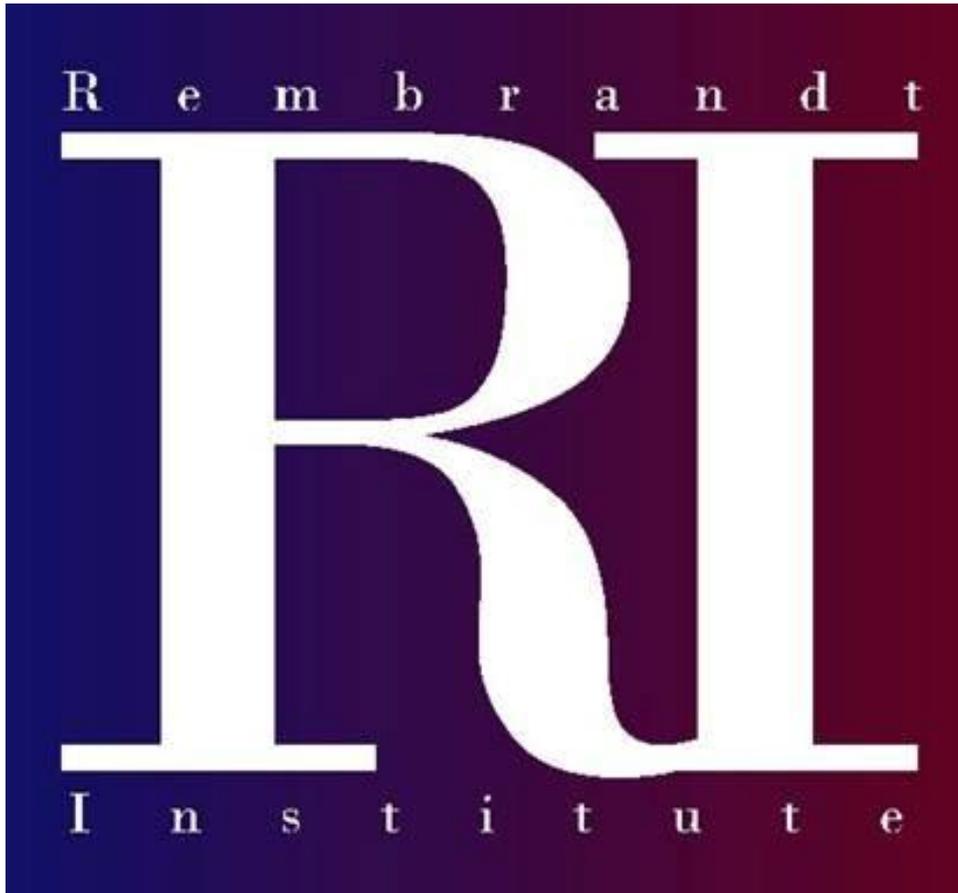


5th Rembrandt Symposium 2014



Rembrandt Institute for Cardiovascular Science

**NH Conference Centre Leeuwenhorst, Noordwijkerhout
November 7, 2014**



Symposium Venue

NH Conference Centre Leeuwenhorst
Langelaan 3
2211 XT Noordwijkerhout
+31 (0)252 378424

www.nh-hotels.nl

Free WIFI Voucher ask at the Front office

Contents

❖	Organizers	2
❖	Introduction	3
❖	Program	4
❖	Floor plan	7
❖	Abstracts Keynote Lectures	8
❖	Abstracts Selected Oral Presentations	12
❖	Titels Poster Presentations	16
❖	Participants with abstract	21

Poster sessions

Gaudi Lounge

1.	Atherosclerosis Clinical	posters 1-3
2.	Atherosclerosis Experimental	posters 4-21
3.	Autoimmunity and Inflammation	posters 22-25
4.	Cardiac Arrhythmia	posters 26-33
5.	Cardiac Function	posters 34-45
6.	Heart Failure	posters 46-58
7.	Imaging	posters 59-60
8.	Metabolism	posters 61-71

Sorbonne 4

9.	Stem Cells	posters 72-76
10.	Thrombosis and Hemostasis	posters 77-89
11.	Vascular Biology	posters 90-109

Organizers

Leiden Vascular Medicine (LVM)

Mw. Dr. I.M. Bajema	LUMC, Pathology
Mw. Prof. dr. M. van Eck	LACDR, Biopharmaceutics
Mw. Prof. dr. M.J.T.H. Goumans	LUMC, Molecular Cell Biology
Prof. dr. L.M. Havekes	LUMC, Endocrinology
Prof. dr. M.V. Huisman	LUMC, Thrombosis and Haemostasis
Prof. dr. J.W. Jukema	LUMC, Cardiology
Mw. Prof. dr. C.L. Mummery	LUMC, Anatomy
Prof. dr. P.H. Reitsma	LUMC, Thrombosis and Haemostasis
Prof. dr. P.C.N. Rensen	LUMC, Endocrinology
Prof. dr. P.H.A. Quax	LUMC, Vascular Surgery
Prof. dr. A.J. van Zonneveld	LUMC, Nephrology

Amsterdam Rembrandt Committee

Mw. Prof. dr. C.R. Bezzina	AMC, Experimental Cardiology
Prof. dr. H.R. Büller	AMC, Vascular Medicine
Prof. dr. V.M. Christoffels	AMC, Anatomy, Embryology and Physiology
Prof. dr. M.J.A.P. Daemen	AMC, Pathology
Prof. dr. Y.M. Pinto	AMC, Experimental Cardiology
Prof. dr. E.S. Stroes	AMC, Vascular Medicine
Mw. Prof. dr. C.J.M. de Vries	AMC, Medical Biochemistry

VU Medical Center

Mw. Prof. dr. J. van der Velden	ICaR-VU/VUmc, Physiology
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Sanquin

Prof. dr. P.L. Hordijk	Sanquin, Molecular Cell Biology
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Rembrandt Symposium 2014 - Organizing committee

Prof. dr. V. Christoffels	AMC, Heart Failure Center
Dr. H.J. Bogaard	ICaR-VU/VUmc, Pulmonology
Prof. dr. M. van Eck	LACDR, Biopharmaceutics
Prof. dr. P.L. Hordijk	Sanquin, Molecular Cell Biology
Prof. dr. M.V. Huisman	LUMC, Vascular Medicine
Dr. M. Nieuwdorp	AMC, Vascular Medicine
Prof. dr. P.C.N. Rensen	LUMC, Endocrinology
Dr. G. Van Nieuw Amerongen	ICaR-VU/VUmc, Physiology
Dr. G.M. Dallinga-Thie	AMC, Experimental Vascular medicine

Rembrandt Symposium 2014 - Secretariat

Mw. A.M. Vree	AMC, Vascular Medicine
Mw. B.M.J. Huges	AMC, Pathology

Introduction

This is the fifth symposium of the Rembrandt Institute for Cardiovascular Science (RICS). In the spring of 2010, the boards of AMC and LUMC decided to combine their research efforts in cardiovascular disease in this Institute. In the meantime also the LACDR, VUmc and Sanquin have joined the RICS.

The name Rembrandt was chosen because this painter was born in Leiden but spent much of his working life also in Amsterdam. Thus we can truly say Rembrandt symbolizes our new collaboration, and hence the name Rembrandt Symposium.

The mission of the Rembrandt Institute is to carry out and stimulate excellent fundamental and etiological research within the fields of cardiovascular biology and disease (e.g. stem cell research, vessel wall biology, immunometabolism, molecular cell biology, genetics, developmental biology).

Within this context the main tasks of the institute are:

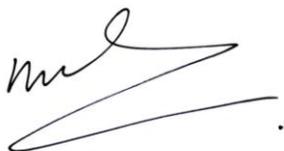
- To carry out fundamental and etiological research within the field of cardiovascular disease
- To obtain collaborative (consortium) grants to finance these research efforts
- To function as an interlocutor for external granting agencies like Heart Foundation, ZonMw, et cetera
- To translate fundamental research into clinically useful applications
- To valorize research within the context of the Bio Science Park Leiden and the Life Sciences Center Amsterdam.

Today's fifth symposium will be devoted to our usual business: the exchange of research findings and new ideas in the form of oral and poster presentations. This year the poster sessions are again especially highlighted with dedicated time to discuss data with your fellow researchers.

At the end of the meeting, the first lustrum round of recipients of the Rembrandt Research Grants will be announced and awards for best posters and oral presentations will be presented.

Fore sure we expect an exciting scientific day!

On behalf of the organizers,

A handwritten signature in black ink, appearing to read 'Mat Daemen', with a long horizontal stroke extending to the right.

Mat Daemen

Program

09.00-09.30 Registration with coffee/tea

09.30-09.35 Opening (Sorbonne 2)

Dr. Max Nieuwdorp (AMC) and Prof. Vincent Christoffels (AMC)

09.35-10.55 PLENARY SESSION 1 (Sorbonne 2)

Chairs: Dr. Janine van Gils (LUMC) and Dr. Max Nieuwdorp (AMC)

09.35-10.00 Keynote lecture 1

Prof. Koos Zwinderman (KEBB, AMC)

Diversity and cardiovascular health: some results from the HELIUS study

The HELIUS study is a Dutch multi-ethnic cohort study which since 2008 has collected data regarding cardiovascular riskfactors from 10000 participants (18-70 years old) of ethnic Dutch, Surinamese of African and of South Asian origin, Turkish or Moroccan origin in the Amsterdam region. Relationship between ethnicity and cardiovascular riskmarkers will be discussed.

10.00-10.15 **Oral presentation selected abstract 1: Diederik Kuster (VUmc)**

In vivo pathophysiology of hypertrophic cardiomyopathy in a highly prevalent 25 bp deletion mutation in MYBPC3.

10.15-10.30 **Oral presentation selected abstract 2: Claudia van Thiel (AMC)**

TRAF-STOP-HDL-nanoparticles reduce atherosclerosis.

10.30-10.55 Keynote lecture 2

Dr. Jaap van Buul (Dept. Molecular Cell Biology, Sanquin)

Dynamic interactions between leukocytes and the endothelium: the diapedesis synapse.

Upon inflammation, leukocytes extravasate from the circulation across the endothelium lining the vessel wall into the underlying tissue in order to clear invading pathogens. This process is known to occur in several steps, also referred to as the multistep paradigm of leukocyte transendothelial migration. It has become increasingly clear that the endothelium is not a passive layer of cells but is actively involved in this process. My lab focuses on the active role of the endothelium in guiding leukocyte migration across the vessel wall and we use a variety of cell biology tools, including real-time microscopy and FRET measurements to study this process in more detail.

11.00-12.00 **Poster presentations (odd numbers) with coffee/tea**

12.00-12.40 **Lunch**

12.40-14.00 PLENARY SESSION 2 (Sorbonne 2)

Chairs: Dr. Jaap van Buul (Sanquin) and Dr. Paul Krijnen (VUmc)

12.40-13.05 Keynote lecture 3

Prof. Paul Quax (Dept. of Vascular Surgery, LUMC)

Regulation of vascular remodelling: Inflammation, Immune modulation and microRNAs

Paul Quax is professor in Experimental Vascular Medicine and working at the department of Surgery of the LUMC and the Einthoven Laboratory for Experimental Vascular Medicine. His research interest is vascular remodeling both in a positive way during neovascularisation, angiogenesis and arteriogenesis, and in a negative way during atherosclerosis, restenosis and vein graft disease. Understanding the common mechanisms in these processes and defining new therapeutic interventions to induce or prevent vascular remodeling is the central theme of his research.

- 13.05-13.20 **Oral presentation selected abstract 3: Anouk Wezel (LUMC)**
Inhibition of 14q32 MicroRNA miR-494 Reduces Atherosclerotic Lesion Formation, Increases Plaque Stability and Lowers Cholesterol Levels.
- 13.20-13.35 **Oral presentation selected abstract 4: Fleur van der Valk (AMC)**
Lipoprotein(a) causes cellular and arterial wall inflammation via epigenetic remodelling.
- 13.35-14.00 Keynote lecture 4
Dr. Harm Jan Bogaard (Dept. of Pulmonology, VUmc)
Go with the flow in pulmonary hypertension
Personal statement
After completing my PhD on hemodynamic responses to exercise in patients with COPD, I worked as a post-doctoral fellow at the UCSD division of physiology San Diego, CA, studying cardiovascular adaptation to high altitude. In 2007, after completing my clinical training, I joined the lab of Norbert Voelkel (Richmond) to study mechanisms of pulmonary hypertension and -associated right heart failure. After identifying a molecular signature of right heart failure, I was able to show that adrenergic receptor blockade effectively reverses right heart remodeling and failure. Currently, I am co-PI of a randomized clinical trial translating these findings to PAH patients. Other projects in which I acted as a PI, concern the detrimental effects of dietary copper insufficiency and histone deacetylase inhibition on right heart adaptation to pressure overload and the comparison of different PAH animal models. Recognizing that the contemporary focus on a cancer-paradigm in PAH research has led to the application of anti-proliferative and anti-angiogenic treatments without a clear rationale, but with potential cardiotoxic side-effects, I have recently decided to gain a better understanding of mechanisms of pulmonary vascular remodeling. I am PI of a Dutch Lung Foundation sponsored project to determine the response of PAH patient-derived lung microvascular endothelial cells to increased shear stress and co-PI of a CVON program to determine the role of TGF β /BMP imbalance in pulmonary hypertension.
- 14.00-15.00 **Poster presentations (even numbers) with coffee/tea**
- 14.40-15.00 Uitreiking Rembrandt project grant 2014**
(for PhD students located in both AMC and LUMC)
Prof. Marcel Levi (AMC) and Prof. Pancras Hoogendoorn (LUMC)
- 15.00-16.40 PLENARY SESSION 3 (Sorbonne 2)**
Chairs: Prof. Wouter Jukema (LUMC) and Prof. Jolanda van der Velden (VUmc)

Rembrandt project awards 2010 final presentations

15.00-15.20 **Lighting-up the runway for cardiac subtype specification in human embryonic**

Stemcells: Henk van Weerd (AMC) / Sabine den Hartogh (LUMC)
PI's: Prof. Vincent Christoffels (AMC) / Dr. Robert Passier (LUMC)

15.20-15.40 **Search for new genetic variants for first and recurrent venous thrombosis**

PhD students: Marisa Cunha (AMC) / Hugoline de Haan (LUMC)
PI's: Prof. Saskia Middeldorp (AMC) / Prof. Frits Rosendaal (LUMC)

Rembrandt project awards 2012 midway-progress presentations

15.40-16.00 **Intestinal microbiota as modifiable factor in the metabolic syndrome and associated cardiovascular disease; role of short and long chain fatty acids**

PhD students: Kristien Bouter (AMC) / Saeed Katiraei (LUMC)
PI's: Prof. Erik Stroes (AMC) / Prof. Ko Willems van Dijk (LUMC)

16.00-16.20 **Brown adipose tissue meets the immune system**

PhD students: Andrea van Dam (LUMC) / Susan van den Berg (AMC)
PI's: Prof. Patrick Rensen (LUMC) / Prof. Esther Lutgens (AMC) / Prof. Menno de Winther (AMC)

16.20-16.40 **RhoGTPases in endothelium: localized activity, cross-talk and relevance for barrier function and inflammation**

PhD students: Nathalie Reinhard (Sanquin) / Manon Pronk (VUMC)
PI's: Prof. Peter Hordijk (Sanquin) / Dr. Geerten van Amerongen (VUMC)

16.40-16.50 **Best oral presentation (1x) and best abstract presentation (6x) prizes**

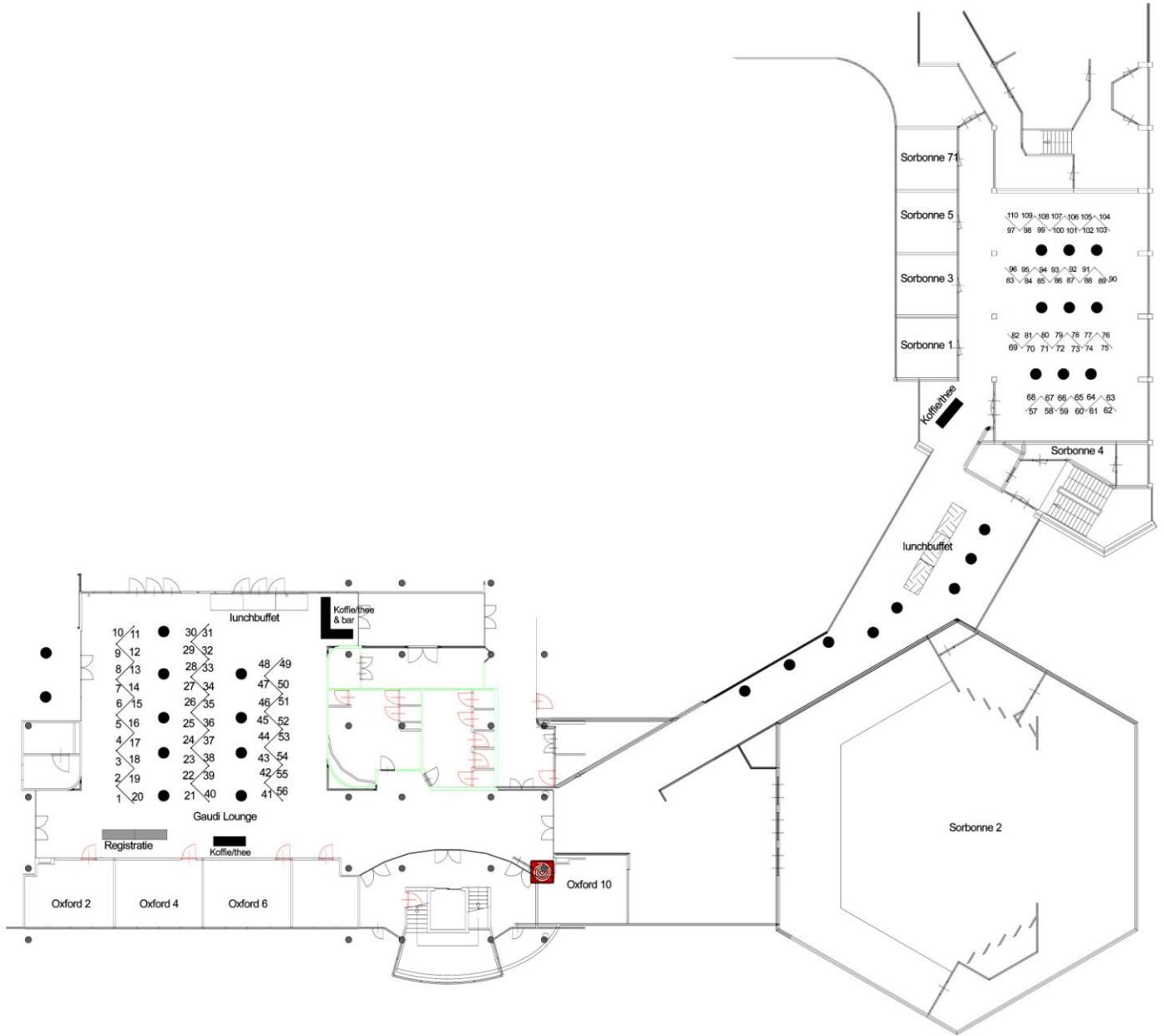
Prof. Pieter Reitsma (LUMC)

16.55 **Closing remarks**

Prof. Vincent Christoffels (AMC)

17.00-18.00 Drinks

Floor plan



Abstract Keynote Lecture 1

Diversity and cardiovascular health: some results from the HELIUS study

Prof. Koos Zwinderman

Dept of clinical epidemiology and biostatistics, AMC

The HELIUS study is a Dutch multi-ethnic cohort study which since 2008 has collected data regarding cardiovascular riskfactors from 10000 participants (18-70 years old) of ethnic Dutch, Surinamese of African and of South Asian origin, Turkish or Moroccan origin in the Amsterdam region. Relationship between ethnicity and cardiovascular riskmarkers will be discussed.

Abstract Keynote Lecture 2

Dynamic interactions between leukocytes and the endothelium: the diapedesis synapse.

Dr. Jaap van Buul

Dept. Molecular Cell Biology, Sanquin

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Abstract Keynote lecture 3

Regulation of vascular remodelling: Inflammation, Immune modulation and microRNAs

Prof. Paul Quax

Dept. of Experimental Vascular Medicine, LUMC

Paul Quax is professor in Experimental Vascular Medicine and working at the department of Surgery of the LUMC and the Einthoven Laboratory for Experimental Vascular Medicine. His research interest is vascular remodeling both in a positive way during neovascularisation, angiogenesis and arteriogenesis , and in a negative way during atherosclerosis, restenosis and vein graft disease. Understanding the common mechanisms in these processes and defining new therapeutic interventions to induce or prevent vascular remodeling is the central theme of his research.

Abstract Keynote lecture 4

Go with the flow in pulmonary hypertension

Dr. Harm Jan Bogaard

Dept. of Pulmonology, ICaR-VU/VUmc

After completing my PhD on hemodynamic responses to exercise in patients with COPD, I worked as a post-doctoral fellow at the UCSD division of physiology San Diego, CA, studying cardiovascular adaptation to high altitude. In 2007, after completing my clinical training, I joined the lab of Norbert Voelkel (Richmond) to study mechanisms of pulmonary hypertension and -associated right heart failure. After identifying a molecular signature of right heart failure, I was able to show that adrenergic receptor blockade effectively reverses right heart remodeling and failure. Currently, I am co-PI of a randomized clinical trial translating these findings to PAH patients. Other projects in which I acted as a PI, concern the detrimental effects of dietary copper insufficiency and histone deacetylase inhibition on right heart adaptation to pressure overload and the comparison of different PAH animal models. Recognizing that the contemporary focus on a cancer-paradigm in PAH research has led to the application of anti-proliferative and anti-angiogenic treatments without a clear rationale, but with potential cardiotoxic side-effects, I have recently decided to gain a better understanding of mechanisms of pulmonary vascular remodeling. I am PI of a Dutch Lung Foundation sponsored project to determine the response of PAH patient-derived lung microvascular endothelial cells to increased shear stress and co-PI of a CVON program to determine the role of TGF β /BMP imbalance in pulmonary hypertension.

Abstracts Oral presentations

In vivo pathophysiology of hypertrophic cardiomyopathy in a highly prevalent 25 bp deletion mutation in MYBPC3

Diederik W.D. Kuster (1,2), David Barefield (1), Suresh Govindan (1), Sivaguru Mayandi (3), Kyoungwan Lee (4), Roger Craig (4) and Sakthivel Sadayappan (1).

1 Dept of Cell and Molecular Physiology, Loyola University Chicago, Maywood IL

2 Dept of Physiology, VU University Medical Center, Amsterdam

3 Univ of Illinois at Urbana-Champaign, Urbana, IL

4 Univ of Massachusetts Medical Sch, Worcester, MA

Background and aim: A polymorphic deletion of 25 base pair (bp) in the cardiac myosin binding protein-C (cMyBP-C) gene, resulted in a modified C10 domain (cMyBP-CC10MUT) that associated with hypertrophic cardiomyopathy (HCM). The 25 bp deletion leads to the replacement of 65 amino acids with a novel sequence of 58 amino acids in the C10 domain at C'-region. Prevalence of this mutation was found to be very high, with >55 million carriers worldwide. However, the mechanism by which this mutation leads to cardiomyopathy is unknown. Hypothesis: cMyBP-CC10MUT expression directly causes contractile dysfunction and leads to the development of HCM.

Methods and results: Expression of cMyBP-CC10MUT in cultured isolated adult rat cardiomyocytes led to improper localization and contractile dysfunction such as reduced fractional shortening and velocities of shortening and relaxation, but did not affect calcium handling in vitro, suggesting that cMyBP-CC10MUT impairs contractile function. To further demonstrate that cMyBP-CC10MUT is sufficient to cause HCM and contractile dysfunction in vivo, transgenic mice were generated in which the C10 domain of cMyBP-C was modified to cMyBP-CC10MUT. Transgenic lines with 50% mutant expression compared to endogenous cMyBP-C show significant increase in heart weight/body weight ratio in females only by 12 weeks of age (4.41 ± 0.09 mg/g NTG, 4.94 ± 0.17 mg/g C10mut), compared to non-transgenic littermates. M-mode echocardiography analysis showed hypercontractile hearts (EF: $53.8\% \pm 4.3\%$ NTG, $66.4\% \pm 4.7\%$ C10mut), but early diastolic dysfunction (E/E' : 32.3 ± 5.7 NTG, 46.3 ± 8.4 C10mut) indicating the presence of HCM phenotype. Histopathological analyses demonstrated that cMyBP-CC10MUT hearts showed no evidence of myofibrillar necr

Conclusions: Expression of cMyBP-CC10MUT protein is sufficient to cause contractile dysfunction and HCM. Results from this study demonstrated the pathophysiology of the cMyBP-CC10MUT, the most common cardiomyopathy associated gene mutation.

Funding: American Heart Association

TRAF-STOP-HDL-nanoparticles reduce atherosclerosis

Claudia van Thiel¹, Pascal Kusters¹, Tom Seijkens¹, Barbara Zarzycka², Marion J. Gijbels¹, Menno P.J. de Winther¹, Christian Weber³, Gerry A.F. Nicolaes³, Willem Mulder^{1,4}, Esther Lutgens¹,

1Dept of Medical Biochemistry, AMC, Amsterdam; 2Dept of Biochemistry, University of Maastricht; 3IPEK, LMU, Munich; 4Mount Sinai School of Medicine, New York.

Background and aim: Inhibition of the co-stimulatory CD40-CD40L receptor/ligand dyad drastically reduces atherosclerosis. However, its long-term blockage results in immune suppression. Inhibition of the CD40-CD40L dyad further downstream in the signaling pathway is therefore required. The interaction between CD40 and its signaling intermediate TNF receptor associated factor 6 (TRAF6) plays a pivotal role in atherosclerosis.

Methods and results: To identify drug like molecules that inhibit the CD40-TRAF6 interaction, an in silico structure-based virtual ligand screening approach was used. Several small molecule inhibitors (SMI) blocking CD40-TRAF6 interactions were identified. Surface plasmon resonance experiments confirmed direct binding of the compounds to the TRAF6 C-domain. Two of these SMIs, the TRAF-STOPS, reduced atherosclerosis by >40% in ApoE^{-/-} mice by hampering monocyte and neutrophil recruitment. In accordance, expression of chemokines and cytokines was remarkably reduced in compound treated macrophages. However, these SMIs had a low solubility, and had a half-life of only 8 hrs, and had to be injected daily. To improve the therapeutic applicability of our TRAF-STOPS, TRAF-STOP 6877002 was packed in HDL-based nanoparticles, and administered twice a week for 6 wks (wk 12-18) to ApoE^{-/-} mice.

The HDL-TRAF-STOP nanoparticles preferentially homed to macrophages, and the expression level in plaque macrophages was high. HDL-TRAF-STOP nanoparticle treatment reduced atherosclerosis by 42.6%.

Conclusions: These newly developed, nanoparticle based CD40-TRAF6 inhibiting SMIs (TRAF-STOPS) are a promising lead for the developments of therapeutics for the treatment of atherosclerosis.

Funding: This work was supported by the Netherlands Heart Foundation (Dr E. Dekker grant to TS, established investigator grant to EL), and the Netherlands Organization for Scientific Research (NWO) (VICI grant to EL).

Inhibition of 14q32 MicroRNA miR-494 Reduces Atherosclerotic Lesion Formation, Increases Plaque Stability and Lowers Cholesterol Levels

Anouk Wezel¹⁻³, Sabine Welten^{2,3}, Wida Razawy¹⁻³, Max Lagrauw¹, Margreet de Vries^{2,3}, Ekambar Kandimalla⁴, Johan Kuiper¹, Paul Quax^{2,3}, Ilze Bot^{1,2*}, Yaël Nossent^{2,3*}

1 Division of Biopharmaceutics, Leiden Academic Centre for Drug Research, Leiden University, 2 Department of Surgery, Leiden University Medical Center and 3 Eindhoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, the Netherlands 4 Idera Pharmaceuticals, Cambridge, MA, USA

** Authors contributed equally to this work*

Background and aim: Atherosclerosis is a multifactorial disease involving inflammatory, metabolic and lipid-related processes. As microRNAs (miRs) regulate expression of up to several hundred target genes, we hypothesized that specific miRs may target not just single aspects of atherosclerosis, but atherosclerosis as a whole. We set out to identify miRs that target genes in all processes involved in atherosclerotic plaque formation. Using www.targetscan.org, we performed a reverse target prediction on a set of 163 atherosclerosis-related genes. We found enrichment of binding sites for multiple miRs from the 14q32 miR-gene cluster.

Methods and results: Expression patterns of three top-ranking 14q32 miRs was measured in various organs involved in atherosclerosis, including the liver, spleen and arteries of hypercholesterolemic mice. Based on these data, miR-494 was selected for further investigations. A Gene Silencing Oligonucleotide (GSO) was used to inhibit miR-494 in apoE^{-/-} mice after placing semi-constrictive collars around both carotid arteries to induce atherosclerotic lesion formation over the course of 28 days. Atherosclerotic plaque analysis revealed a reduced lesion size in mice treated with GSO-494 (GSO-Control: $47 \pm 11 \times 10^3 \mu\text{m}^2$; GSO-494: $16 \pm 3 \times 10^3 \mu\text{m}^2$). Moreover, plaque stability was increased in mice treated with GSO-494, determined by both a significant decrease in necrotic core size (GSO-494: 80% decrease compared to GSO-Control) and a significant increase in plaque collagen content (GSO-Control: $6.6 \pm 1.6\%$; GSO-494: $12.7 \pm 2.1\%$). Furthermore, inhibition of miR-494 resulted in decreased plasma total cholesterol levels (GSO-Control: $30.4 \pm 1.1 \text{ mM}$; GSO-494: $26.4 \pm 0.7 \text{ mM}$) and decreased VLDL fractions.

Conclusions: Inhibition of miR-494 leads to reduced plaque size, increased plaque stability and reduced plasma cholesterol levels, rendering this miR a promising novel therapeutic target in the prevention of atherosclerotic lesion formation.

Funding: This study was supported by grants from the Dutch Heart Foundation (A.W.: 2010B029 and H.M.L.: 2010B244), the Netherlands Organisation for Scientific Research (A.Y.N.: Veni 916.12.041), the Leiden University Fund/Nypels- van der Zee Fund (2219/5-4-12\NZ) and the Netherlands Institute for Regenerative Medicine (S.M.J.W.: NIRM, FES0908). We acknowledge the support from the Netherlands CardioVascular Research Initiative: "the Dutch Heart Foundation, Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development and the Royal Netherlands Academy of Sciences" for the GENIUS project "Generating the best evidence-based pharmaceutical targets for atherosclerosis" (CVON2011-19).

Lipoprotein(a) causes cellular and arterial wall inflammation via epigenetic remodelling.

Fleur van der Valk¹, Siroon Bekkering², Jeffrey Kroon³, Niels Riksen², Max Nieuwdorp¹, Sam Tsimikas, Jaap van Buul³, Mihai Netea², Erik Stroes¹.

1Department of Vascular Medicine, AMC, Amsterdam, The Netherlands.

2Department of Experimental Internal Medicine, Radboud, Nijmegen, The Netherlands.

3Department of Vascular Medicine, Sanquin, Amsterdam, The Netherlands.

4Department of Cardiovascular Medicine, UCSD, LaJolla, California.

Background and aim: Lipoprotein(a) (Lp(a)) is an independent causal risk factor for cardiovascular disease, however, its pathogenic mechanism has remained conjectural. Recently, Lp(a) was described as the preferential carrier of oxidized phospholipids (oxPL) in plasma, which represent a family of danger signals readily detected by innate immune cells. Therefore, we hypothesized that Lp(a) has pro-atherosclerotic inflammatory effects in humans.

Methods and results: First, we performed multimodal imaging studies demonstrating an increased atherosclerotic burden and inflammatory activity via magnetic resonance and positron emission tomography, respectively, in subjects with isolated Lp(a) elevation and matched controls in vivo. To determine the role of cellular activation, we performed ex vivo characterization studies on monocytes isolated from subjects with raised Lp(a) and controls, demonstrating the increased expression of activation and transmigration markers on monocytes analyzed by flow cytometry. The pathophysiological relevance of monocyte activation was validated by re-infusion of image-traced autologous leukocytes in vivo into Lp(a) subjects and controls. Finally, we used an in vitro model to dissect the causality and mechanism by which Lp(a) effectuates monocyte activation, and we found that Lp(a), in specific via its oxPL load, induces long-lasting alterations in the epigenome of circulating monocytes resulting in a pro-inflammatory state.

Conclusions: Taken together, Lp(a) elicits monocyte activation via epigenetic remodeling leading to accelerated monocyte influx and increased arterial wall inflammation. These data imply that Lp(a)-induced monocyte activation may contribute to the increased cardiovascular risk, thereby offering new therapeutic options for patients with elevated Lp(a).

Poster presentations

Atherosclerosis Clinical

- 1 J. van Capelleveen (AMC):** Mutations in ABCA8 are associated with low HDL-C suggesting an important role in HDL metabolism
- 2 S. Bernelot Moens (AMC):** Increased arterial wall inflammation in patients with rheumatoid arthritis in remission
- 3 K. Ritz (AMC):** Etiology and mechanisms of intracranial atherosclerosis

Atherosclerosis Experimental

- 4 E. Prins (LUMC):** Post-transcriptional regulation of γ -adducin by the RNA-binding protein Quaking during monocyte to macrophage differentiation
- 5 H. Hartwig (AMC):** PNeutrophils in human atherosclerosis
- 6 T. van der Heijden (LACDR):** Identify the adaptive immune pathways unique to atherosclerosis in the context of dyslipidemia
- 7 H. Lagraauw (LACDR):** Acute stress exposure reduces atherosclerotic plaque stability via mast cell activation
- 8 A. Hamers (AMC):** Liposomal Prednisolone delivery to the atherosclerotic plaque
- 9 S. van de Tuin (LACDR):** Anacetrapib decreases (V)LDL-cholesterol by increasing the uptake of VLDL remnants by the liver
- 10 Baoyan Ren (LACDR):** Macrophage Akt2 deficiency does not affect Atherosclerosis Development in LDL
- 11 R. van der Geest/M.Hoekstra (LACDR):** Glucocorticoid-mediated immunosuppression underlies the cholestasis-induced atherosclerosis resistance
- 12 J. van den Bossche (AMC):** Inhibiting epigenetic enzymes to improve atherogenic macrophage functions
- 13 V. Frodermann (LACDR):** Proteasomal Inhibition Reduces Atherosclerotic Lesion Development
- 14 J. Nahon (LUMC):** PRG4 as a potential novel target in atherosclerosis
- 15 R. van der Sluis (LUMC):** Absence of PLTP function in SR-BI Knockout Mice Shifts Lipids from HDL to VLDL/LDL and Reduces Atherosclerosis
- 16 E. Kritikou (LACDR):** Effects of LPA1-receptor antagonism on atherosclerosis
- 17 L. Hoving (LUMC):** The effect of the dietary fiber inulin on atherosclerosis in APOE*3-Leiden.CETP mice
- 18 E. Smeets (AMC):** E3 ubiquitin-protein ligase Cbl-b in atherosclerosis
- 19 M. de Vries (LUMC):** VEGFR2 blockade in murine vein graft ameliorates lesion growth and enhances plaque stability by reducing intraplaque haemorrhage
- 20 D. Bink (AMC):** Vessel characteristics may explain the lack of intracranial atherosclerosis in mice
- 21 K. Dekkers (LUMC):** Elevated triglyceride levels induce DNA methylation changes in circulating cells

Autoimmunity and Inflammation

- 22 F. Stephan/G. Marsman (Sanquin):** Nucleosome release from late apoptotic cells is inhibited by autoantibodies present in SLE
- 23 W. Fuijkschot (LUMC):** Accumulation of N (ϵ)-(carboxymethyl)lysine in intramyocardial blood vessels and blood vessels of the brain in apo E $-/-$ mice is age-related and inhibited by docosahexaenoic acid in the heart
- 24 S. Aarts (AMC):** The effects of small molecule inhibitors of the CD40-TRAF6 interaction on experimental autoimmune encephalomyelitis (EAE)

- 25 P. de Groot (AMC):** Short-chain fatty acid metabolism and the gut microbiome in type 1 diabetes

Cardiac arrhythmia

- 26 H. van Weert (AMC):** A large permissive regulatory domain controls TBX3 expression in the cardiac conduction system
- 27 S. Stefanovic (AMC):** Genome-wide analysis identifying the epigenetic signature underlying the sinoatrial node identity
- 28 G. Kosmidis (LUMC):** Effects of Readthrough Promoting Drugs in Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes Carrying Nonsense SCN5A Mutations.
- 29 S. Podliesna (AMC):** HEY2, a novel susceptibility gene for Brugada Syndrome, controls depolarization and repolarization gradients in the RVOT and across the ventricular wall
- 30 V. Portero (AMC):** Electrophysiological effects of late sodium current inhibitor GS967 in Scn5a-1798insD mouse and human SCN5A-1795insD iPSC-derived cardiomyocytes
- 31 G. Marchal (AMC):** Electrical and structural abnormalities in homozygous Scn5a-1798insD mutant embryos
- 32 Z. Neshati (LUMC):** Forced NFAT3 expression in hypertrophic myocardial cultures prevents focal tachyarrhythmias by inhibiting triggered activity through reverse L-type calcium channel remodelling
- 33 M. Engels (LUMC):** Fusion of Cultured Human Ventricular Scar Cells with Cardiomyocytes Reduces Arrhythmogenicity by Preventing Early Afterdepolarizations through Increased Repolarization Force

Cardiac function

- 34 M. Chugtai (LUMC):** Morphogenesis of the bicuspid aortic valve in the NOS3 knock out mouse
- 35 E. van Deel (VUmc):** Altered Substrate Stiffness Affects Sarcomere Function and Ca²⁺ Dynamics
- 36 B. Kruithof (LUMC):** Mimicking Heart Valve Disease In An Ex Vivo Flow Model
- 37 B. Jensen (AMC):** Evolution of the sinus venosus of the heart
- 38 K. van Duijvenboden (AMC):** Powerful Prediction of Enhancer Sites Through Integration and Modeling of Functional Genomic Signatures
- 39 K. Dingenouts (LUMC):** DPP4 inhibition increases MNC homing but deteriorates cardiac recovery in Eng^{+/-} mice
- 40 W. Jong (AMC):** NLRP3 INFLAMMASOME RECEPTOR AFFECTS STAT3 SIGNALLING BUT PLAYS NO ROLE IN ACUTE MYOCARDIAL INFARCTION DUE TO LOW EXPRESSION IN A CLOSED-CHEST CARDIAC I/R MODEL
- 41 C. Zuurbier (AMC):** GOING FROM THE LAB TO THE CLINIC: WE NEED MORE PRE-CLINICAL STUDIES BEFORE EMBARKING ON WASTEFUL CLINICAL TRIALS: A FOLIC ACID CASE STUDY
- 42 A. Najefi (VUmc):** Sexual dimorphic response to exercise in hypertrophic cardiomyopathy- associated MYBPC3-targeted knock-in mice
- 43 N. Rol (VUmc):** Exploring the role of TGF-beta in Pulmonary Arterial Hypertension.
- 44 A. Bronzwaer (AMC):** Individual differences and stability of cardiovascular control in response to orthostatic stress
- 45 J. Verbree (LUMC):** Individual differences and stability of cardiovascular control in response to orthostatic stress

Heart failure

- 46 R. Mohan (AMC):** Early specification and progressive restriction of the cardiac conduction system lineage during heart development

- 47 S. Duim (LUMC):** Cardiac endothelial cells express Wilms' tumor-1 Wt1 expression in the developing, adult and infarcted heart.
- 48 D. Bos (VUmc):** Renal Denervation Reduces Pulmonary Vascular Remodeling through Renin Angiotensin System in Experimental Pulmonary Arterial Hypertension
- 49 C. Happe (VUmc):** Pneumonectomy combined with SU5416 induces severe angio-obliterative pulmonary hypertension in rats
- 50 R. Wust (VUmc):** Mitochondrial and bio-energetic dysfunction in rat myocardium in chronic heart failure
- 51 A. Ruiz-Villalba (AMC):** Epicardial-derived interstitial fibroblasts and bone marrow-derived interaction determines post-infarction ventricular remodeling
- 52 L. Medzikovic (AMC):** Elevated diastolic Ca²⁺ and enhanced β -adrenergic-induced cardiac hypertrophy in Nur77-KO mice
- 53 G. Balestri (AMC):** INCREASED IN VIVO MITOCHONDRIAL OXYGENATION WITH RIGHT VENTRICULAR FAILURE
- 54 I. Bollen (VUmc):** THE ROLE OF TITIN ISOFORM COMPOSITION IN DILATED CARDIOMYOPATHY AND PERIPARTUM CARDIOMYOPATHY
- 55 A. Jansweijer (AMC):** Truncating TTN mutations cause a relatively mild and treatable form of DCM
- 56 S. Stienen (AMC):** Absolute Discharge Levels or Relative Reduction in NT-proBNP during Admission for Acute Decompensated Heart Failure as a Target to Reduce 6-month Mortality?
- 57 A. Vermeer (AMC):** Transthyretin amyloidosis: a phenocopy of hypertrophic cardiomyopathy
- 58 E. Lodder (AMC):** Homozygous Mutations in GNB5 and SYDE2 in patients with autosomal recessive bradycardia

Imaging

- 59 L. Smits (AMC):** Distinguishing hepatic steatosis from steatohepatitis by magnetic resonance imaging enhanced with ultrasmall superparamagnetic iron oxide particles
- 60 Ahmet Guclu (VUmc):** Myocardial efficiency is an important determinant of functional improvement after aortic valve replacement in aortic valve stenosis patients: a combined PET and CMR study

Metabolism

- 61 R. van den Berg (LUMC):** Light at night promotes adiposity: crucial role for brown adipose tissue
- 62 J. van den Heuvel (LUMC):** A novel selective glucocorticoid receptor modulator reduces obesity as well as adipose tissue and liver inflammation
- 63 S. van den Berg (AMC):** Blocking CD40-Traf6 interactions by small molecule inhibitor 6860766 ameliorates the complications of diet induced obesity in mice
- 64 R. Nederlof (AMC):** Hexokinase binding to mitochondria regulates mitochondrial oxygen consumption and energy production and protects against ischemic insult through ROS reduction
- 65 P. Khedoe/G.Hoeke (LUMC):** Brown adipose tissue takes up plasma triglycerides mostly after lipolysis
- 66 J. Geerling (LACDR):** Metformin lowers plasma triglycerides by promoting VLDL-triglyceride clearance by brown adipose tissue in mice
- 67 S. Udayappan (AMC):** Intestinal Ralstonia pickettii drives visceral adipose tissue inflammation and insulin resistance
- 68 A. van Dam (LUMC):** Salsalate activates brown adipose tissue: implications for the treatment of type 2 diabetes
- 69 M. van den Boogert (AMC):** CDG 2 plus patients with Golgi trafficking disorders have high plasma VLDL-cholesterol

- 70 R. Surendran (AMC):** Impaired insulin signaling in T2DM leads to decreased expression of GPIHBP1
- 71 B. Sjouke (AMC):** Effects of Supra-Physiological Levothyroxine Dosages on Lipids, Lipoproteins and Liver Parameters in Healthy Volunteers: A Randomized Controlled Crossover Study

Stem cells

- 72 M. Hoekstra (AMC):** The SCN5A1795insD/+ Mutation Results in Increased Intracellular Calcium Concentrations in Human Cardiomyocytes Derived from Induced Pluripotent Stem Cells
- 73 A. Smits (LUMC):** Optimising the cardiac post-injury response; identifying novel regulators of epicardial EMT
- 74 M. Aleksinskaya (LUMC):** Chronic kidney disease is associated with hematopoietic stem cell niche dysfunction
- 75 C. Veerman (AMC):** Effects of Readthrough Promoting Drugs in Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes Carrying Nonsense SCN5A Mutations
- 76 J. Maring (LUMC):** Exosomes in Cardiac Repair

Thrombosis and Hemostasis

- 77 M. van der Stoep (LUMC):** IMPAIRED PLATELET RESPONSE TO COLLAGEN IN HYPERLIPIDEMIC MICE
- 78 H. Levels (AMC):** Proteome of human plasma Very Low-Density Lipoprotein and Low-Density Lipoprotein exhibits a link with coagulation and lipid metabolism
- 79 M. Heestermans (LUMC):** INVOLVEMENT OF PLATELET AND NEUTROPHIL POPULATIONS IN THE DEVELOPMENT OF RNA INTERFERENCE-INDUCED VENOUS THROMBOSIS
- 80 M. Hofman (Sanquin):** Requirements for VWF mediated targeting of IGFBP7 to Weibel-Palade bodies
- 81 C. Tieken (LUMC):** Tissue Factor predicts survival and regulates tumor progression in osteosarcoma
- 82 B. Unlu (LUMC):** A regulatory role for alternatively spliced tissue factor in blood clotting
- 83 C. Tieken (LUMC):** Ectopic Factor VII expression diminishes survival in breast cancer
- 84 C. van der Sluijs (LUMC):** Large-scale production of recombinant proteins using a bioreactor
- 85 A. Ouweneel (LACDR):** Silencing Antithrombin and Protein C in ApoE knockout mice: A Potential Model for Atherothrombosis
- 86 S. Korshidi (LUMC):** Improving the functional expression of human factor IX by heterologous substitution of the signal peptide and propeptide sequences
- 87 D. Verhoef (LUMC):** Evolutionary conservation of regulatory structural elements in blood coagulation factor V in the Serpentes suborder
- 88 L. Wierstra (AMC):** Low-dose intra-arterial thrombolysis in acute limb ischemia results in less major bleeding
- 89 I. Rietveld (LUMC):** Factor V is associated with a limited increased risk for venous thrombosis

Vascular Biology

- 90 L. Rotteveel (VUmc):** Imaging of the activin-like kinase 5 with [11C]-isobutyl ((5-(benzo[d]thiazol-6-yl)-4-(4-methylthiazol-2-yl)-1H-imidazol-2-yl)methyl)carbamate as positron emission tomography tracer
- 91 W. Bakker (LUMC):** P Cardiac function Impaired macrophage polarization in endoglin haplo-insufficiency leading to defective tissue repair is recovered by counter balance the TGFbeta pathway

- 92 M. Dane (LUMC):** Prolonged Shear Stress Modifies the Composition of the Endothelial Glycocalyx
- 93 D. van Breevoort (Sanquin):** Regulation of stimulated and basal release of Weibel-Palade bodies by syntaxin-3 containing SNARE-complexes
- 94 S. Meiler (AMC):** GITR-GITRL system, a novel player in atherosclerosis
- 95 P. Bus (LUMC):** Mice transgenic for apolipoprotein C1 develop proteinuria and progressive glomerulosclerosis
- 96 M. Pronk (VUmc):** RhoC in endothelial cells: a new key regulator of vascular permeability?
- 97 S. Meiler (AMC):** Role of CD27-CD70 in atherosclerosis
- 98 M. Boshuizen (AMC):** Crosstalk between interferon-beta, foam cell formation and inflammatory responses
- 99 J. Amado-Azevedo (VUmc):** RhoGTPases and RNAi: a large-scale screen using ECIS® to measure endothelial integrity in real-time
- 100 S. Wanga (AMC):** Enhanced calcification markers in Marfan mouse and Marfan patient aorta.
- 101 M. Dallinga (AMC):** CD34 marks angiogenic tip cells in human vascular endothelial cell cultures
- 102 S. Hibender (AMC):** In Marfan Mice, Resveratrol inhibits Aortic Dilatation more potently than Losartan
- 103 C. van Thiel (AMC):** Filamin A: a novel binding partner of CD40 in atherosclerosis and required for translocation of CD40 to lipid rafts in endothelial cells
- 104 S. Welten (LUMC):** Inhibition of Individual 14q32 MicroRNAs Drastically Increases Neovascularization and Blood Flow Recovery after Ischemia
- 105 A. de Raaf (VUmc):** Intact serotonin signaling is not required for the development of severe angioproliferative pulmonary hypertension in rats
- 106 B. van den Berg (LUMC):** Genetic endothelial hyaluronan deletion results in glomerular injury and albuminuria
- 107 B. Franken (AMC):** Suppressing Inflammation in Marfan Syndrome: Be Careful!
- 108 L. Weijermans (LUMC):** Preventing mitochondrial complex I dysfunction and loss of oxidative capacity by SS-31 in renal I/R injury
- 109 R. Bierings (Sanquin):** Regulation of stimulated and basal release of Weibel-Palade bodies by syntaxin-3 containing SNARE-complexes
- 110. C. van der Bruggen (VUMC)** Right ventricular adaptation and treatment response in pulmonary arterial hypertension patients with a bone morphogenetic protein receptor 2 mutation

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