel, Thijs van Mens, Hayang Yang**

Thijs van Mens
(PhD candidate AMC)

The Graduate School PhD course program is a wonderful extra element for your PhD. It is always hard to plan ahead and make time for a course. But in my experience, the courses are almost always a very worthwhile investment of your time. You find yourself applying what you have learned without realizing that you had picked this skill or knowledge up from a course a few months earlier. I would recommend that every new ACS PhD student follow the relevant courses as early as possible, so that you can get the most out of it while working for your PhD.

Hayang Yang
(PhD candidate AMC, member of APROVE Science Night Committee AMC/VUmc)

Since 2010, APROVE has been organizing a Science Night for all AMC PhD students. This year, for the first time, we organized this event together with ProVUmc in line with the merging of AMC and VUmc. In order to start new collaborations and research projects, we have to get to know each other and what better place than the Science Night to do this! Science Night is a big social event for PhD students with fascinating talks about science and including dinner and drinks. The theme of the last Science Night 2018 was 'Science after tomorrow' with topics covering: designer babies, gender inequality in the research workplace, new statistical toolbox for big data, and possibilities of rehabilitation robots and exoskeletons. As part of APROVE and ProVUmc, Science Night Committee contributes to the aim of providing an opportunity where you can learn, develop and have fun with your fellow PhD candidates. So next year, we hope to see you all at the Science Night 2019!

Alexandra van Dissel
(PhD candidate AMC and APROVE board)

APROVE is the association for AMC PhD candidates (Amc PROmovendi-VEreniging). Founded in 2006, APROVE strives to offer both a professional and social network for PhD candidates at the AMC and its affiliated centers. The APROVE board has 12 PhD representatives from various research departments, including the department of Cardiology. Throughout the year, APROVE organizes a variety of events, where you can learn, develop your personal skills, explore your career options, but above all have fun and meet fellow PhD candidates. We believe meeting other PhD candidates is important for expanding your network beyond your comfort zone.

Events include the Science Night Symposium, Career Event, Thesis Printers Fair, Pimp my Workshops and the AMC-VUMC Zuiderzee Klassieker. From this year onwards, APROVE and ProVUMC will join forces to organize more events for both AMC and VUMC PhD candidates.

Furthermore, APROVE represents the AMC PhD students in the national PhD network and on the AMC Graduate School board.

VUmc Education Committee

COEN OTTENHEIJM (CHAIR OF THE EDUCATION COMMITTEE VUMC)

The PhD education committee has seven members, of which four are highly motivated PhD students and three are senior scientists in the ACS. The main responsibilities of the committee include approving the Education and Supervision plan of newly appointed PhD students, and organizing PhD symposia on 'special interest' topics (for example 'how to present your data in graphs'). To guarantee that the PhD student-members represent the wide variety of research topics of the ACS, they are recruited from four different departments (Intensive Care, Cardiology, Physiology, and Epidemiology & Biostatistics). The committee meets every two months.

Since April 2015, newly appointed PhD students are required to obtain 30 education credits during the course of their PhD research. The nature of these credits is part of the Education and Supervision plan, and the education committee checks whether the PhD student has included the mandatory courses (for example, 'Scientific Integrity'). The committee also provides the PhD student with advice on the alignment of the proposed courses with the PhD research topic. The PhD symposia inform the students on topics that are, typically, not covered in the mandatory courses. These symposia are well received and attended by a large number of PhD students.

Organisation by ACS scientists

Below the four student-members, each highlighting a topic that is central to the education of ACS PhD students.

MARLOES VAN DEN BERG (PHD CANDIDATE VUMC) – TRAINING/ OBP VUMC

The ACS education committee has been working to clarify the Doctorate Regulations of the VUmc for new PhD-students of the ACS and their supervisors. The regulations apply to PhD-students who started after the 1st of April 2015 at the VUmc, and means that students have to spend 840 hours (30 ECs) of their time on training. This is important, because if the training requirements are not met, the PhD-student will not be allowed to do his or her dissertation. To avoid this, new PhD-students have to make a Training and Supervision plan at the beginning of their PhD, and send this within the first three months to the ACS education committee. Here we check whether the proposed plan is complementary to the PhD-project, and whether it covers the 30 ECs. After approval the PhD-student can continue according to the training plan.

HEDER DE VRIES (PHD CANDIDATE VUMC) – ETHICS COURSE FOR VUMC

For me, the most important lessons were learning to recognize the 'gray areas' between solid scientific integrity and research misconduct. Scientists are confronted with these situations on a daily basis, for example authorship questions (who is an author, what is the order), sloppy statistics ('let's try another test, maybe then it will be significant?') and doing continued research on the ideas of others ('is this plagiarism, or is it improvement?'). The course makes you consider the implications of such situations, and provides you with practical tips to make these situations easier to discuss with your colleagues and supervisors.

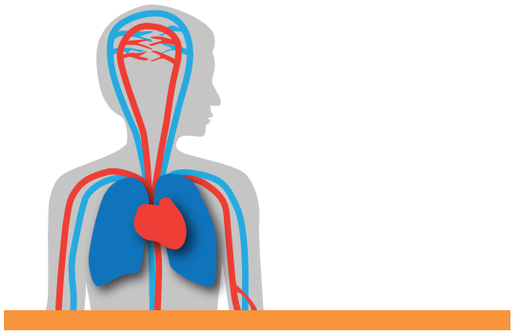
left to right: **Coen Ottenheijm, Erik Serné, Isabelle Vergroesen, Nina van der Hoeven, Marloes van den Berg, Sharon Remmelzwaal, Heder de Vries**

SHARON REMMELZWAAL (PHD CANDIDATE VUMC) - PAPENDAL COURSE FOR AMC/VUMC

The PhD training course is an annual course that takes place in October, is organized by the Netherlands Heart Institute and is held at the sport center Papendal. Each of the three programs (Atherosclerosis & Thrombosis, Cardiac Function & Adaptation, and Vascular Biology) offers a week of interesting presentations and stimulating assignments. Besides fun sports activities and good food, PhD students from ACS and other institutes have the chance to learn about each other's projects. This course is a great start for your research career in cardiology!

NINA VAN DER HOEVEN (PHD CANDIDATE VUMC) – PHD AFTERNOONS FOR AMC/VUMC

Every year the ACS education committee organizes two ''PhD afternoons'' for all ACS PhD students from both VUmc and AMC. It is mandatory for VUmc PhD students to attend one of these afternoons to receive education credits, but we encourage students go to all the PhD afternoons. The PhD afternoons are often organized on a Friday, are free and include lunch. The topics covered in the previous two PhD afternoons were: ''How to win a scientific poster award'' where tips and tricks on how to create an award-winning poster were exchanged, ''Kickstart your career'' where you were trained to impress at every job interview, and a statistics course where students could introduce their own specific topics. The PhD afternoons are very popular and to maintain their popularity we are keen to receive input on themes for upcoming PhD afternoons (email: ni.vanderhoeven@vumc.nl). We hope to see you all at the next PhD afternoon.



Cardiovascular consequences of Diabetes type II

Professor Max Nieuwdorp and Dr. Daniël van Raalte work together at the Amsterdam Diabetes Center and ACS on the pathophysiology and cardiovascular consequences of both type 1 and type 2 diabetes. Obesity and type 2 diabetes are reaching epidemic proportions worldwide. This has devastating effects as patients with diabetes suffer from macrovascular and microvascular complications, causing physical and psychological distress, and imposing a large financial burden on global healthcare systems. As current treatment strategies are unable to prevent type 2 diabetes and halt the complications of the disease, novel treatment options are being pursued.

Reduce cardiovascular mortality and diabetic kidney disease'

Max Nieuwdorp (l) and **Daniël van Raalte** (r)

Nieuwdorp and van Raalte run several translational research lines with a "from bench to bedside" approach. With studies of both type 1 and type 2 diabetes, involving the laboratory of experimental vascular medicine and the clinical research unit, they are also building large patient cohorts (bariatric surgery, fatty liver disease).

An important focus concerns the role of low-grade inflammation and the role of intestinal microbiota in cardiometabolic disease. Intestinal microbiota have been linked to the development of both type 1 and type 2 diabetes. Max Nieuwdorp has performed landmark intervention studies showing that fecal transplantation affects metabolic abnormalities. In his studies funded by a Vidi and LeDucq grants, he focuses on the interaction between microbiota and training of the intestinal immune system in type 1 and type 2 diabetes mellitus. More specifically, the search for involved plasma metabolites and bacterial strains is important as this may provide us with new diagnostic and therapeutic leads. Daniël van Raalte is studying the role of intestinal microbiota in dysfunction of the insulin-producing islets of Langerhans with personal fellowships from the

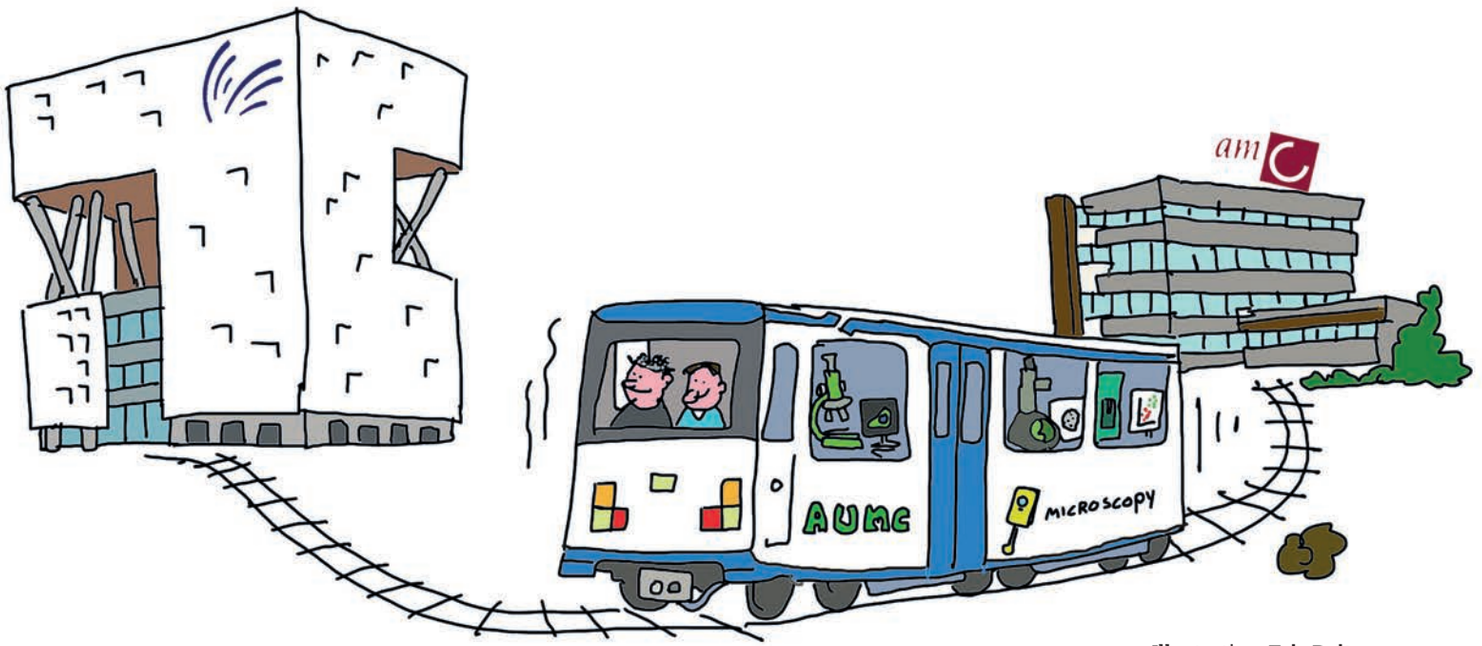
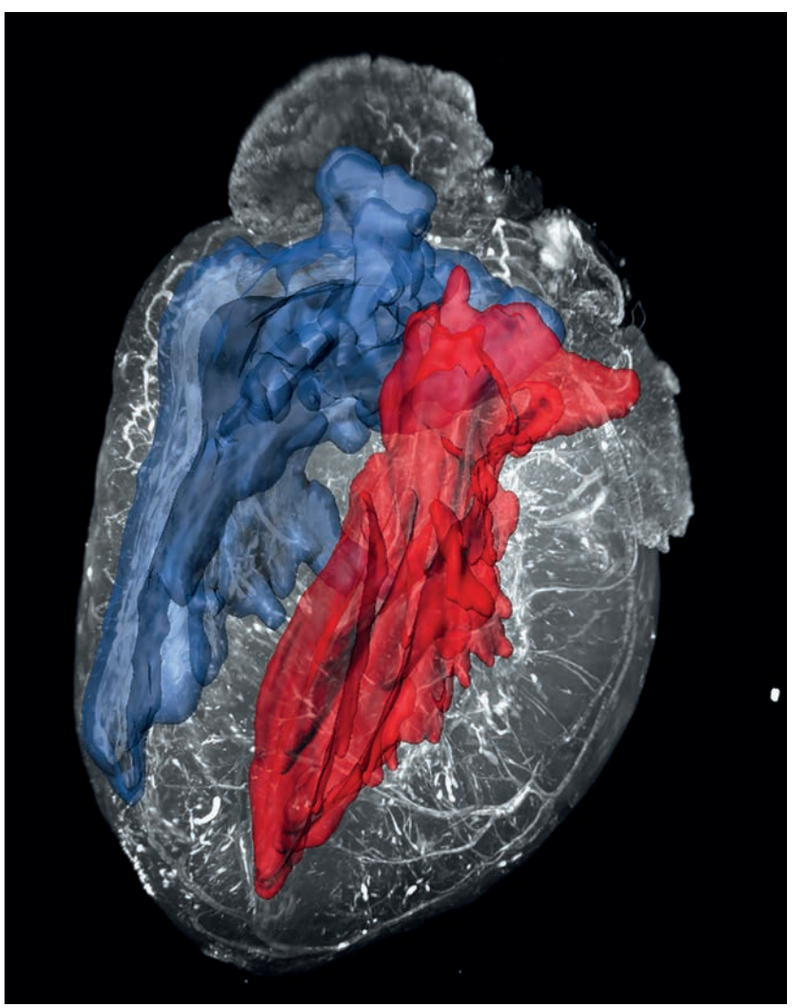


Illustration: **Eric Reits**

Dutch Diabetes Foundation and EU Marie Curie that have allowed for a postdoctoral internship in Vancouver at the University of British Columbia.

In addition to the more fundamental studies, van Raalte and Nieuwdorp collaborate with industrial partners to study effects of novel glucose-lowering medications that have recently become more readily available for type 2 diabetes patients. As such, sodium-glucose linked cotransporter (SGLT)-2 inhibitors and glucagon-like peptide (GLP)-1 receptor agonists were shown to reduce cardiovascular mortality and diabetic kidney disease in large trials. In studies involving state-of-the-art phenotyping of glucose metabolism, renal physiology, electrolyte homeostasis and functional imaging, the mechanisms underlying the cardiorenal benefit of these agents are being scrutinized.

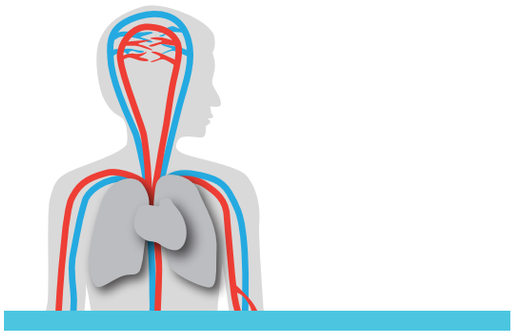
In the last three years Professor Max Nieuwdorp and Dr. Daniël van Raalte have been successful in building an enthusiastic research group that currently employs eight postdocs and 22 PhD students bridging the Amstel.



3D Lightsheet microscopic image showing the heart vasculature (white) with both atria and ventricles rendered in red and blue (the heart was made transparent using a special protocol developed at AO|2M).
Photo dr. R.J.P. Musters.

The Amsterdam Investigator-initiateD Absorb strategy all-comers trial – the AIDA trial

left to right: **Joanna Wykrzykowska, Ruben Tijssen, Jose Henriques**



Metallic drug eluting stents, coated with a polymer coating containing antiproliferative medication, have become the cornerstone of percutaneous treatment of atherosclerotic coronary artery disease. However, they have some shortcomings: the presence of these permanent metallic coronary cages, prevents complete arterial healing, impairs vasomotion and may be associated with the occurrence of neoatherosclerosis, incomplete endothelialization, and polymer hypersensitivity resulting in late and very late stent thrombosis. Bioresorbable scaffolds were designed to potentially overcome these remaining shortcomings of metallic drug eluting stents as they could theoretically allow for dynamic coronary vessel wall remodelling and late lumen enlargement after its expected resorption time.

In daily practice, the most commonly used bioresorbable scaffold was the ABSORB bioresorbable vascular scaffold (Absorb BVS). The Absorb BVS is composed of a polymer backbone coated with a drug & polymer matrix containing the antiproliferative drug everolimus, and is designed to be completely resorbed in 24-48 months.

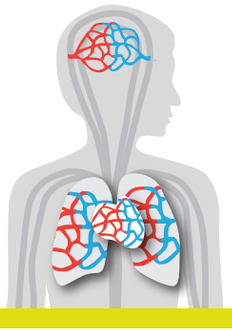
While the Absorb BVS obtained a CE mark in 2010 and shortly after gained acceptance in ordinary interventional practice, at the time that the AIDA trial started, there were no adequately powered, randomized studies addressing safety and efficacy in this setting. We therefore performed the AIDA investigator-initiated, non-inferiority, randomized trial comparing the Absorb BVS with the Xience everolimus eluting metallic stent in a patient population reflecting daily practice.

AIDA was a single-blinded, investigator-initiated, non-inferiority, randomized (1:1) clinical trial that enrolled 1845 patients in five centers across the Netherlands. The primary endpoint of the trial was target vessel failure (a composite of cardiac death, myocardial infarction and target vessel revascularization).

NEJM publication of preliminary results of the AIDA trial

After a safety review, the data and safety monitoring board recommended early reporting of the data of the AIDA trial because of safety concerns. The median follow-up was 707 days. There was no significant difference in the rate of target-vessel failure between the patients who received a bioresorbable scaffold and the patients who received a metallic stent. The bioresorbable scaffold was associated with a higher incidence of device thrombosis than the metallic stent over 2 years of follow-up.

After the review of the preliminary results of the AIDA trial, patients treated with the Absorb BVS, were advised by the Dutch Cardiology Society to contact their cardiologist in order to discuss restarting, or prolonging, dual antiplatelet therapy until 3 years following Absorb BVS implantation instead of 1 year (unless contra-indicated). The preliminary outcomes of the AIDA trial were presented at EuroPCR 2017, and were published in the The New England Journal of Medicine (NEJM) of June 2017. The complete 2-year results of the AIDA-trial are expected in Spring 2018. Absorb BVS is no longer commercially available in Europe. Long term follow up of AIDA and other studies will hopefully allow the gathering of knowledge necessary for the development of new generation bioresorbable devices. After the recent experiences with the current generation bioresorbable scaffolds, the Task Force of the European Association of Percutaneous Coronary Intervention recommended that future clinical trials with bioresorbable scaffolds versus metallic drug eluting stents should have its primary end-point after complete resorption of the scaffold.



The Leducq Epigenetics of Atherosclerosis Network

Epigenetic processes are regulatory mechanisms that control how the DNA of cells is used. Epigenetics is best characterized in developmental biology and we know that epigenetic processes tightly regulate organ development and cellular specialization. Over the past decade, particularly because of technological advances, such as large scale sequencing approaches, there is an increased understanding that all cellular responses are regulated by epigenetics. In the field of immunology we now know that epigenetic remodeling of the genome heavily controls immune responses.

For our "Leducq Epigenetics of Atherosclerosis Network" (LEAN), we have brought together clinicians, cell and molecular biologists and experts in epigenetic pharmacology to study how inflammatory cells (mainly monocytes and macrophages) are regulated by epigenetic processes and thereby control development of atherosclerotic disease. The conception of LEAN originated from several AMC Ruysch lectures that led to discussions on setting up collaborations for epigenetics. It has also been building on a network of scientific friendships that had already developed over the previous decades. In 2013, Chris Glass from UCSD and Menno de Winther from AMC applied for a transatlantic network program from Leducq and following two unsuccessful rounds were awarded the grant in 2016.

In cardiovascular patients or patients at risk for developing cardiovascular disease cohorts we are investigating how changes in the epigenetic profile of monocytes and macrophages associate with disease. We are also investigating new pharmacological approaches, including those targeted at the enzymes that control epigenetic processes to suppress monocyte and macrophage activation in disease. In addition to this, we are searching for novel epigenetic enzymes that are relevant for atherosclerosis development.

Epigenetic remodeling of inflammatory cells'

On the team of Menno de Winther at the AMC, Koen Prange and Tanya Kuznetsova (both postdocs) together with Lisa Willemsen (PhD student) are working on several aspects of the Leducq project. We are investigating human cohorts, from Lille (Bart Staels group) and the AMC (Erik Stroes) to single out characteristic epigenetic changes that associate with disease. Moreover, we are setting-up innovative new ways to investigate epigenetics in extremely low cell numbers to allow detailed characterization of precious patient samples.

Every six months we have Leducq consortium meetings alternating between Europe and the US. The consortium aims to advance the field of epigenetics of atherosclerosis by synergistically collaborating. The groups bring together different areas of expertise and are highly dedicated and involved. There is a great deal of exchange of ideas, techniques and reagents. Furthermore, young investigators get to spend time in the different labs. The Fondation Leducq funding has really given us the opportunity to make great advances in the field. With our consortium, we aim to define how epigenetic processes affect inflammation in disease development and whether interventions in the epigenome can be used to influence disease outcome.

left to right: **Lisa Willemse, Koen Prange, Tanya Kuznetsova, Menno de Winther**

ACS SYMPOSIA AND CONFERENCES 2018 - 2019

Amsterdam Cardiovascular Sciences Activities 2018

FEBRUARY 5	Microcirculation
MARCH 5	Diabetes & Metabolism
APRIL 9	Heart Failure & Arrhythmias
MAY 7	Atherosclerosis & Ischemic syndromes
JUNE 4	Pulmonary Hypertension & Thrombosis
JULY 5	4th ACS conference, Oosterkerk
SEPTEMBER 3	Diabetes & Metabolism
OCTOBER 1	Microcirculation
NOVEMBER 5	Heart Failure & Arrhythmias
DECEMBER 3	Atherosclerosis & Ischemic syndromes

Amsterdam Cardiovascular Sciences Activities 2019

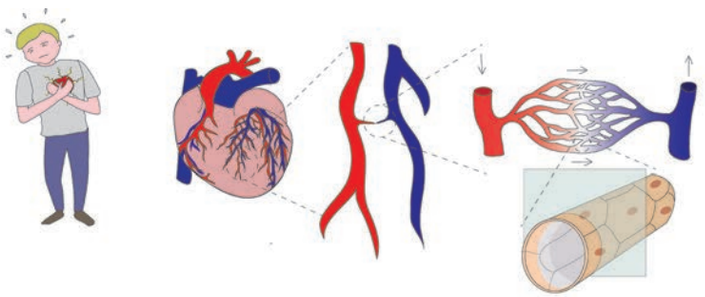
FEBRUARY 4	Pulmonary Hypertension & Thrombosis
MARCH 4	Diabetes & Metabolism
APRIL 1	Microcirculation
MAY 6	Heart Failure & Arrhythmias
JUNE 3	Atherosclerosis & Ischemic syndromes
JULY 4	5th ACS conference, Oosterkerk
SEPTEMBER 2	Pulmonary Hypertension & Thrombosis
OCTOBER 7	Diabetes & Metabolism
NOVEMBER 4	Microcirculation
DECEMBER 2	Heart Failure & Arrhythmiass

Impressions of monthly ACS Symposium and Buffet

The Microcirculation

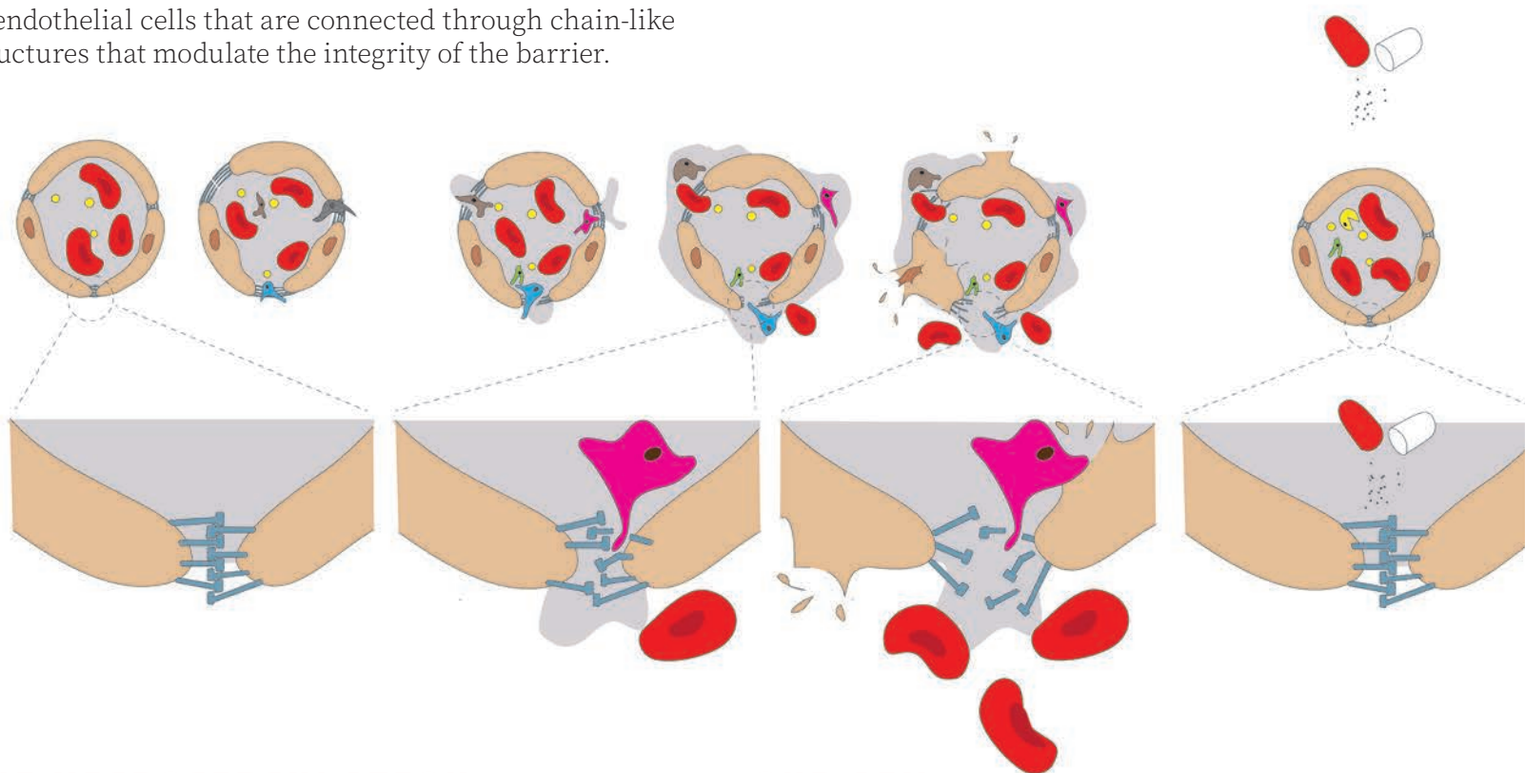
INFLAMMATION

Inflammation weakens the barrier, enabling the passage of white blood cells. However, with chronic inflammation and high blood pressure, the chain-like structure can rupture, resulting in the outflow of blood plasma, i.e., the vessels become leaky. When the barrier further loses integrity and endothelial cells become damaged, then even red blood cells can leak through the vessels.



THE ENDOTHELIUM

The endothelium - the inner lining of a blood vessel – forms the barrier between blood and tissue. This barrier consists of endothelial cells that are connected through chain-like structures that modulate the integrity of the barrier.



THE MICROCIRCULATION

The microcirculation – an extensive network of the smallest blood vessels – is responsible for the delivery of oxygen and nutrients and for the removal of waste products at the cellular level.
The microcirculation is essential for keeping organs vital, including the heart.

OUR AIM

Our aim is to prevent vessel leakage in order to preserve cardiac function.
Our focus is on maintaining barrier function by strengthening the chain-like structures that keep the endothelial layer intact.

ACS awards 2017-2018

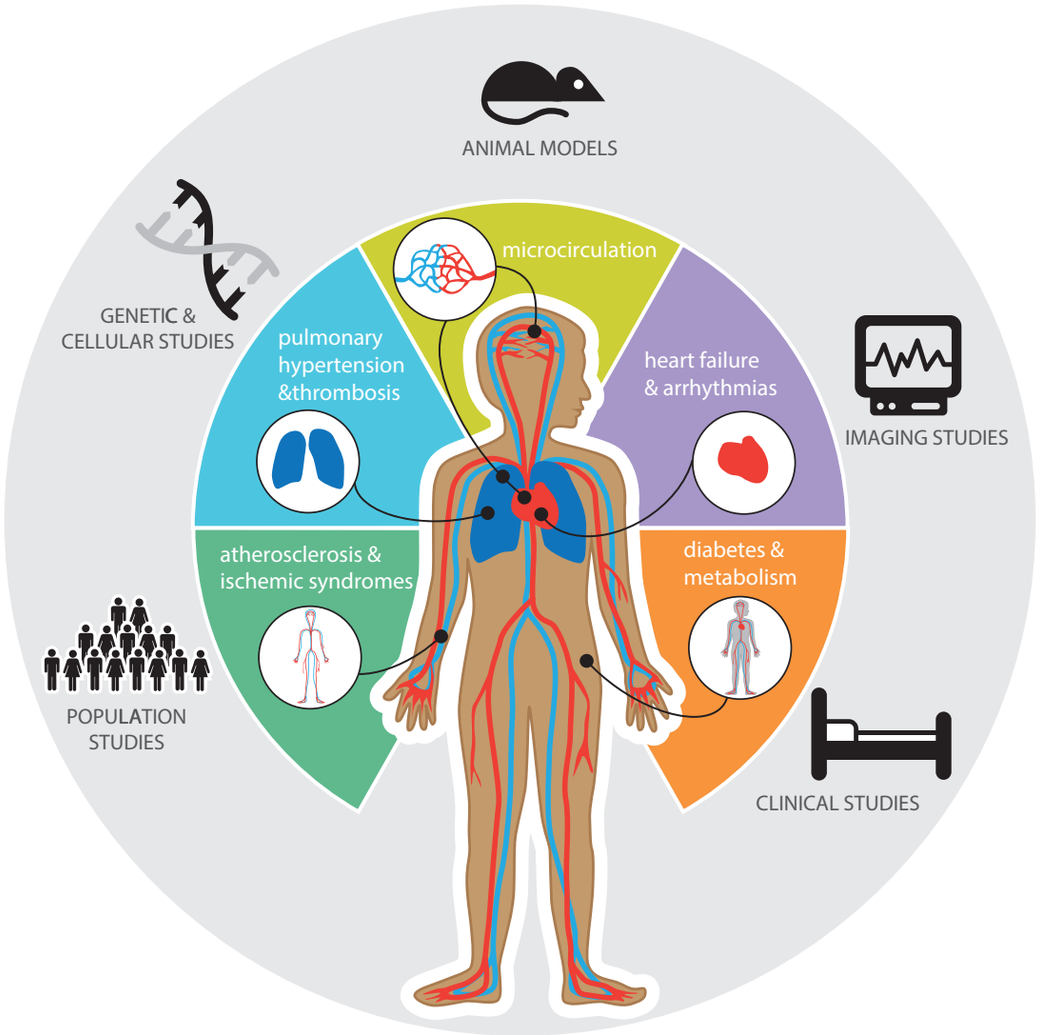
2017

Peter Hordijk & Stephan Huveneers	The Push and Pull of (dys) balanced endothelial integrity	OIO
Reinier Boon & Riekelt Houtkooper	The role of long non-coding RNAs in regulating cardiac metabolism during aging	OIO
Carlie de Vries, Ed Eringa, Daniel van Raalte & Max Nieuwdorp	Prevention of aging-related type 2 diabetes and vascular disease through LIM-domain only protein FHL2	OIO
René Musters	Extension of the Leica TCS SP8 STED 3X platform with a OKO-labs microscopy environment, with climate control and live-cell stage incubator together with a Navigator-stage-module extension of software possibilities	ACS-VUmc Equipment grant
Peter Hordijk & Carlie de Vries	96 well ECIS machine and Reader (Extension)	ACS-VUmc Equipment grant
Harm Jan Bogaard & Robert Szulcek	GentleMACS tissue dissociator with MultiMACS 24 cell separator	ACS-VUmc Equipment grant

2018

Coert Zuurbier & Jolanda van der Velden	Targeting genetic heart disease with diabetes medication	OOTB
Carol Ann Remme & Diederik Kuster	Keeping cardiomyocytes dynamic and exciting: a novel approach to prevent mechanical and electrical dysfunction in cardiomyopathy	OOTB
Noam Zelcer & Elga de Vries	The nuclear receptors Liver X Receptors (LXRS) couple lipid metabolism to control of vascular integrity of the blood-brain barrier	OOTB
Louis Handoko & Ot Bakermans	TrimetaziDine as a Performance-enhancING drug in heart failure with preserved ejection fraction (DoPING-HFpEF)	OOTB
Leo Heunks, Coen Ottenheijm & Janneke Horn	Positive end expiratory pressure (PEEP) applied during mechanical ventilation as a novel mechanism to explain critical illness associated diaphragm weakness	OOTB
Yu-Sok Kim & Johannes van Lieshout	Effect of treatment modality on cerebrovascular control and cognitive function in patients with end-stage renal disease - hemodiafiltration vs. hemodialysis	OOTB
Peter van Tintelen & Bianca Brundel	A giant molecule underlying a major disease?	OOTB
Ibrahim Danad	CT perfusion Imaging for the assessment of functionally relevant CAD as Indexed by 15O[H2O] PET and Fractional Flow Reserve	MD/PhD
Rik Olde Engberink	The endothelial surface layer as orchestrator of interstitial Na+ homeostasis	MD/PhD
Ralf Harskamp	Triage in acute chest pain evaluation in primary care (TRACE)	MD/PhD
Thijs van Mens	Defining the role of gut microbiome pathways in venous thromboembolism pathophysiology	MD/PhD
Debbie Kalkman	Prevention of in-stent restenosis in diabetic patients with coronary artery disease	Postdoc
Marit Wiersma	LMNA and DES mutations: Undissolved role for cardiomyocyte proteostasis and AF promotion in familial atrial fibrillation	Postdoc
Paul Wijnker	A disturbed redox-balance triggers cardiac disease in inherited cardiomyopathy	Postdoc
René Musters	Extension of AO/2M Nikon A1-DUS MULTISPECTRALE-DETECTOR, improvement of platform functionality	ACS-VUmc Equipment grant
Diederik Kuster & Charissa van den Brom	Fluorescent Western blot imager	ACS-VUmc Equipment grant
Yu-Sok Kim & Frans van Ittersum	Trans Cranial Doppler	ACS-VUmc Equipment grant
Yu-Sok Kim & Frans van Ittersum	Servo-controlled finger plethysmograph (Nexfin® or ClearSight EV1000®)	ACS-VUmc Equipment grant

Amsterdam Cardiovascular Sciences



Amsterdam UMC
Universitair Medische Centra