# ACS 2019

JULY 2019

One Scientific Research Board of ACS

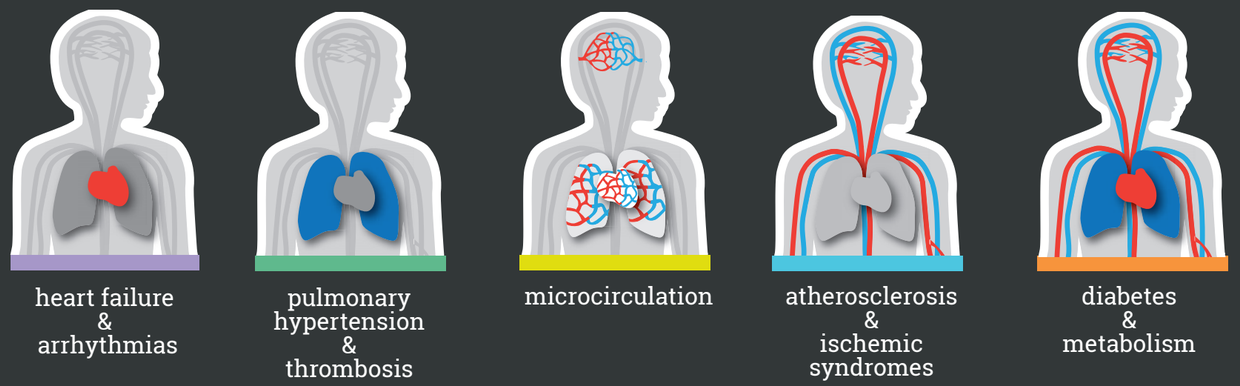
Meet our new professors

## First ACS PhD retreat

## Vascular surgery at Amsterdam UMC

**Mission** To design novel treatment strategies to prevent and cure cardiovascular disease.

**Vision** To strengthen our top European Cardiovascular Research Institute by organizing education, research and clinical activities within the current 5 Research Programs.






# PhD students in the lead for ACS

**Bert Groen & Jolanda van der Velden**
Directors of the ACS

While many of our 'senior' scientists (principal investigators) have been extremely successful with publications in high-impact journals and in obtaining prestigious personal and consortium grants, the future of the research institute very much depends on the young ones. The active involvement of Young ACS in the organization of our annual conference and monthly symposia has been greatly appreciated. Moreover, many young scientists were awarded prestigious personal externally funded grants, and we have been very impressed with the high quality of research proposals and presentations by postdoctoral students at the ACS postdoc grant interviews. This year, the first PhD retreat was organized by eight enthusiastic PhD students from both sides of the Amstel river. They put together a wonderful program including exciting workshops, where the PhD students were leading the presentations and discussion. Yes, there is a lot of potential among our future principal investigators. But what exactly is the definition of 'young' and 'senior'? Grant restrictions are based for example on age or time limitations after obtaining a PhD, with extensions possible for clinical training, number of children, or any other life event which has a proven 'negative' impact on your career. Funding agencies struggle with age-related criteria, and at the same time, ageing appears to be a flexible term in a society which is becoming older and older.

Whether we are young or old, we all try to stay young at heart. And as life expectancy continues to increase, we are joining in the efforts to prevent biological ageing of our cardiovascular system in line with our ageing bodies. One of the uniting topics of ACS scientists is vascular ageing. ACS researchers have been joining forces to better understand the ageing process of the vasculature that has an impact on the function and quality of the vital organs in our bodies. It is here, in the heart, lungs, brain and kidneys, where we aim to enhance quality of life. Not only by telling people to improve their way of life by not smoking, exercising more, and not drinking alcohol, but also through the identification of pathophysiological and genetic factors that prime the body for advanced ageing, and which may be tweaked to prevent disease and improve quality of life.

*Bert Groen & Jolanda van der Velden*


## CONTENTS


5 Scientific Research Board of ACS

6 ACS PhD retreat: the first edition

8 Numbers & Facts

9 Cardiovascular Aging

10 PAREL-AAA: synergy between AMC and VUmc vascular surgery

12 Pulmonary Hypertension Research at Amsterdam UMC

14 Meet our new professors

16 ACS symposia and events 2019-2020

17 Biological insights to find novel therapies for treatment-resistant forms of heart failure

18 Personal grants

21 "Mend a broken heart"

22 The diaphragm: a vital pump

24 PhDs in the spotlight

26 Preventainment

27 ACS awards 2018-2019



**Colophon:**

**Design and layout:** Karen Folkertsma
**Photographs:** DigiDaan
**Drawings:** Josine de Winter & Pleuni Hooijman (Sketch University)
**English editing:** Lisa Kohn

**Directors ACS:** Bert Groen & Jolanda van der Velden

**Coordination:**
Anne-Lieke van Deijk
Bert Groen
John van Meer
Jolanda van der Velden
Isabelle Vergroesen

**Website:**
www.amsterdam-cardiovascular-sciences.org


# Scientific Research Board of ACS

As of January 2019, Amsterdam Cardiovascular Sciences (ACS) has a single joint Research Board for both locations of Amsterdam UMC. The board of directors of Amsterdam UMC has asked ACS and Amsterdam Neurosciences to start a pilot in which research protocols, originating from either location, undergo a similar evaluation by the Research board of ACS, before being submitted to the respective METC.

*Research protocol requests can be sent to i.vergroesen@amsterdamumc.nl for evaluation.*

## WHAT IS THE GENERAL PROCEDURE?

Any researcher who needs permission from the METC to perform research with patients has to fill out a special form that was developed for ACS VUmc in 2017. In December 2018, with the help of experienced clinicians, the form was improved in combination with an evaluation form for reviewers of the research institute.

There are 10 items that are scored to assess the quality of the study design. If needed, the reviewer will formulate questions about parts of the protocol that are unclear in order to optimize the protocol before submission to the METC. If the reviewer has serious objections/concerns, a second reviewer will be asked to give his/her opinion. The researcher is then asked to respond to all questions. After receiving the researcher's answers the reviewer(s) will either approve or disapprove the protocol request.

If the protocol is approved, an approval letter will be sent to the researcher, with the full report of the evaluation process, including the reviewer(s) questions and answers of the researcher. This should aid the METC in their decision. The communication(s) between researcher and ACS will be forwarded to the METC.

## WHAT IS THE ROLE OF THE RESEARCH BOARD?

The Research Board has a monitoring function and evaluates research protocol on scientific content along the points indicated on the form supplied to the applicants. In addition, as the ACS Research Board consists of clinicians from different specialties, study protocols may benefit from broad and specific knowledge (e.g. epidemiology, and specific interventions). The monitoring process thus aims to improve the overall quality of study designs, and partially moves the scientific evaluation process from METC to ACS. The Research Board meets every 3 months to review all approved protocols. The board will strive to respond within a period of two weeks so that the submitted protocols will be quickly evaluated. The board also has the flexibility to evaluate and adjust the process if necessary.

**Majon Muller,** chair Scientific Research Board of ACS

Top to bottom and left to right: Bert Groen, Peter Hordijk, Dop Simonides, Frances Handoko-de Man, Hilde Herrema, Angelique Spoelstra-de Man, Jolanda Kluin, Marc Vervloet, Esther Lutgens, Harm Jan Bogaard, Bert-Jan van den Born, Isabelle Vergroesen, Connie Bezzina, Jolanda van der Velden, John van Meer, Max Nieuwdorp.

# ACS PhD retreat: the first edition

This year the first edition of the ACS PhD retreat took place on the 14th and 15th of March at the conference hotel Kontakt der Kontinenten, in Soesterberg. ACS glossy reporter John van Meer interviewed the organizing committee about the retreat.

**Who initiated the idea for the retreat?**

The idea for the retreat was initiated by ACS directors Jolanda van der Velden and Bert Groen and was enthusiastically received by members of the education committee of the VUmc. Sharon Remmelzwaal and Marloes van den Berg, both PhD students and members of the education committee, were happy to put this plan into action. A small survey was sent out to ACS PhD students and eight of them were willing to help in organizing the retreat. This group is a nice representation of the clinical and preclinical researchers from both sides of the Amstel: Jisca Majolée, Sabine van Oort, Sanne Verberk, Jeske van Diemen, Ingrid Bistervels, Roisin Bavalia, Jolien Neefs and Twan van Velzen.

**What was the goal of the retreat?**

As a committee our main focus was to bring ACS PhD students together, to learn about each other's research projects and, of course, have some fun and relax! This was quite a challenge because we wanted to offer the attending PhD students a chance to present their research projects, without the jam-packed schedule you sometimes see at other scientific conferences.

**How was the scientific program put together?**

To avoid a full schedule, we chose to have short scientific parallel sessions instead of long plenary sessions. These sessions had a nice variation of short oral presentations, and pitches about new research projects, with plenty of time for discussion. These were alternated with workshops and moderated walks through the posters.

Of course, there were also plenary sessions, for example at the start of the retreat ACS director Jolanda van der Velden officially opened the two days, and she and Bert Groen moderated the first plenary session. In this session, three nominated speakers competed for the best abstract award. The favorite presenter, chosen by the audience, won a prize of 150 euros!

In addition to the sessions, we invited keynote speakers to both days: Max Nieuwdorp told us an inspiring story about his research, and Menno de Bree closed the retreat with a critical note about work and happiness.

**That sounds like a full scientific program, was there also some time for social activities?**

Yes, as we said before, the idea of the retreat was to bring ACS PhD students together. Frequent coffee breaks between sessions and enough time for good food and conversation during breakfast, lunch and dinner gave the PhD students the opportunity to have some social time. On Thursday evening, we organized a pub quiz with fun questions and a lot of musical intermezzos, followed by drinks in the bar.

**How does the organizing committee look back on the retreat?**

We are very satisfied and proud to say that the first PhD retreat was a success. The organization went smoothly, and everything went according to plan. The relaxed and open atmosphere of the retreat contributed to an environment where PhD students dared to ask questions during presentations and network with each other. Finally, the location was perfect for the retreat, we had a lot of help from the friendly staff.

## The PhD retreat brings ACS PhD students together

**Will there be a second edition of the ACS PhD retreat?**

As far as we are concerned, yes! We think that a retreat is a great way to meet new people and get to know the various research topics in the ACS. Furthermore, we think that having an annual PhD event helps the PhD students to feel connected with and involved in ACS.

We are already looking for enthusiastic PhD students who want to help organize next year's PhD retreat. **If you're interested: send an email to acsretreat@gmail.com. We are looking forward to the next edition!**

Impression of the first ACS PhD retreat

**Save the date: next ACS PhD retreat will be on March 12-13, 2020!**

# Numbers & Facts

## Symposia organized last year

2 annual meetings: 4th Annual ACS Meeting and 9th Rembrandt Symposium
1 ACS PhD retreat (2 days)
9 monthly ACS symposia, 5 of which were pitch events where ACS PIs pitched their research
571 scientist and students subscribed and attended the monthly symposia
79 educational lectures and discussions at these symposia

## ACS grant rounds organized last year and starting in 2019

1 PhD call resulting in 3 ACS PhDs
1 Out of the Box call resulting in 4 grants of €25,000
1 Postdoc call resulting in 2 postdoc positions of € 70,000
1 Equipment call resulting in 2 grants of a total € 114,000

## ACS published in 2018

1 ACS glossy
27 ACS newsletters

## ACS PhD defenses and inaugural lectures in 2018

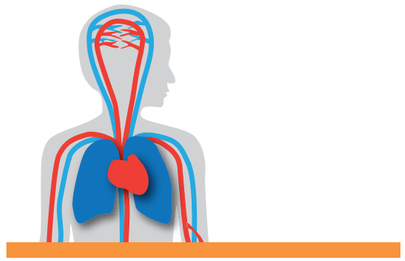
66 PhD defenses
7 Inaugural lectures

## ACS members in 2019

420 PhD students
77 Postdocs
159 Principal Investigators
110 Staff members



# Cardiovascular Aging



The Cardiovascular Aging Research Group was started in 2016 by Professor Majon Muller, internist and head of the department of geriatrics. The group consists of 3 senior researchers, 1 postdoc, 4 PhD students, a data manager and several talented (medical) students. Close collaboration exists with the department of Vascular Medicine, the Cardiology department and the Alzheimer Center.

Cardiovascular diseases (CVD), including coronary heart disease and stroke, are the main causes of death in the Netherlands and in the western world. The vascular aging process that underlies this is a complex process in which endogenous (genetic, epigenetic) and exogenous (lifestyle, cardiovascular) risk factors interact. These risk factors eventually lead to various cardiovascular phenotypes ranging from healthy or 'cardiovascular fit' to 'cardiovascular frail'. Thanks to better and more effective treatments, the number of people with chronic CVD has increased enormously. This larger group of elderly patients with CVD faces a multitude of problems including polypharmacy, cognitive and physical functional disorders and a reduced quality of life. It is precisely in this large elderly CVD patient group that standard treatment strategies (according to the guidelines) are less effective.

At the first, recently opened, Heart-Brain Center in the Netherlands, we are striving to improve clinical care for elderly patients with chronic cardiovascular diseases and to make connections with scientific research for this patient group.

The Heart-Brain Center and the Cardiovascular Aging research group have a number of ongoing studies.

1. We have been investigating whether blood pressure changes in the elderly with a vulnerable vascular system, lead to changes in cerebral blood flow and brain pathology.
2. In a broader context, we have been participating in research in prescribing and deprescribing of cardiovascular preventive drugs in frail older populations. An important question is whether we should use other target values in vulnerable elderly patients with respect to, for example, blood pressure and glucose values.
3. We have been investigating the role of the gut microbiome in the aging of the heart-brain connection.
4. We have been actively engaging in identifying frail elderly patients with CVD and in setting-up innovative care-programs for elderly patients with CVD using value-based health principals.

**Vascular aging underlies cardiovascular diseases**

Presenting results during the research meeting

# PAREL-AAA: synergy between AMC and VUmc vascular surgery

## Unraveling the pathophysiology of aortic aneurysms and updates of treatment through a multicenter joint data, image and bio-bank

KAK KHEE YEUNG, RON BALM, WILLEM WISSELINK, MARK KOELEMAIJ, JAN BLANKENSTEIJN, VIVIAN DE WAARD, DINK LEGEMATE

top to bottom and left to right: **Research group: Jan Vrijdag, Nick van Reijen, Reza Indrakusuma, Sana Mulay, Anna Geraedts, Stefan Smorenburg, Sylvana de Mik, Chantal Stockem, Marjolein de Wit, Sabrina Doelare, Victoria Tedjawirja, Natalija Bogunovic, Kak Khee Yeung, Orkun Doganer, Rutger Lely, Willem Wisselink**

**Introduction**

Abdominal aortic aneurysm (AAA) is a pathologic dilatation of the abdominal aorta. It is a widespread condition with ~5000 hospital admissions per year in the Netherlands. The natural course of AAA is to grow and rupture, which causes massive bleeding and is associated with a mortality rate of up to 80%. At present, the pathophysiology of aneurysmal disease is still unclear, limiting the ability to develop non-surgical treatments for prevention and/or stabilization of aneurysms. Various factors are implicated in the development of AAA pathology: lifestyle (including smoking), aging, atherosclerosis, biomechanical stress on the aortic wall (hypertension) as well as genetic factors.

To better understand AAA pathophysiology and its natural course, it is imperative to carry out research, which combines, genetic factors, biomarkers with longitudinal data and imaging markers.

**AAA bank**

A multicenter databank, biobank and image-bank has been established in the Netherlands: the 'Parel Aneurysma van de Abdominale Aorta' (The Pearl of Abdominal Aortic Aneurysm) (AAA-bank). The AAA-bank was created by the collaboration of the Amsterdam UMC (Academic Medical Center Amsterdam (AMC) and VU medical center (VUmc)) and Leiden University Medical Center (LUMC). All adults with AAA fitting the criteria will be included for as long as they are being treated by their vascular surgeon. At every patient contact, clinical data and imaging data are collected and stored in the central databank. Biomaterials are also collected during follow-up visits including blood for DNA and RNA, urine and AAA tissue; the latter is collected only if open surgical repair was performed. In addition to the AAA-bank, we also have a LIVE biobank of cultured smooth muscle cells, fibroblasts and live sectioned aortic tissues and a vibratome so that we can conduct stimulation in-vitro experiments.

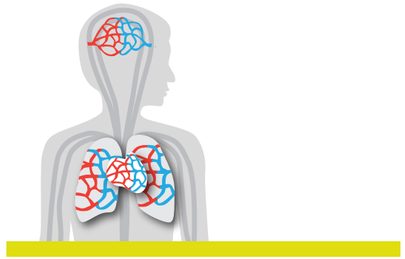
**Aims**

1. To gain insight into the pathophysiology of AAA.
2. To gain more knowledge about the rupture risk of AAA.
3. To evaluate and improve treatment of patients with an AAA.

**Studies**

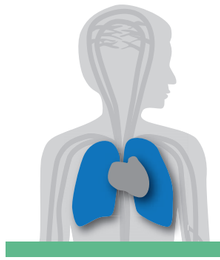
The aorta is essentially a large muscular tube that transports blood to the organs. The medial layer is the thickest, consisting of vascular smooth muscle cells (SMC) and extracellular matrix (ECM). SMC can be either, contractile to sustain blood pressure or synthetic to produce ECM to preserve the structure of the aortic wall. One of our main basic-research lines is the study of the contractile and proliferative function of SMC. We relate the latter findings to rupture, aneurysm growth rate and genetic mutations. We are currently building 3D bio-engineered vessels with SMC and endothelial cells of AAA patients to investigate factors like shear stress, pressure, and to perform stimulation experiments with hormones and a number of different medications. Patient studies focusing on the outcome differences between genders are also being conducted. Another of the patient studies being carried out with the collected biomaterials is the 'Predicting aneurysm growth and rupture with longitudinal biomarkers' (PARIS) study. The PARIS study aims to determine the association between AAA progression and the evolution of serum levels of proteases and cytokines.

Together we are providing new insights into pathophysiology, which will eventually lead to effective medical therapies and prevention of aortic aneurysms and rupture.



**Preventing abdominal aortic aneurysms and rupture**

Principal Investigators **Jan Blankensteijn, Dink Legemate, Vivian de Waard, Ron Balm, Kak Khee Yeung, Willem Wisselink**



# Pulmonary Hypertension Research at Amsterdam UMC

Part of the research in the department of Pulmonary Medicine is focused on the disease Pulmonary Arterial Hypertension (PAH). This is a devastating disease characterized by progressive remodeling of pulmonary arterioles resulting in increased pulmonary vascular resistance and pulmonary artery pressure. The right ventricle (RV) of the heart that pumps blood through the pulmonary circulation has to cope with a 5-fold increase in afterload. Eventually, PAH patients die of RV failure.

Our current research can be divided into three themes:

1. Early diagnosis
2. Pulmonary vascular remodeling
3. Right ventricular heart failure

**1. Early diagnosis**

Although current PAH drugs offer no cure, early and aggressive treatment of PAH with vasodilators is associated with an improved outcome. Unfortunately, because the initial symptoms of PAH are relatively nonspecific (e.g. fatigue and exercise intolerance), a diagnosis of PAH is rarely made at an early stage. Patients seldom seek medical advice, and physicians usually don't recognize PAH until it is too late and severe right ventricular heart failure has already developed. As a result, PAH is detected late in the course of the disease with a majority of patients already displaying severe functional and hemodynamic compromise. Therefore, we are currently developing imaging methods and biomarkers that will help in the detection of the disease when it is at its most modifiable stage (CVON-DOLPHIN, CVON-PHAEDRA-IMPACT, OPTICS).

**2. Pulmonary vascular remodeling**

The transforming growth factor beta (TGFβ) family plays an important role in the pathobiology of PAH. In approximately 1 in 4 patients, a genetic cause of PAH can be identified in the BMPR2 gene. A genetic BMPR2 mutation has even been found in 20% of patients with idiopathic PAH. The CVON-PHAEDRA consortium has identified novel compounds that are able to restore BMPR2 signaling. We are currently investigating the effects of these novel drugs on pulmonary vascular remodeling and RV adaptation (PHAEDRA-IMPACT).

**3. Right ventricular heart failure**

The RV in patients with pulmonary arterial hypertension (PAH) is exposed to an extreme (4-5 fold) increase in load due to progressive pulmonary vascular remodeling. Importantly, the fate of a patient with PAH is not determined by the degree of pressure overload but rather by the response of the RV to the increased pressure. Therefore, we are currently investigating which factors may influence the adaptation mechanisms of the right ventricle, with a specific focus on gender and genetic alterations in the BMPR2 (NHS Dekker). In addition to this, we are evaluating novel treatment strategies that are directed to limit oxygen consumption, RV dilatation or RV diastolic stiffness (NWO-VICI, NWO-VIDI).

**Aiming to detect Pulmonary Arterial Hypertension in the early stages**

left to right: **Mo Arkani, Jessie van Wezenbeek, Berend Westerhof, Josien Smits, Jeroen Wessels, Megan Kok, Xiaoqing Sun, Anton Vonk, Xue Manz, Ahmed Abdallah (visiting researcher), Aida Llucia Valldeperas, Peter Bonta, Harm Jan Bogaard, Eva Peters, Masafumi Fukumitsu, Frances Handoko-de Man**

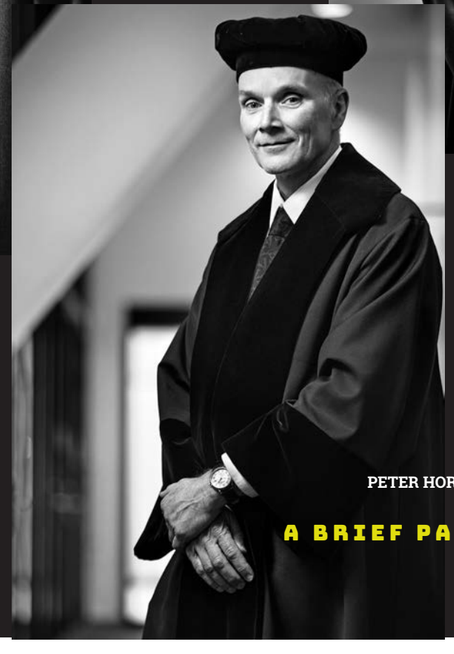
# MEET OUR NEW PROFESSORS

PRABATH NANAYAKKARA

**HOPING TO FIND**

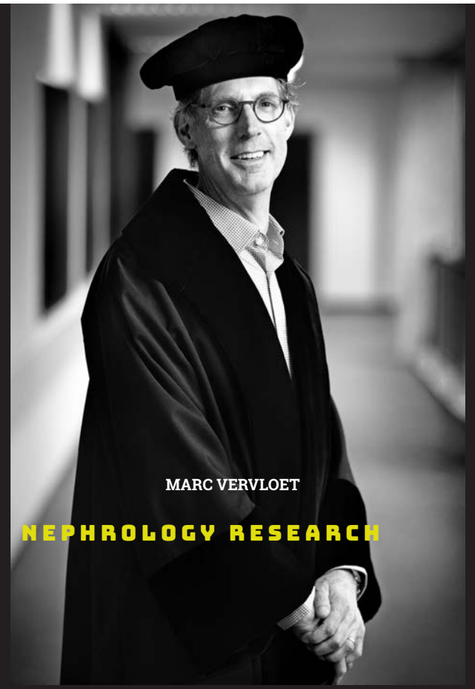
JOLANDA KLUIN

**THE ROAD NOT TAKEN**



PETER HORDIJK

**A BRIEF PAUSE ON MOTION**



MARC VERVLOET

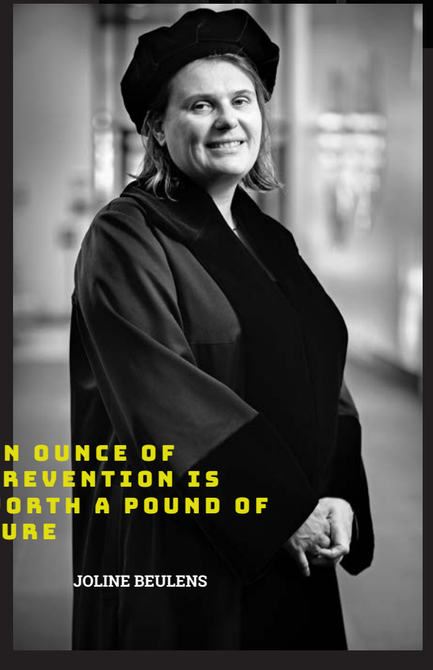
**NEPHROLOGY RESEARCH**

JAAP VAN BUUL

**TRAVEL WITH AN OPEN MIND: THE BLOOD VESSEL AS CHINESE WALL**

RIEKELT HOUTKOOPER

**MIND THE GAP!**



JOLINE BEULENS

**AN OUNCE OF PREVENTION IS WORTH A POUND OF CURE**

# ACS SYMPOSIA AND EVENTS 2019 - 2020

## Amsterdam Cardiovascular Sciences Activities 2019

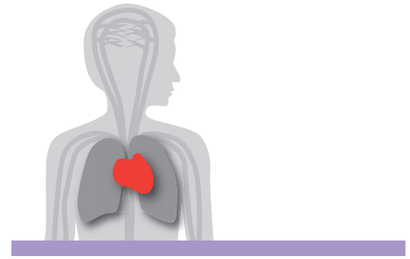
| | |
|---|---|
| **FEBRUARY 4** | Pulmonary Hypertension & Thrombosis |
| **MARCH 4** | Diabetes & Metabolism |
| **MARCH 14-15** | 1st ACS PhD retreat |
| **APRIL 1** | Microcirculation |
| **MAY 6** | Heart Failure & Arrhythmias |
| **JUNE 3** | Atherosclerosis & Ischemic syndromes |
| **JULY 4** | 5th ACS conference |
| **SEPTEMBER 2** | Pulmonary Hypertension & Thrombosis |
| **OCTOBER 7** | Diabetes & Metabolism |
| **NOVEMBER 4** | Microcirculation |
| **DECEMBER 2** | Heart Failure & Arrhythmias |

## Amsterdam Cardiovascular Sciences Activities 2020

| | |
|---|---|
| **FEBRUARY 3** | Atherosclerosis & Ischemic syndromes |
| **MARCH 2** | Pulmonary Hypertension & Thrombosis |
| **MARCH 12-13** | 2nd ACS PhD retreat |
| **APRIL 6** | Diabetes & Metabolism |
| **MAY 11** | Microcirculation |
| **JUNE 8** | Heart Failure & Arrhythmias |
| **JULY 2** | 6th ACS conference |
| **SEPTEMBER 7** | Atherosclerosis & Ischemic syndromes |
| **OCTOBER 5** | Pulmonary Hypertension & Thrombosis |
| **NOVEMBER 2** | Diabetes & Metabolism |
| **DECEMBER 7** | Microcirculation |



# Biological insights to find novel therapies for treatment-resistant forms of heart failure



Generally applied therapies have improved survival of heart failure patients. However, for genetic cardiomyopathies these treatments often fail because they are treated like patients who have developed heart failure due to very different and more common diseases, such as myocardial infarction. This ignores the specific underlying pathophysiology of such genetic cardiomyopathies. The lack of effect of this one-size-fits-all approach leaves a large group of often quite young patients with therapy-resistant cardiomyopathies. Some of these have grave prognoses, like cardiomyopathy caused by a LMNA mutation or an RBM20 mutation.

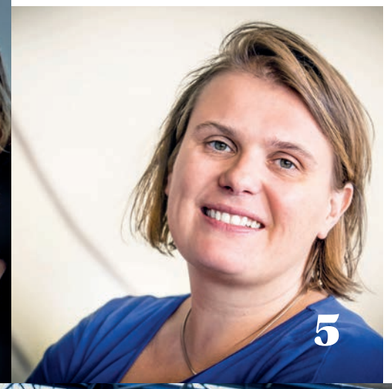
Dr. Yigal Pinto and Dr. Esther Creemers have been working together in the Department of Experimental Cardiology at the Amsterdam UMC location AMC to unravel underlying mechanisms of hereditary forms of heart failure. A gene, in which mutations frequently lead to heart failure is the splicing factor RNA-binding motif protein 20 (RBM20). RBM20 mutation carriers present with a clinically aggressive form of dilated cardiomyopathy (DCM), associated with young age at diagnosis, increased risk of arrhythmias, and high mortality. In a recent publication in Circulation, the team of Pinto and Creemers reported on a novel mechanism that underlies the occurrence of cardiac arrhythmias in RBM20 mutation carriers. Using RBM20 knockout mice, cardiac biopsies of human RBM20 mutation carriers and bioinformatics approaches they have revealed that the loss of RBM20 disturbs $Ca^{2+}$ handling in cardiomyocytes and leads to more proarrhythmic $Ca^{2+}$ releases from the sarcoplasmic reticulum. These experimental data have clinical implications, as they suggest that RBM20 mutation carriers may benefit from treatment with $Ca^{2+}$ blockers to reduce their arrhythmia burden.

In addition to these translational studies, Pinto and Creemers have also collaborated on more fundamental studies of RNA biology in the heart. They not only found that the splicing factor RBM20 is involved in alternative splicing of linear pre-mRNA molecules, but that this protein is also instrumental for the production of circular RNA molecules, generated by a back-splicing reaction of the spliceosome.

In the recently awarded CVON ARENA-PRIME grant, Yigal Pinto has teamed up with Dr. Leon de Windt (University of Maastricht) and Dr. Eva van Rooij (Hubrecht Laboratory, Utrecht) to contribute to better treatment of heart failure, by bringing RNA therapies closer to clinical application. In this CVON program, allele-specific siRNAs will be explored as a novel therapy for treatment resistant forms of DCM, such as Lamin A/C mutation carriers.

**Working together to unravel underlying mechanisms of hereditary forms of heart failure**

**Esther Creemers** (l) and **Yigal Pinto** (r)








**1** left to right: **Marjet Oppelaar, Rosa Wouda, Liffert Vogt, Eliane Wenstedt**
**2** **Frances Handoko-de Man**
**3** **Tom Seijkens** (photograph by Elmer Bets)
**4** left to right: **Sebastiaan Blok, Dirkjan Kauw, Marinka Oudkerk Pool, Michiel Winter**
**5** **Joline Beulens**
**6** **Elisabeth Lodder** (photograph by Paulien Kluver)
**7** **Jaap van Buul** (l) and **Coen Ottenheijm** (r)
**8** **Jeffrey Kroon**



# Personal Grants

**Liffert Vogt,** Nephrology, Senior Kolffgrant Dutch Kidney Foundation 2019: *Changing the sodium homeostasis paradigm: role of macrophages and glycosaminoglycan crosstalk in sodium sensitivity*

**Michiel Winter,** Cardiology, NHS Dekker junior staff-member 2018: *mHealth in grown-up congenital heart disease*

**Tom Seijkens,** Medical Biochemistry & Internal Medicine, NHS Dekker doctor in training to be a specialist 2018: *Targeting CBL-B in atherosclerosis: putting the brake on inflammation!*

**Frances Handoko-de Man,** Pulmonology, NHS Dekker senior postdoc 2018: *Pulmonary artERial hypertenSion: bonE morPHOgeNetic protein and Estrogen signaling out of control (Persephone)*
Vidi 2017: *The right ventricle in pulmonary hypertension: stiff and out of shape*

**Jeffrey Kroon,** Vascular Medicine, Veni 2018: *Steer blood vessel metabolism against atherosclerosis*

**Joline Beulens,** Epidemiology & Biostatistics, Vidi 2017: *Heart of stone?*

**Elisabeth Lodder,** Experimental Cardiology, Vidi 2017: *Increasing the pace of the heart*

**Jaap van Buul,** Sanquin Research and Landsteiner Laboratory, Vici 2018: *Gatekeepers of the vasculature*

**Coen Ottenheijm,** Physiology, Vici 2018: *The diaphragm: a breath-taking muscle*

# mHealth in grown-up congenital heart disease

## INTERVIEW WITH MICHIEL WINTER NHS DEKKER JUNIOR STAFF-MEMBER LAUREATE

**What is your research about?**

My research is about mobile health (mHealth) in adult patients with congenital heart disease. The number of adult patients with congenital heart disease is rapidly increasing. Although their cardiac anomaly is often surgically corrected, these patients can never be considered cured. The large majority of patients experience cardiac symptoms, like palpitations. These symptoms lead to frequent visits to the outpatient clinic, the emergency department, and to hospital admission. We expect that mHealth will partly release this burden, as monitoring of cardiac parameters at home can facilitate early detection of deterioration, and swift therapeutic response or reassurance. This could even make visits to the hospital unnecessary.

**Why did you choose this project?**

I think there is a big future for mHealth, one way or another. With the Dekker grant it has been possible to advance this research and has allowed us to focus on our patients' needs and not the consumer interests of the big commercial companies. By developing it ourselves we can create something relevant for the ones that need it the most.

**Which aspects of research do you find interesting?**

Although mHealth is getting a lot of media-attention, it is not an integrated part of our daily practice. I am sure that dedicated mHealth research will facilitate the introduction of mHealth in our hospitals. We will start with young patients that know how smartphones and apps work. And if this really works, then we can expand the use of mHealth to a broader selection of patients with heart problems. The future for mHealth is exciting with many challenges ahead. I am sure this conversation will be different five years from now, as mHealth will be much more a part of our daily work.

**Which effects of the ACS alliance do you notice?**

To be honest I haven't noticed much of the ACS alliance, as we had already had excellent collaboration with our colleagues from the VUMC for many years. As the focus of the ACS is more and more clinical, I am sure it will become more known to clinicians and who will welcome the monthly symposia.



EU FUNDING

# "Mend a broken heart"

**Dr. Reinier Boon (dept. Physiology) has received 1.1 million euros as part of the European CardioReGenix consortium (15 million euros)**

Soon after the discovery of the DNA double helix (1950s and 1960s), it became clear that a large portion of the human genome does not actually code for protein. This portion was first dismissed as 'junk' DNA, but much later, after the entire genome was sequenced, it became apparent that most of this 'non-coding' DNA was actually transcribed into RNA. These molecules were termed non-coding RNAs. Until non-coding RNAs were studied in detail, it was thought that they were mere transcriptional noise. Now we know that many non-coding RNAs are important regulators of many cellular processes, like survival and cell death.

**developing optimal cardiac gene delivery strategies that induce robust gene expression in cardiac cells**

**Diewertje Bink** (l) and **Reinier Boon** (r)

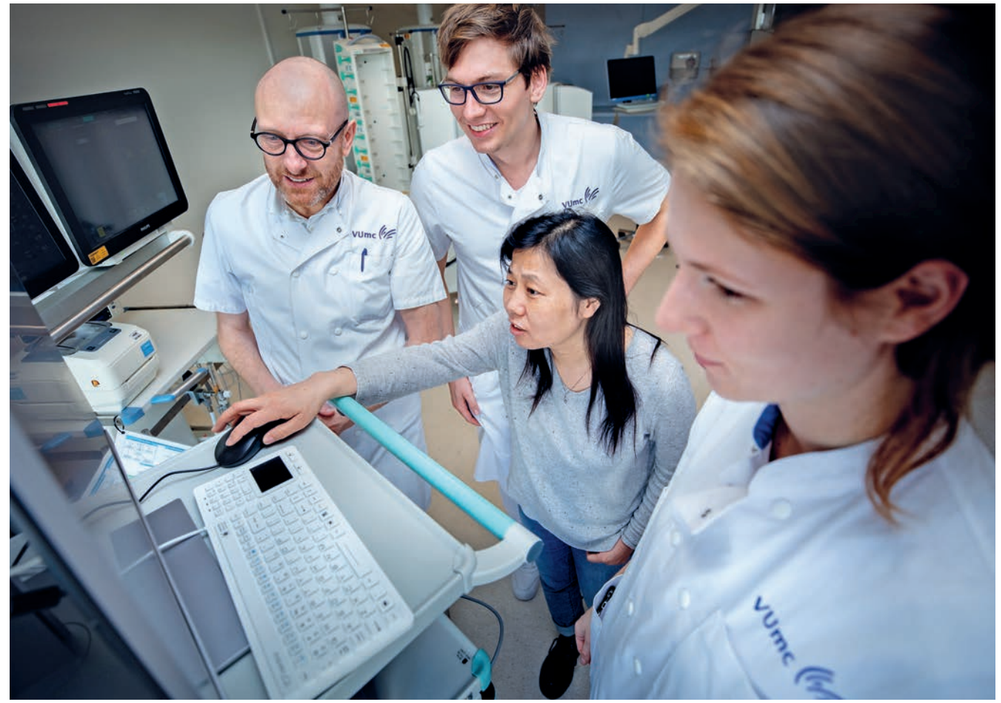
People who suffer an acute myocardial infarction (heart attack) usually survive this initial event, thanks to excellent state-of-the-art care. However, part of the hearts of these patients remain non-functional, resulting in lasting heart problems. To fully heal a heart after an acute myocardial infarction, one needs to restore heart function at a cellular level. To achieve this, damaged cardiac muscle cells (cardiomyocytes) need to be replaced or revived and blood vessels need to grow in the wound area to provide oxygen and nutrients. In addition, scar forming cells (fibroblasts) need to be inhibited. The CardioReGenix consortium aims to induce cardiac regeneration using non-coding RNAs.

The European CardioReGenix consortium made up of partners in both academia and academic spin-off enterprises across Europe (Belgium, Germany, UK, Finland, Italy and the Netherlands). Experiments are aimed at developing optimal cardiac gene delivery strategies that induce robust gene expression in cardiac cells, including cardiomyocytes, fibroblasts and endothelial cells, without targeting non-cardiac cells. The consortium will also identify the most promising non-coding RNAs to be used for cardiac delivery to induce regeneration.

# The diaphragm: a vital pump

Leo Heunks & Coen Ottenheijm

The respiratory muscle pump is composed of a large number of muscles that act together to drive alveolar ventilation. The diaphragm is the most important muscle for inspiration, but when loading imposed on the diaphragm increases, other muscles are recruited to facilitate inspiration including the scalene muscles, sternocleidomastoid muscles and eventually the abdominal wall muscles for active expiration. When the respiratory muscle pump is unable to maintain adequate CO2 elimination or oxygen uptake, a life-threatening condition occurs. This may develop under conditions of high respiratory loading such as pneumonia, sepsis or trauma. As no drugs are approved to improve respiratory muscle function, mechanical ventilation is the only lifesaving medical intervention for patients with acute respiratory failure. However, it is now recognized that in mechanically ventilated patients, mechanical ventilation respiratory muscle weakness may rapidly develop. The teams led by Coen Ottenheijm (dept. of Physiology) and Leo Heunks (dept. of Intensive Care) aim to elucidate the mechanisms underlying the development of respiratory muscle weakness in mechanically ventilated patients. The unique collaboration between these preclinical and clinical groups allows us to approach this important clinical problem from different perspectives.



left to right: **Leo Heunks, Heder de Vries, ZhongHua Shi, Annemijn Jonkman**

## ANIMAL MODELS

At the department of physiology, animal models for long-term mechanical ventilation are used to understand the impact of mechanical ventilation on respiratory muscle structure and function. By using specific genetic knock out models, we have demonstrated the importance of titin, a molecular mechano-sensor in the development of diaphragm weakness in ICU patients.

## HUMAN DIAPHRAGM BIOPSIES

A unique feature of our group is the ability to obtain biopsies from the diaphragm of ventilated patients. This provides important insights in the pathophysiology of respiratory muscle weakness in these patients. The department of physiology has dedicated equipment that allows detailed analysis of the contractile performance of muscle fibers from these biopsies.

## IN VIVO DIAPHRAGM FUNCTION

Using multiple pressure transducers positioned in the stomach and esophagus we are able to asses contractile performance of the respiratory muscle pump in ventilated patients. This provides an opportunity to investigate the contractile performance of the respiratory muscles at different time points during ICU admission. Electrical activity of the respiratory muscles is acquired using dedicated catheters. Sophisticated analysis of this signal allows early detection of dysfunction and fatigue of the diaphragm. In addition, it allows us to evaluate the effects of novel drugs that aim to improve contractile efficiency of the respiratory muscles in vivo.

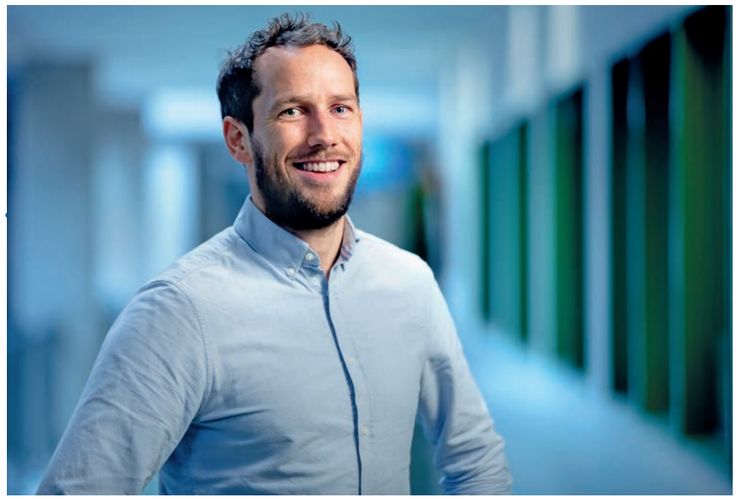
**Unique collaboration between preclinical and clinical groups to study respiratory muscle weakness in ventilated patients**

## IMAGING

Our groups are investigating the feasibility and validity of novel radiological techniques to assess respiratory muscle function. We are currently focusing on tissue doppler imaging, speckle tracking ultrasound and dynamic MRI. This is done in collaboration with the department of radiology at Amsterdam UMC locations VUmc and AMC.

The techniques described above are not solely used in critically ill patients, but also in patients with other diseases, including congenital myopathies, chronic obstructive pulmonary disease (COPD) and heart failure. If you are interested in or would like more information on the techniques described above or about respiratory muscle dysfunction in any condition, please contact Coen Ottenheijm at the department of physiology (C.Ottenheijm@vumc.nl), or Leo Heunks at the department of intensive care (L.Heunks@vumc.nl).

# PHDS IN THE SPOTLIGHT



## PhD student Jan Schnitzler,
### dept. Experimental Vascular Medicine

**What is your research about?**

My research investigates the inflammatory effect of lipoprotein (a) [Lp(a)] on endothelial cells (EC). Based on our current findings, we now know that EC become inflamed upon exposure to Lp(a) and as a consequence this facilitates increased monocyte migration and therefore the progression of atherosclerosis.

So, we hypothesized that ECs change their metabolism under inflammatory conditions initiated by Lp(a) to generate energy. What we found is that Lp(a) indeed alters EC metabolism via increased activity of the glycolytic pathway and targeting this strongly reduces monocyte transmigration.

Thus, by inhibiting monocyte influx in the vessel wall we can decrease the progression of atherosclerosis.

**Why did you choose this PhD project?**

Since my Master Biomedical Sciences I have had a profound interest in cardiovascular research. This interest was probably triggered by the cardiovascular complications of both my parents a couple of years ago (they are doing great now!). When I was approached by a former colleague to join the research group of Prof. Erik Stroes as a PhD-student, it didn't take long to say yes!

**Which aspects of the research do you like?**

Firstly, I like that curiosity is generally rewarded, even though your patience is sometimes tested to the limit. Furthermore, I enjoy the freedom that research offers for example, my supervisor Dr. Jeffrey Kroon developed a completely new line of research in our group. And, importantly, my research wouldn't be half as much fun without my colleagues.

**What effects of the ACS alliance do you notice?**

First of all, ACS funding has made this research possible. Secondly, the monthly symposia are very interesting and informative; you stay up-to-date and get to know your colleagues who are active in your field. The PhD-retreat in March is another great example of the ACS alliance to which I am really looking forward to attending.

**ACS FUNDING MADE THIS RESEARCH POSSIBLE**

**What do you want to do when you "grow up"?**

I am not sure yet! I will probably stay in the academic research world, perhaps as a Postdoc. On the other hand, I want to expand my horizons and to look for possibilities of finding a position in the pharmaceutical industry, as well. However, only time will tell what the future holds.



## PhD student Nicole Dekker,
### dept. Anesthesiology

**What is your research about?**

I investigate alterations in the microvasculature that are observed in patients undergoing cardiac surgery when using a cardiopulmonary bypass machine that takes over the function of the heart and the lungs during surgery. The use of this machine is associated with contact activation and a systemic inflammatory response, weakening the barrier of the vascular wall resulting in edema formation. The microvascular network, critical for organ perfusion and function, is particularly vulnerable to these changes. During my PhD, I investigate several signaling pathways involved in vascular barrier regulation and aim to identify possible therapeutic targets to preserve microcirculatory perfusion during these procedures.

**Why did you choose this PhD project?**

My PhD project was the result of my scientific internship in the Department of Anesthesiology, as a part of the Medical Master's program. I was intrigued by vascular physiology and fundamental research when doing my bachelor in Biomedical Sciences. After I obtaining my bachelor's degree, the "VUMC ZIGMA" Medical Master provided me with the opportunity to train to be a physician and a researcher and to start an MD/PhD track. In the department of Anesthesiology, I enjoy being part of a translational research line and combining my biomedical and medical backgrounds. A research grant from the Dutch Heart Foundation "Dekkerbeurs" has allowed me to work on my PhD project in the laboratory for the past two years.

**COMBINING MY BIOMEDICAL AND MEDICAL BACKGROUNDS**

**Which aspects do you like within research?**

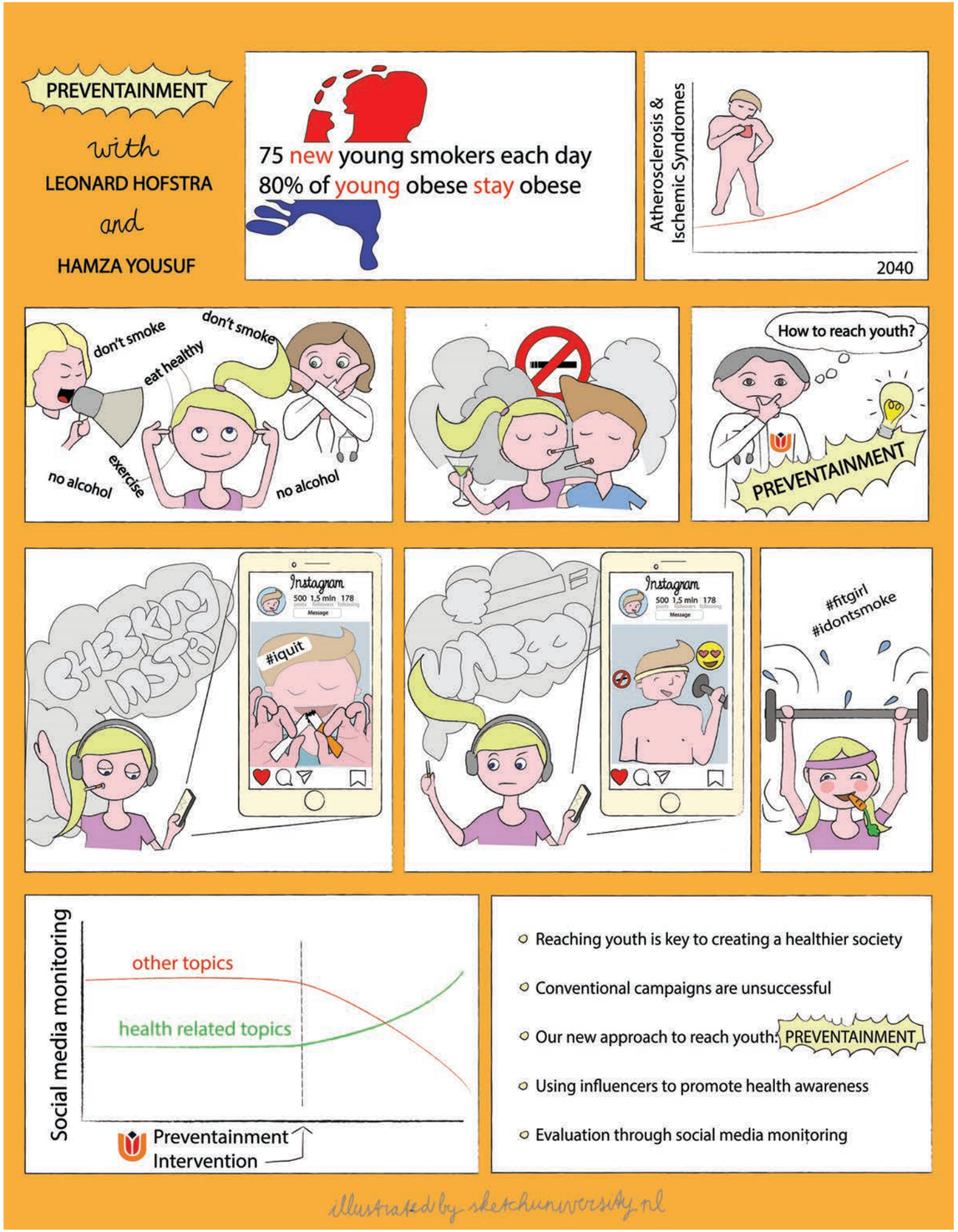
Many aspects! It is incredibly fun to learn new things and to try to unravel the complexity of the human body and disease. It also encourages you to be analytical, creative and problem solving. To me, these are also essential skills for a medical doctor.

**What effects of the ACS alliance do you notice?**

I haven't noticed a lot of differences in daily practice yet. However, due to the meetings and PhD courses organized by ACS, I have gotten to know a lot more of other PhD students and research groups. In this way, the ACS alliance definitely facilitates interaction between departments and encourages collaborations between research groups.

**What do you want to do when you "grow up"?**

Eventually, I hope to combine working as a medical specialist with scientific research. It would be great to be part of a translational research line and bring clinical observations to the lab and vice versa.




# ACS awards 2018-2019

ACS awarded: PhD grants (€200,000), Postdoc grants (€70,000), Out of the Box grants (€25,000) and ACS-VUmc Equipment grants to stimulate innovative collaborative research

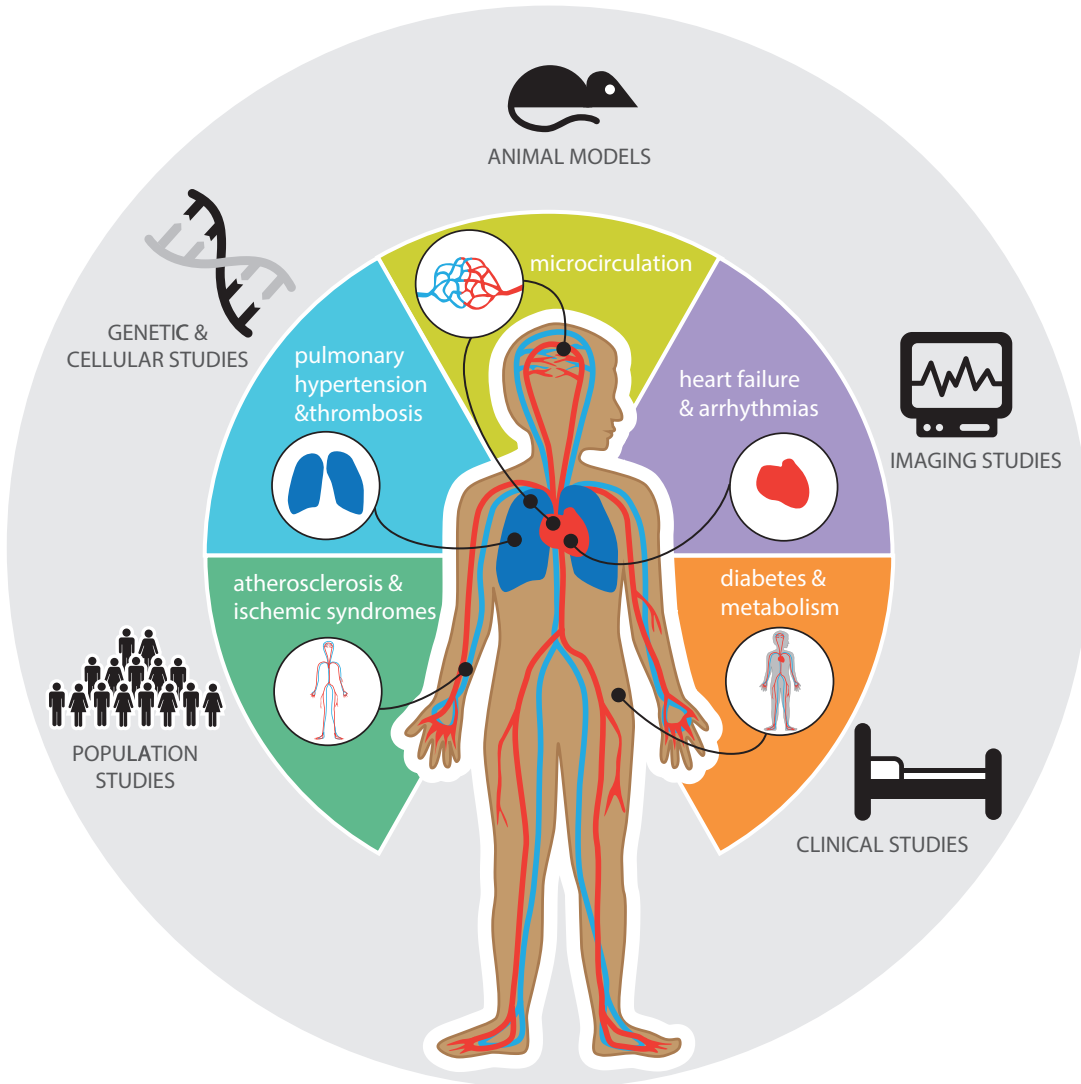
## 2018 AUTUMN

| | | |
|---|---|---|
| Reinier Boon & Stephan Huveneers | Towards Protective Building Blocks for the Endothelial Barrier | PhD |
| Max Nieuwdorp, Majon Muller, Han Levels & Mike Peters | The gut microbiome and aging of the vascular system | PhD |
| Menno de Winther, Jan van den Bossche & Michel van Weeghel | Local immunometabolites shape inflammatory macrophages and atherosclerosis progression | PhD |
| Ed Eringa, Gustav Strijkers & Carlie de Vries | Contrast ultrasonography for identifying and understanding perfusion defects in organ failure | ACS-VUmc Equipment grant |
| Marco Götte & Alexander Vonk | MRI-Compatible Multi-Channel Hemodynamic Monitoring System, Philips In Vivo MR Expression 400 | ACS-VUmc Equipment grant |

## 2019 SPRING

| | | |
|---|---|---|
| Roddy Walsh | Identifying genetic factors that influence variable penetrance and disease expressivity in hypertrophic cardiomyopathy | Postdoc |
| Natalija Bogunovic | Prdm protein family as novel transcriptional regulators of aortic aneurysm pathology | Postdoc |
| Daniël van Raalte & Carlie de Vries | LIM-domain only protein FHL2 secreted? An unexpected finding requiring further research | OOTB |
| Jurjan Aman & Stephan Huveneers | Linking early endothelial barrier injury to vascular remodeling: a role for SOX17 in the onset of pulmonary hypertension | OOTB |
| Vivian de Waard & Dimitra Micha | The two genetic Marfan subtypes deserve a mouse model for preclinical studies | OOTB |
| Esther Creemers & Bianca Brundel | Uncovering atrial cardiomyocyte proteostasis derailment and atrial fibrillation | OOTB |

# Amsterdam Cardiovascular Sciences




Amsterdam UMC
Universitair Medische Centra