LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

ANNUAL REPORT

2018-2019

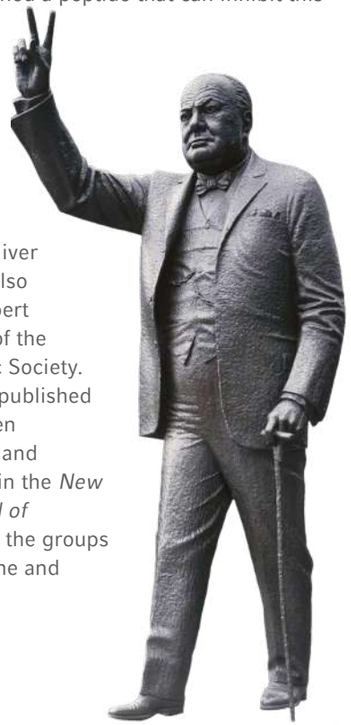
Institute for Cardiovascular Prevention

IPEK

Editorial

Over the last two years, IPEK has seen major developments and accomplishments. Of course, we should all comply with the convincing heuristic rule of ethics inspired by Nicolas Nassim Taleb (the author of Black Swan): “Take a minute to decide whether you would rather be praised and not praiseworthy or whether you would rather be praiseworthy and not be praised.” Nevertheless, keeping the record is sometimes called for and I am glad to acknowledge and reflect on this period’s most important achievements by those whose hard work is the essence of success and at the very heart of this Institute.

In 2018, with the advent of the new DZHK junior research group on molecular adaption to cardiac stress, its leader Alexander Bartelt was appointed as a W2 Professor for Cardiovascular Metabolism. A number of awards were presented to IPEK scientists: Yvonne Döring received the W.H. Hauss-Prize of the German Atherosclerosis Society, Alexander Bartelt the Friedmund Neumann Prize 2018 from the Schering Foundation, and Esther Lutgens the Outstanding Achievement Award of the European Society of Cardiology. The groups of Oliver Söhnlein and Andreas Schober prominently published the influence of circadian rhythms and non-coding RNA interactions on atherosclerosis in *Cell Metabolism* and *Nature Communications*, respectively. A number of IPEK researchers and their groups were awarded a continued large-scale funding in the collaborative research centre CRC1123 as well as in ERA-CVD and Leducq transatlantic networks on the mechanisms of atherosclerosis. In 2019, Changjun Yin et al. identified a role of apolipoprotein E in inhibiting active C1q complement through complex formation as a hallmark and common mechanism for unresolved inflammation in Alzheimer’s disease and atherosclerosis. These important findings published in *Nature Medicine* won Changjun Yin the Bayer Thrombosis Award in 2019. Carlos Silvestre-Roig and Quinte Braster contributed equally to a study published in *Nature*, demonstrating how neutrophil-derived histone H4 exacerbates plaque destabilization by inducing smooth muscle-cell death and designed a peptide that can inhibit this process. For their work, they received the Rolf Becker-Prize together with the responsible senior author Oliver Söhnlein, who also received the Albert Fraenkel-Prize of the German Cardiac Society. Esther Lutgens published on a link between haematopoiesis and atherosclerosis in the *New England Journal of Medicine*, while the groups of Johan Duchene and Remco Megens characterized the origin and function of non-classical monocytes in *Science Immunology*. This enabled a funding network awarded by the British Heart Foundation and DZHK.



Success is not final, failure is not fatal.
It is the courage to continue that counts...
Winston Churchill

For those, deserving but so far less successful or fortunate during peer review, I wish to refer to Hidde Ploegh’s brilliant *Nature* comment in 2011, where he elegantly captures the sometimes wasteful tyranny of reviewers from top journals and outlines his ideas how to end it: The scientific community should rethink how manuscripts are reviewed. Referees should be instructed to assess the work in front of them, not what they think should be the next phase of the project. They should provide unimpeachable arguments that demonstrate the study's lack of novelty or probable impact, or that lay bare flawed logic or unwarranted conclusions. They should abandon the attitude that screams: "look, I've read it, I can be as critical as the next dude and ask for something that's not yet in the manuscript", a reflexive approach to reviewing that has unfortunately become more or less standard. Many reviewers are also, of course, authors, who will receive such unreasonable demands … and relish the chance to inflict their experiences on others. While this clearly requires some introspection from all of us, others may take a more cynical approach and follow a running joke in academia about Reviewer 2, who is the one that does not bother to read the manuscript and only offers condescending or even offensive comments. Until all obstacles can successfully be overcome all obstacles, the Facebook group “Reviewer #2 must be stopped” may offer some consolation.

Emanating from and reflecting on some of my past editorials, i.e. a variation to the recurring theme of slow science, I would like to further develop and define our scientific ductus, which somehow resembles evolution more than revolution. Scientific progress like evolution must indeed be neither too slow nor too fast. Too slow means extinction from lack of adaption. Too fast prevents retaining the benefits of past improvements, hence again extinction.

So, very much like the Bach family, whose outstanding command of traditional and classical songs and music enabled them to improvise and polyphonically merge different melodies (beautifully mirrored in the eponymous 30th Goldberg variation Quodlibet), thereby creating completely new and unexpected pieces, we see this concerted effort as a model for the IPEK to strive for achieving the next innovative and groundbreaking advances in vascular medicine.

Christian Weber

Contents

Christian Weber is Chair in Vascular Medicine and the Director of the Institute for Cardiovascular Prevention at Ludwig-Maximilians-University (LMU) Munich, Germany, since 2010. After graduating and completing his training in internal medicine at LMU and Harvard Medical School, Boston, he was board-certified in clinical cardiology and appointed as a Chair in Molecular Cardiology at RWTH Aachen University. As a Dutch VICI laureate, he continues to serve as an Adjunct Professor at the Cardiovascular Research Institute Maastricht (CARIM) at Maastricht University. As an outstanding scientist and internist, Prof. Dr. Christian Weber, has made ground-breaking contributions to understanding the pathogenesis of atherosclerosis towards new therapeutic avenues. Throughout the years, Dr. Weber has been defining the role of inflammation and immune mediators in atherosclerosis. He has pioneered and identified mechanisms by which chemokines and microRNAs are implicated in atherosclerosis and has made a number of innovative discoveries that are of fundamental relevance and high translational potential beyond the field of internal medicine. His conceptual and technical innovations have set international standards for internal and vascular medicine. Since 2014, he is the spokesman of the DFG Collaborative Research Centre (CRC 1123) on the topic of atherosclerosis and therapeutic targets. He also coordinates the partner site Munich Heart Alliance in the German Centre for Cardiovascular Research (DZHK).

So far, these findings have led to > 615 publications (383 originals, 118 of which as a first/last authors) with a cumulative impact factor > 4800, which have been cited > 40,000/58,000 times and have achieved an h-index of 105/125 (Scopus or GoogleScholar). These outstanding achievements in the field have been honoured by foundations and societies through a number of national and international awards. Dr. Weber has been awarded the GlaxoSmithKline Science Prize, Paul Martini Prize, Arthur Weber Prize, Alexander Schmidt Prize, Outstanding Achievement Award of the ESC, ATVB Special Recognition Award of the AHA and Galenus von Pergamon Prize. He is also a VICI Prize winner and Professor at the University of Maastricht, Editor-in-Chief of Thrombosis & Haemostasis and Senior Editor of Arteriosclerosis, Thrombosis & Vascular Biology and is the co-founder of Carolus Therapeutics Inc. As a rare award at the European level, Dr. Weber has received two ERC Advanced Grants and is listed by the information portal ExpertScape as the world's leading expert on atherosclerosis.

As an academic teacher, Dr. Weber is committed to actively promoting and mentoring the next generation of researchers and has supervised > 20 PhD students and > 17 postdocs. With his support, many young scientists have become important figures in international atherosclerosis research, and have been awarded professorships or full professorships, e.g. Profs Lutgens, Zernecke, Schober, Soehnlein, Gerdes, and Doering. He has significantly served global vascular medicine as a leader of many organizations, e.g. ESC, IVBM and DZHK.

Institute Director

The Institute for Cardiovascular Prevention (IPEK) is organised into two independent divisions, with an interplay between clinical care and research. In addition to its director, the institute is led by twenty-five group leaders with distinct research fields, including two C3 professors, three W2 professors and eight associate professors, who supervise individual research groups. The Institute also comprises the DFG "Atherosclerosis" Collaborative Research Center 1123, the Editorial Office of the journal Thrombosis & Haemostasis and is one of the Institute of the Munich Heart Alliance (MHA) the German Center for Cardiovascular Research (DZHK).

Organisation

August-Lenz-Stiftung

Hintergrund

Kurze Historie des Instituts für Prophylaxe und Epidemiologie der Kreislaufkrankheiten und der August-Lenz-Stiftung.

Das heutige Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten entwickelte sich historisch aus zwei Wurzeln: Bereits in den frühen Wirtschaftswunderjahren nahmen kardiovaskuläre Erkrankungen erkennbar zu. Auf Betreiben des Bayerischen Landtags schuf die Medizinische Fakultät der Ludwig- Maximilians-Universität deshalb bereits 1954 einen neuen Lehrstuhl für Prophylaxe der Kreislaufkrankheiten. Es standen jedoch zunächst keine Mittel für eine ausreichende Ausstattung des Lehrstuhls zur Verfügung. Zu dessen kommissarischem Leiter wurde Prof. Dr. Gustav Schimert ernannt. Prof. Schimert, seit 1949 außerplanmäßiger Professor an der II. Med. Klinik der Universität, gewann offenbar bei seiner Behandlung die besondere Wertschätzung des Münchner Bankiers und Industriellen August Lenz. Dieser beschloss daraufhin, eine Stiftung zur erhütung von Kreislauferkrankungen zu errichten und so die adäquate Ausstattung des Lehrstuhls und die Gründung eines Instituts zu ermöglichen.

Der Stifter, Bankier August Lenz, wurde 1910 in München als Sohn eines Bäckers und späteren Getränkefabrikanten geboren. Er brachte es durch großes geschäftliches Geschick ab 1925 vom Lehrling des Bankhauses Marx, das er bereits wenig später als Makler an der Börse München vertrat, binnen 10 Jahren bis zum Teilhaber der Privatbank. Diese wurde später in August-Lenz Bank umbenannt und war mit innovativen Bankdienstleistungen vor allem in der privaten ermögensverwaltung erfolgreich. Nachfolger der August-Lenz-Bank existieren noch heute in mehreren bayerischen Städten. August Lenz wurde bald auch Vorstandsvorsitzender der AGROB AG und der Berufsgenossenschaft und Familienausgleichskasse der keramischen Industrie. Er erkannte auch in diesen Funktionen früh die zunehmende Gefährdung durch vorzeitig auftretende Kreislauferkrankungen und neben der individuellen auch die volkswirtschaftliche Bedeutung ihrer Prävention.

Mit Urkunde vom 17.12.1956 errichtete August Lenz deshalb seine Stiftung zur Verhütung von Kreislaufkrankheiten. Ziele der Stiftung sind die Erforschung insbesondere der Frühformen von Kreislauferkrankungen und ihre Verhütung. Nach vertraglicher Anbindung der August-Lenz-Stiftung an die Universität München, Fertigstellung des unter Beteiligung der Stiftung errichteten Gebäudes an der Pettenkoferstraße und Zustiftungen aus Industriekreisen konnte schließlich im März 1959 das Institut zur Prophylaxe der Kreislaufkrankheiten eröffnet werden. Es untersteht dem jeweiligen Inhaber des Lehrstuhls. Im Kuratorium sind bis heute der Dekan der Medizinischen Fakultät, die anderen internistischen Lehrstuhlinhaber und das Kultusministeriumvertreten. Auch der Stifter engagierte sich stets persönlich im Kuratorium für das Gedeihen seiner Stiftung. August Lenz verstarb aber bedauerlicherweise bereits 1960 an den Folgen einer Gallenblasen-Operation. In seinem Testament bedachte er seine Stiftung generös mit weiteren Zuwendungen.

Zum ersten Inhaber des Lehrstuhls für Prophylaxe wurde nach längerem Kommissariat am 1.5.57 Prof. Dr. Gustav Schimert berufen und zum ersten Vorstand der August-Lenz-Stiftung und Direktor des Instituts ernannt. Prof. Dr. Gustav Schimert stammte aus einer siebenbürgisch-deutschen Medizin-Professoren-Familie und erkannte als Professor für Innere Medizin an der II. Med. Klinik früh die Chancen, die sich aus den innovativen Ergebnissen der amerikanischen Framingham-Studie eröffneten. Er initiierte als einer der Ersten in Deutschland Längsschnitt-Studien an klinisch Gesunden zur Früherkennung von Kreislaufkrankheiten und Querschnitts-Vergleiche mit Infarktpatienten um Kausalfaktoren und Prädiktoren von Gefäßerkrankungen zu finden und zu behandeln. Neben den bereits belegten Risikofaktoren für Arteriosklerose galt sein besonderes Interesse auch der Pulswellenanalyse, die früh Veränderungen der mechanischen Eigenschaften der Gefäßwände und der Leistung des Herzmuskels anzeigen kann.

Als Nachfolger von Prof. Schimert wurde 1988 Prof. Dr. Peter C. Weber berufen. Nach Stationen in München und Boston konzentrierte sich seine Forschung auf die günstigen Effekte von omega-3 Fettsäuren. Omega-3 Fettsäuren sind besonders in Seefisch enthalten und ihnen werden die epidemiologisch auffällig niedrigen Infarktraten von sich traditionell ernährenden Eskimos und Japanern zugeschrieben. Prof. Peter C. Weber konnte mehrere Mechanismen nachweisen, über die omega-3 Fettsäuren, die Blutplättchen, die Blutdruckregulation und den Herzrhythmus günstig beeinflussen. Inzwischen hat die erhöhte präventive Zufuhr von omega-3 Fettsäuren weite Verbreitung gefunden.

Als Nachfolger von Prof. Peter C. Weber konnte 2010 Prof. Dr. Christian Weber, vorher Direktor des Instituts für molekulare kardiovaskuläre Forschung am Klinikum der RWTH Aachen, auf den Lehrstuhl berufen und als Vorstand der August-Lenz-Stiftung und des Instituts gewonnen werden. Prof. Christian Weber ist international führender Forscher auf dem Gebiet der Chemokine und Chemokin-Rezeptoren, die entscheidende Signale bei der Enstehung und Rückbildung der Arteriosklerose und bei Entzündungen vermitteln. Seine Forschungsergebnisse haben zu zahlreichen hochrangigen Publikationen geführt. Der an Infarkt- und Arteriosklerose-Modellen bereits belegte Nutzen eröffnet völlig neue präventive und therapeutische Ansatzpunkte auch für Patienten mit Herzkreislauferkrankungen.

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09/2019
ERC STARTING GRANT

IPEK group leader Alexander Bartelt received a prestigious Starting Grant from the European Research Council (ERC) for a project on the role of muscle cells in metabolic homeostasis, named PROTEOFIT. His group seeks to define how the heart copes with stress, while his ERC-funded project PROTEOFIT focuses on the molecular biology of metabolic processes in muscle cells and exercise.

08/2019
ELECTION LEOPOLDINA

IPEK Director Christian Weber has been elected to be a member of the Academia Leopoldina. As such, Christian Weber is honoured to give public lectures, contribute to the identification and election of new members and to participate in the initiation and organization of scientific conferences.

04/2019
BHF-DZHK PARTNERSHIP

PIs from the UK and from Germany among whom IPEK director Christian Weber, successfully obtained Partnership Funding from the British Heart Fundation (BHF) together with the German Centre for Cardiovascular Research (DZHK).

10/2018
ERA-NET CVD FUNDING

IPEK scientists Sarah-Lena Puhl and Remco Megens obtained ERA-CVD Funding for a period of three years. They paired up with international partners in Canada, Poland, Italy, Belgium and the Netherlands.

09/2018
GRADUATE PROGRAM

With the second period CRC 1123 Funding, we are delighted to have launched a new Integrated Research Training Group (IRTG) to recruit and train exceptional young scientists in the field of atherosclerosis in September 2018. The IRTG1123 is coordinated by IPEK members Prof. Sabine Steffens together with Dr Joana Viola and Dr. Rebecca Dijk-Blom.

08/2018
LEDUCQ FUNDING

An international consortium involving IPEK researchers Andrés Hidalgo and Oliver Söhnlein has been awarded large-scale funding from the French-American Leducq Foundation. The consortium aims to find out how clonal hematopoiesis contributes to the development of atherosclerosis by investigating three gene mutations in genetically modified mice.

News

06/2018
ESC COUNCIL

Christian Weber has been elected as Vice-Chair of the Council on Basic Cardiovascular Science of the European Society of Cardiology for the mandate period 2018-2020. He will then serve as the incoming Chair of the ESC Council on Basic Cardi ovascular Science for the period of 2020-2022.

06/2018
CRC1123

The 35 principal investigators based in different research campuses, from which 14 in the IPEK, were awarded a four year funding extension from the DFG for their Collaborative Research Centre 1123 “Atherosclerosis: Mechanisms and Networks of Novel Therapeutic Targets”. The large-scale collaborative effort coordinated by Christian Weber, encompasses a total of 20 multidisciplinary basic and clinical research projects.

News

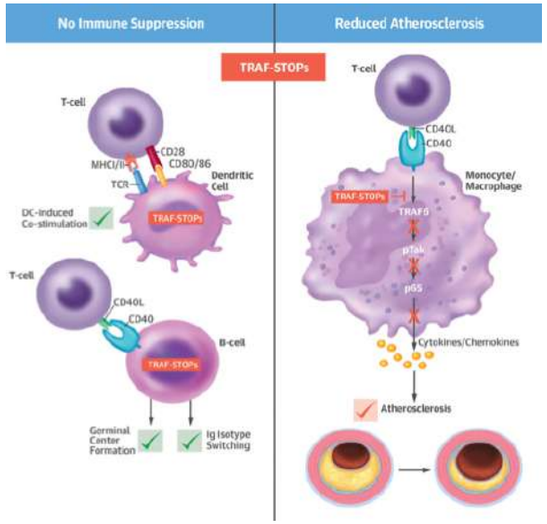
Immune activation and communication in atherosclerosis

Dorothee Atzler & Esther Lutgens

Our lab aims to elucidate mechanisms of immune cell activation and communication in atherosclerosis. Our main interests are co-stimulatory molecules, amino acid metabolism and epigenetic reprogramming.

Dr. Dorothee Atzler, PhD - Group Leader
Prof. Esther Lutgens, MD - Group Leader
Dr. Katrin Nitz, PhD - PostDoc
Michael Lacy - PhD cand.
Yuting Wu - PhD cand.
Sigrid Reim - RA
Tobias Badmann - Animal care taker
Abbie Liu, B.Sc. - HiWi
Eleonora Lambardi - HiWi

The co-stimulatory CD40-CD40L signaling axis has been identified as a pivotal regulator of immune responses in atherosclerosis. However, therapeutic long-term inhibition of CD40L would severely compromise the immune system thus excluding it as a viable treatment option. During the past years we pursued two novel approaches to resolve atherosclerotic plaque inflammation through inhibition of CD40-CD40L signalling. First, we developed 2 compounds that selectively block CD40-TRAF6 interactions (TRAF-STOPs). The beauty of these compounds is that they only target CD40-TRAF6 interactions, while leaving CD40-TRAF2/3/5 interactions intact, thereby preserving CD40 signaling and immunity. Seijkens et al. reported that both TRAF-STOPs powerfully inhibit (existing) atherosclerosis by reducing leukocyte recruitment and macrophage activation. We also show that TRAF-STOP's targeted delivery (through high density lipoprotein nanoparticles) to plaque macrophages allows for more effective treatment.



TRAF-STOP Treatment reduces atherosclerosis and preserves immunity. Binding of CD40L to CD40 results in the recruitment of tumor necrosis factor receptor-associated factors (TRAFs), and propagation of signaling.

Research groups

In our second approach, we hypothesized that cell-specific inhibition might present a better approach to target the CD40-CD40L axis. We know that both T cells and platelets are the primary producers of CD40L but the contribution of these different CD40L expressing cell types to atherosclerosis is unclear. To investigate the effects of T cell and platelet CD40L on atherogenesis, we generated mice with a T cell specific or platelet specific deletion of CD40L as well as a dendritic cell specific deletion of CD40 and backcrossed them to Apolipoprotein E-knockout mice to study atherosclerosis. Unpublished data illuminated for the first time the divergent cell type specific mechanisms of CD40-CD40L signaling in atherosclerosis and highlight a crucial role for the CD40L-CD40 T cell-DC axis in atherogenesis.

Key Publications

Lutgens et al. *Immunotherapy for cardiovascular disease.* **Eur Heart J.** 2019;40(48):3937-3946.

Seijkens et al. *Deficiency of the T cell regulator Casitas B-cell lymphoma-B aggravates atherosclerosis by inducing CD8+ T cell-mediated macrophage death.* **Eur Heart J.** 2019;40(4):372-382.

Nitz et al. *Amino Acids and Their Metabolism in Atherosclerosis.* **Arterioscler Thromb Vasc Biol.** 2019;39(3):319-330.

Lacy et al. *Interactions between dyslipidemia and the immune system and their relevance as putative therapeutic targets in atherosclerosis.* **Pharmacol Ther.** 2019;193:50-62.

Bahls et al. *Low-Circulating Homoarginine is Associated with Dilatation and Decreased Function of the Left Ventricle in the General Population.* **Biomolecules**. 2018;8(3). *equally contributed.

Seijkens et al. T*argeting CD40-Induced TRAF6 Signaling in Macrophages Reduces Atherosclerosis.* **J. Am Coll Cardiol .** 2018; 10.1016/j.jacc.2017.11.055 IF: 18,639

Atzler et al. *DARC matter(s) for inflammatory cells.* **Cardiovasc Res.** 2018;114(2):e11-e13. IF: 7,014

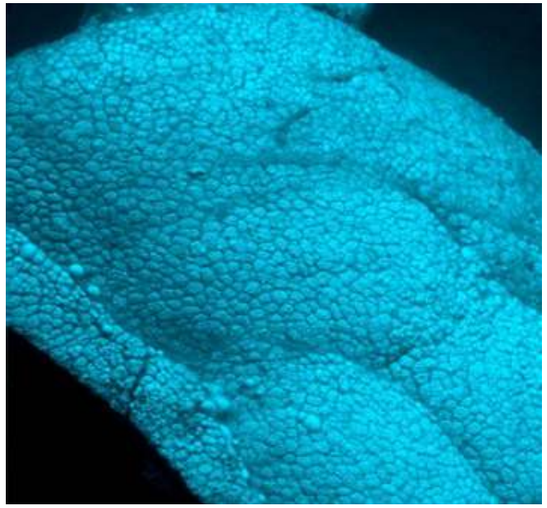
Cardiovascular Immunometabolism

Alexander Bartelt

The Bartelt lab is dedicated to understanding the molecular basis of healthy and unhealthy metabolism and its associated disorders obesity, diabetes and cardiovascular diseases. One main focus is on mechanisms of metabolic adaptation and stress resistance using cellular and animals for a bench-to-bedside approach.

Prof. Dr. rer. nat. Alexander Bartlet - Group Leader
Dr. Maude Giroud, PhD - PostDoc
Dr. Nazia Hilal, PhD - PostDoc
Dr. med. vet. Henrika Jodeleit, VDM - PostDoc
Dr. Sajjad Khani, PhD - PostDoc
Imke Lemmer, M.Sc. - PhD student
Anahita Ofoghi, M.Sc. - PhD student
Nienke Willemsen, M.Sc. - PhD student
Janina Caesar, B.Sc.- Master's student
Stefan Kotschi, cand. med. - MD student
Thomas Pitsch - TA
Silvia Weidner - TA
Ana Bici - research assistant

Since its foundation in the summer of 2018 the Bartelt lab has been upgrading the new space at Max-Lebsche-Platz in Großhadern to a fully operating lab including establishing instrumentation and protocols for high-end cardiometabolic research, including e.g. a state-of-the-art animal facility, indirect calorimetry, and a Seahorse Analyzer. We are now up and running several third party-funded projects. Funded by the German Center for Cardiovascular Research (DZHK) we are currently exploring the role of proteostasis and proteasomal protein quality control during myocardial infarction. The European Research Council (ERC) has awarded us starting grant to explore the role of proteostasis and proteasomal protein quality control in muscle function and exercise. We are part of the collaborative research center (SFB) 1123, studying the role of proteostasis and proteasomal protein quality control in adipose inflammation and atherogenesis. Our research is further supported by the Friedrich-Bauer-Stiftung and the FöFoLe program of the Medical Faculty of Ludwig-Maximilians-University.



Brown Fat

Prof. Bartelt is also a Principal Investigator at the Institute for Diabetes and Cancer, Helmholtz Center Munich and associated member of the Helmholtz Diabetes Center as well as visiting scientist at the Department of Molecular Metabolism, Harvard T.H.Chan School of Public Health, Boston, USA. Aside from that Prof. Bartelt was awarded the Friedmund Neumann Award of the Ernst Schering Foundation in 2018, has been elected to the Editorial Board of Molecular Metabolism.

Key Publications

Bartelt et al. *The new age of radiomic risk profiling: perivascular fat at the heart of the matter.* **Eur Heart J**. 2019 Nov 14;40(43):3544-3546.

Leiria et al. *12-Lipoxygenase Regulates Cold Adaptation and Glucose Metabolism by Producing the Omega-3 Lipid 12-HEPE from Brown Fat.* **Cell Metab.** 2019 Oct 1;30(4):768-783.e7.

Worthmann et al. *Effects of Pharmacological Thermogenic Adipocyte Activation on Metabolism and Atherosclerotic Plaque Regression.* **Nutrients.** 2019 Feb 23;11(2). pii: E463.

Treviño-Villarr et al. Jh et al. D*ietary protein restriction reduces circulating VLDL triglyceride levels via CREBH-APOA5-dependent and -independent mechanisms.* **JCI Insight.** 2018 Nov 2;3(21). pii: 99470.

Bartelt et al. *Brown adipose tissue thermogenic adaptation requires Nrf1-mediated proteasomal activity.* **Nat Med.** 2018 Mar;24(3):292-303. doi: 10.1038/nm.4481. Epub 2018 Feb 5.

Chemokines in Cardiovascular Disease

Yvonne Döring

We focus on chemokine(-receptor) biology on leukocytes and vascular cells in the context of cardiovascular disease. We are particularly interested in cell-specific roles of chemokines in chronic arterial vascular inflammation. Furthermore, we study the influence of chemokines in anti-inflammatory immune responses and macrophage polarization in atherosclerosis.







Dr. rer. nat. Yvonne Döring, PhD - Group leader
Dr. Emiel van der Vorst, PhD - Postdoc
Dr. Yi Yan, PhD - Postdoc
Selin Gencer, MSc - PhD student
Madeleine Müller, MSc - PhD student
Linsey J.F. Peters - Master student
Yvonne Jansen - TA
Soyolmaa Bayasgalan - TA

CXCL12 in atherosclerosis

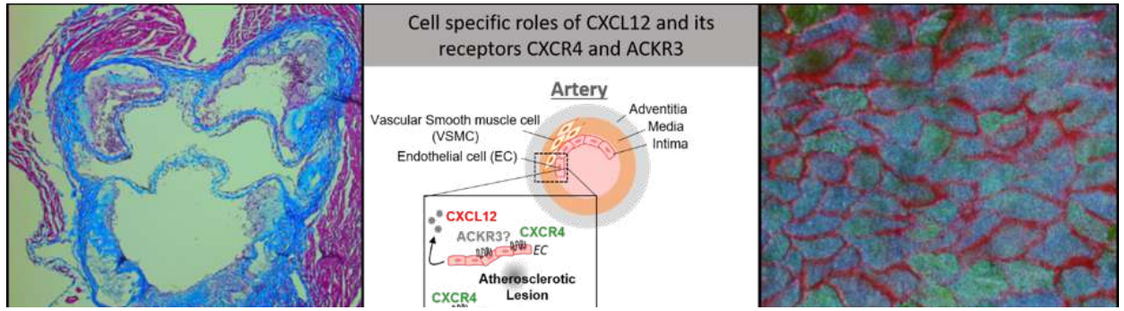
Genome-wide association studies have established a link between the genomic locus 10q11, which hosts the CXCL12 gene, and the risk for coronary artery disease (CAD). However, nature and directionality of this association remained elusive. Recently, a Mendelian randomization study identified CXCL12 as a causal mediator of CAD (Sjaarda J et al. Blood CSF1 and CXCL12 as causal mediators of coronary artery disease. J Am Coll Cardiol 2018;72:300-310). To unravel mechanisms underlying the association of plasma CXCL12 and CAD, we employed a set of models specifically interrogating the impact of cell-specific CXCL12 deficiency in mouse models of atherosclerosis. The latter studies revealed that effects of CXCL12 on atherosclerosis rely on CXCL12 production in ECs, thus identifying arterial EC-derived CXCL12 as a crucial driver of atherosclerosis and contributor to CXCL12 levels. Interestingly somatic deficiency in CXCR4 did not reveal equivalent protective effects as deletion in vascular cell types (Döring & Noels et al. Circulation 2017), implying pro-atherogenic functions of CXCR4 in a different compartment or other receptors mediating effects.

Aim2 and plaque destabilization

Recent findings underline an important role of IL1β-orchestrated inflammatory processes during atherosclerosis. IL1β is released from its pro-form as a consequence of inflammasome activation. Given the abundance of cell death in atherosclerotic lesions, we here studied how activation of dsDNA-sensing Aim2 inflammasome contributes to atherosclerosis. Our data indicate that the accumulation of dsDNA in progressing lesions coincides with enhanced expression of Aim2, the latter being restricted to macrophages. Genetic deletion of Aim2 in hypercholesterolemic mice generates lesions characterized by overt deposition of collagen, thicker fibrous caps, and smaller necrotic cores. In line, specific activation of Aim2 in macrophages generates a cytokine profile suppressing collagen synthesis in smooth muscle cells. Pharmacological inhibition of Aim2 in established lesions resulted in enhanced lesion stability. Thus, the dsDNA-Aim2 axis controls the inflammatory response downstream of lesional cell death. Its disruption offers represents an innovative lesion-stabilizing strategy.

Pro-atherogenic functions of ChemR23

Expression of the chemokine-like receptor ChemR23 (chemerin receptor 23) has been specifically attributed to plasmacytoid dendritic cells (pDCs) and macrophages and ChemR23 has been suggested to mediate an inflammatory immune response in these cells. Consequently we were interested in identifying the mechanisms by which ChemR23 acts on macrophages and pDCs in atherosclerosis. Using a transgenic mouse model, we found that deficiency of ChemR23 in the context of atherosclerosis was associated with reduced lesion formation and reduced leukocyte adhesion to the vessel wall, as well as diminished plaque growth, a decreased number of lesional macrophages with an increased proportion of M2 cells and a less inflammatory lesion composition. Additional experiments further revealed an alternatively activated macrophage phenotype, an increased cholesterol efflux and a systemic reduction in pDC frequencies. ChemR23-deficient pDCs did not accumulate in atherosclerotic lesions to the same extent as their wild type counterpart. Hence, hematopoietic ChemR23-deficiency increases the proportion of alternatively activated M2 macrophages in atherosclerotic lesions and attenuates pDC homing to lymphatic organs and recruitment to atherosclerotic lesions, which synergistically restricts atherosclerotic plaque formation and progression.



(Left) Haematoxylin staining of a mouse aortic root with atherosclerotic lesions; (Middle) Schematic overview of published and ongoing research on the role of CXCL12 and its receptors CXCR4 and ACKR3 in experimental atherosclerosis; (Right) Close up of mouse arterial endothelium, VE-cadherin lining the endothelial cells is visualized with a fluorescent antibody (red).

Key Publications

Kiouptsi et al. *The Microbiota Promotes Arterial Thrombosis in Low-Density Lipoprotein Receptor-Deficient Mice.* **mBio.** 2019 Oct 22;10(5).

van der Vorst et al. G-*Protein Coupled Receptor Targeting on Myeloid Cells in Atherosclerosis.* **Front Pharmacol.** 2019 May 22;10:531.

Gencer et al. *Atypical Chemokine Receptors in Cardiovascular Disease.* **Thromb Haemost.** 2019 Apr;119(4):534-541.

Döring et al. *CXCL12 Derived From Endothelial Cells Promotes Atherosclerosis to Drive Coronary Artery Disease.* **Circulation.** 2019 Mar 5;139(10):1338-1340.

van der Vorst et al. *Hematopoietic ChemR23 (Chemerin Receptor 23) Fuels Atherosclerosis by Sustaining an M1 Macrophage-Phenotype and Guidance of Plasmacytoid Dendritic Cells to Murine Lesions-Brief Report.* **Arterioscler Thromb Vasc Biol.** 2019 Apr;39(4):685-693.

van der Vorst et al. *Novel Features of Monocytes and Macrophages in Cardiovascular Biology and Disease.* **Arterioscler Thromb Vasc Biol.** 2019 Feb;39(2):e30-e37.

Paulin et al. *Double-Strand DNA Sensing Aim2 Inflammasome Regulates Atherosclerotic Plaque Vulnerability.* **Circulation.** 2018 Jul 17;138(3):321-323.

van der Vorst et al. *Metabolomic profiling of atherosclerotic plaques: towards improved cardiovascular risk stratification.* **Eur Heart J.** 2018 Jun 21;39(24):2311-2313.

Atypical Chemokine Receptors in inflammation and disease

Johan Duchêne

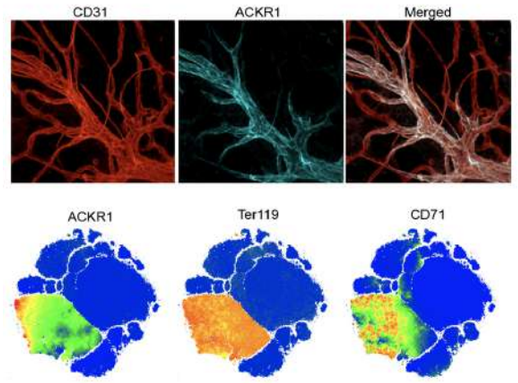
The main objective of our research is to investigate the molecular and cellular mechanisms of immune responses, with a special focus on the contribution of chemokines and their receptors in inflammation and disease.




Dr. Johan Duchêne, PhD - Group Leader
Dr. rer. nat. Aindrila Biswas, PhD - PostDoc
Maria Aslani, MD - PhD student
Markus Haberbosch - TA

Chemokines, also known as chemotactic cytokines, were first identified to control immune cell migration in the context of inflammation and later in homeostatic conditions. Chemokine receptors are expressed on all immune cells and their activation by chemokines mediate leukocyte cell migration. In addition to these 'classical' chemokine receptors, chemokines also bind to atypical chemokine receptors (ACKRs). ACKRs fail to induce signalling pathways, but can instead internalize, scavenge, transport or present chemokines and thus regulate the bioavailability of chemokines. While 'classical' chemokine receptors have been extensively studied in inflammation, the roles of ACKRs are still only poorly understood. Therefore, more efforts are needed to better understand ACKRs functions in steady state and inflammation.

ACKR1 in immune response (Aindrila Biswas)
ACKR1, also known as Duffy-antigen, binds inflammatory chemokines and was ascribed a unique expression profile in erythrocytes, venular endothelial cells and cerebellar Purkinje neurons. Individuals of African ancestry carry a genetic variant, rs2814778(G), in the gene encoding ACKR1. This variant results in the specific absence of ACKR1 expression on erythroid cells while its expression is maintained in endothelium and cerebellum, causing a Duffy-negative phenotype. Using CRISPR/Cas9 genome editing, we recently



ACKR1 is expressed by endothelial and erythroid cells. Top: Immunostaining showing the expression of ACKR1 in post-capillaries venules. Bottom: t-SNE plot showing the expression of ACKR1 on erythroid cells.

generated a new erythroid-deficient mouse model which carries the mouse equivalent of the human rs2814778(G) polymorphism. We are currently investigating the function of erythroid-ACKR1, using this mouse model which phenocopies Duffy-negative individuals, in the context of atherosclerosis, an inflammatory cardiovascular disease.

ACKR3 in hematopoiesis (Maria Aslani)
Hematopoiesis is the process that generates all blood cells. Hematopoietic stem cells are found in the bone marrow where they self-renew and differentiate into different blood cell types. CXCL12 is a homeostatic chemokine highly abundant in the bone marrow, which controls hematopoietic stem cells maintenance and retention. While CXCL12 binds to CXCR4, which is expressed by hematopoietic stem cells, it can also bind to ACKR3. However, it remains unknown whether ACKR3 regulates hematopoietic stem cells behavior. We have been investigating, using Ackr3-reporter and Ackr3-specific knock-out mouse models, the function of ACKR3 on hematopoietic stem cells biology.

Tracking monocytes
(in collaboration with R. Megens and M. Bianchini)
Monocytes can be divided into two major subsets, known as classical and non-classical monocytes, which serve different functions in the immune system. Up to now, non-classical monocytes have been viewed solely as surveillance cells that circulate in the bloodstream and serve to recruit other immune cells to sites of damage in the walls of blood vessels. We have now identified a specific marker, namely PD-L1, for these cells. Using this marker, we have been able to show that non-classical monocytes also play a direct regulatory role in the adaptive immune response in certain tissues. Indeed, we demonstrated that non-classical monocytes are able to infiltrate a specific type of inflamed tissue – known as tertiary lymphatic organs – for instance in the context of myocardial infarction, where they function as direct regulators of the adaptive immune response by modulating the activities of T cells. We are currently investigating the development of monocytes in the context of inflammation and western diet.

Key Publications

Bianchini et al. *PD-L1 expression on nonclassical monocytes reveals their origin and immunoregulatory function.* **Sci Immunol.** 2019; 4(36), eaar3054.

Gencer et al. *Atypical Chemokine Receptors in Cardiovascular Disease* **Thromb Haemost.** 2019; 119(4):534-541

Lutgens E, Atzler D, Doring Y, Duchene J, Steffens S, Weber C. Immunotherapy for cardiovascular disease. **Eur Heart J.** 2019;40:3937-3946.

Horckmans et al. *Pericardial adipose tissue regulates granulopoiesis, fibrosis and cardiac function after myocardial infarction.* **Circulation.** 2018;137:948-960

Neuroimmune Cardiovascular Interface

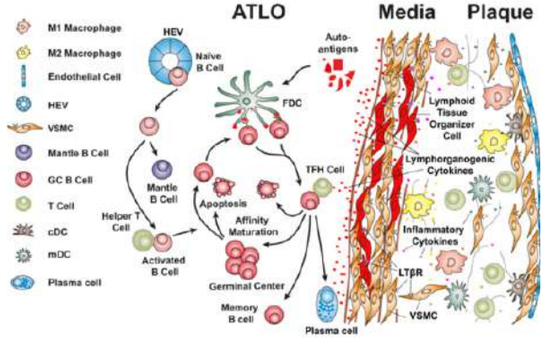
Andreas Habenicht

Our group focuses on three areas of the immunology of cardiovascular diseases during aging: i. Define common molecular mechanisms of atherosclerosis and Alzheimer´s disease; ii. Search for atherosclerosis-specific autoimmune lymphocytes; and iii. Identify and delineate a multisynaptic atherosclerosis brain circuit (ABC).

Prof. Dr. med. Andreas Habenicht - Group Leader
Dr. rer. nat. Changjun Yin - Group Leader
Dr. rer. nat. Sarojo Mohanta - Group Leader
Xi Zhang, PhD student
Chuankai Zhang, PhD student
Shu Lu, PhD student
Yuanfang Li, PhD student
Ting Sun, PhD student
Zhe Ma, PhD student
Yutao Li, PhD student
Zhihua Wang, PhD student

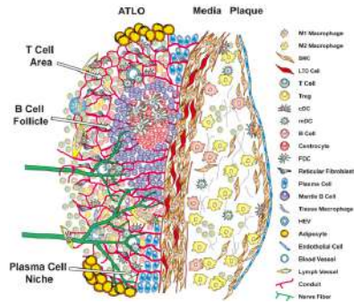
Atherosclerosis and Alzheimer´s disease
ApoE has been implicated in Alzheimer´s disease (AD), atherosclerosis, and other unresolvable inflammatory conditions but a common mechanism of action remains elusive. We found in ApoE-deficient mice that oxidized lipids activated the classical complement cascade (CCC) resulting in leukocyte infiltration of the choroid plexus (ChP). C1q-ApoE complexes emerged as markers for ongoing complement activity of diseased ChPs, AD plaques, and atherosclerosis in vivo. C1q-ApoE complexes in human ChPs, AD plaques, and arteries correlated with cognitive decline and atherosclerosis, respectively. Treatment with siRNA against C5 which is formed by all complement pathways, blocked generation of anaphylatoxin C5a, and attenuated murine ChP inflammation, Aβ-associated microglia accumulation, and atherosclerosis. Thus, ApoE via formation of C1q-ApoE complexes inhibits the CCC in prototypic unresolvable inflammatory diseases and reducing C5 attenuates disease burden.

Atherosclerosis and autoimmunity
A fundamental unresolved issue in the pathogenesis of atherosclerosis is whether the advanced and clinically significant disease is associated with the generation of arterial wall-specific autoantigens recognized by autoimmune T cells or B cells. Our group has proposed a hypothesis how such autoimmune lymphocytes (shown for B2 B cells in Figure) may be generated. Accordingly, we have begun to isolate germinal center B2 cells from artery tertiary lymphoid organs (ATLOs) that develop in the adventitia, i.e. the outer connective tissue coat of arteries, using aged ApoE-/- mice as the experimental model.



Schematic representation of hypothetical B2 B cell autoimmune reactions in advanced atherosclerosis. We investigate the possibility that the germinal centers of ATLOs are involved in the generation of autoimmune B2 cells. Taken from Yin, C. et al. 2016. Frontiers in Immunology 7 (387).

Atherosclerosis and the peripheral nervous system
Atherosclerosis may be connected to the peripheral nervous system. It came to our attention several years ago that the peripheral nervous system uses the adventitia as their major conduit to reach all tissues. Following this line of reasoning, we speculate that the nervous system can sense and possibly affect atherosclerosis via a proxy actor, i.e. immune cell aggregates in the adventitia. To date, we observed that there is strong axon neogenesis in the adventitia adjacent to atherosclerotic plaques in ApoE-/- mice (Mohanta et al. 2020; unpublished data).



Key Publications

Hu et al. *Vascular Smooth Muscle Cells Contribute to Atherosclerosis Immunity.* **Front Immunol.** 2019;10:1101.

Varasteh et al. *Molecular Imaging of Fibroblast Activity After Myocardial Infarction Using a (68)Ga-Labeled Fibroblast Activation Protein Inhibitor, FAPI-04.* **J Nucl Med.** 2019;60:1743-1749.

Varastehet al. *Targeting mannose receptor expression on macrophages in atherosclerotic plaques of apolipoprotein E-knockout mice using (68)Ga-NOTA-anti-MMR nanobody: non-invasive imaging of atherosclerotic plaques.* **EJNMMI Res.** 2019;9:5.

Yin et al. *ApoE attenuates unresolvable inflammation by complex formation with activated C1q.* **Nat Med.** 2019;25:496-506

Bianchini et al. PD-L1 expression on nonclassical monocytes reveals their origin and immunoregulatory function. **Sci Immunol.** 2019;4.

Renz et al. beta2 Adrenergic-Neurotrophin Feedforward Loop Promotes Pancreatic Cancer. **Cancer Cell.** 2018;34:863-867.

Williams et al. *Limited Macrophage Positional Dynamics in Progressing or Regressing Murine Atherosclerotic Plaques-Brief Report.* **Arterioscler Thromb Vasc Biol.** 2018;38:1702-1710.

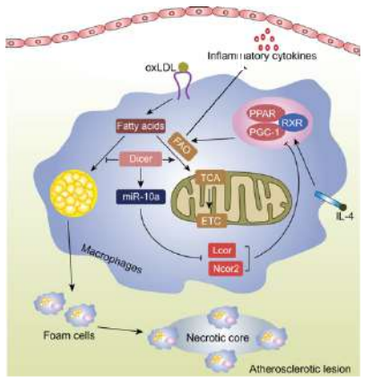
Experimental Vascular Medicine - microRNAs in atherosclerosis

Andreas Schober

We are studying how microRNAs regulate endothelial and macrophage function, and thus affect atherosclerosis. Therefore, we investigate the mechanisms by which microRNAs mediate the maladaptive response of endothelial cells to turbulent blood flow and hyperlipidemia. In macrophages, we evaluate the role of microRNAs in mitochondrial function and intracellular lipid accumulation.

Prof. Dr. med. Andreas Schober - Group Leader
Dr. rer. nat. Maliheh Nazari-Jahantigh - PostDoc
Dr. rer. human. biol. Ela Karshovska - PostDoc
Yuanyuan Wei, PhD - PostDoc
Saffiyeh Saboor Maleki - PhD student
Isabelle Maria Baatsch - PhD student
Aamoun Popal, cand. med.
Mati Kakar, cand. med.
Rokia Mohibulla, cand. med.
Brigitta Brumec, cand med. dent.
Claudia Geissler - MTA
Anna Eberlein - MTA
Anja Fusco, MTA
Lourdes Ruiz-Heinrich, MTA

In addition to inflammation, endothelial Dicer affects Notch1 and -catenin signaling pathways, induces DNA damage and micronuclei formation in endothelial cells (ECs) and inhibits endothelial proliferation at predilection sites of atherosclerosis. This effect of endothelial Dicer is mediated by the targeting of the long, non-coding RNA lncWDR59 by miR-103-3p. Because lncWDR59 competitively binds to the Notch1 inhibitor Numb, suppression of lncWDR59 by miR-103-3p reduces Notch1 activity and endothelial proliferation. Moreover, Notch1 activates -catenin, which in turn increases lower levels of Notch1 activity due to miR-103-3p-mediated suppression of lncWDR59, but reduces higher levels of Notch1 activity when the targeting of lncWDR59 by miR-103-3p is absent. This Notch1 activity-dependent role of -catenin is regulated by lncWDR59-mediated upregulation of Sox17, which modulates gene transcription by -catenin signaling in a context-specific manner. Moreover, Sox17-induced -catenin activity limits oxidized LDL-induced micronuclei formation and micronucleic DNA damage in ECs. By inhibiting this protective effect of -catenin, miR-103-3p-mediated suppression of lncWDR59 increases hyperlipidemia-induced DNA damage and micronuclei formation in ECs. Thus, lncWDR59 can limit EC maladaptation by Notch1-mediated endothelial proliferation and protect ECs during proliferation from micronucleic DNA damage through -catenin activation. ECs still able to proliferate despite the inhibitory effect of miR-103-3p, are more vulnerable to hyperlipidemia-induced chromosomal instability and micronuclei DNA damage, which



impairs endothelial regeneration and propagates endothelial dysfunction. This effect of miR-103-3p can turn the protective role of endothelial proliferation in atherosclerosis into aberrant proliferation, which promotes endothelial dysfunction and lesion formation. In contrast to ECs, knockout of Dicer in macrophages increases the development of atherosclerosis, and promotes macrophage apoptosis and the expression of inflammatory mediators. Moreover, Dicer knockout impairs oxidative phosphorylation (OXPHOS) in anti-inflammatory macrophages. Notably, Dicer also mediates the increase in oxygen consumption and mitochondrial oxidation in macrophage-derived foam cells, which limits intracellular lipid accumulation, probably by oxidizing fatty acids. The most common target of macrophage miRNAs is ligand-depended corepressor (LCOR), which contains numerous highly conserved miRNA-binding sites in its 3'-UTR. LCOR interacts and inhibits retinoid X receptor alpha, which promotes the expression of OXPHOS-related genes and increases mitochondrial function through interacting with peroxisome proliferator-activated receptor gamma coactivator (PGC)-1. Among the miRNAs predicted to target LCOR in macrophages, miR-10a-5p most strongly promotes OXPHOS through targeting LCOR. Blocking the interaction between miR-10a-5p and LCOR in macrophages by target site-specific antisense oligonucleotides increases atherosclerosis in mice, suggesting that miRNA-mediated OXPHOS in macrophages protects from atherosclerosis. miR-10a-5p increases OXPHOS also by interacting with another corepressor of nuclear receptors, nuclear receptor corepressor 2, which inhibits the activity of the PPAR.

Key publications

Natarelli et al. *miR-103 promotes endothelial maladaptation by targeting lncWDR59.* **Nat Commun.** 2018;9:2645

Wei et al. *Dicer in macrophages prevents atherosclerosis by promoting mitochondrial oxidative metabolism.* **Circulation.** 2018;138:2007-2020

Molecular mechanisms of impaired wound healing

Christian Ries

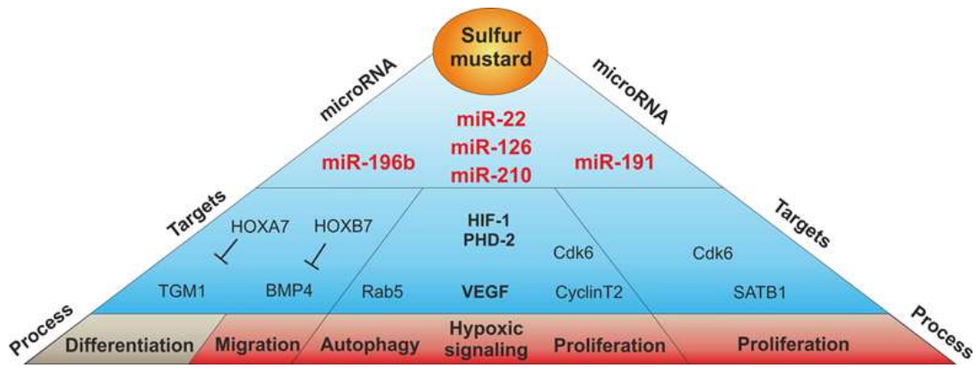
Prof. Dr. rer. nat. Christian Ries
Dr. rer. nat.Virginia Egea - Postdoc
Dr. med. vet. Karina Lutterberg, - Postdoc

Migrating cells such as keratinocytes, fibroblasts, monocytes and mesenchymal stem cells, play key roles in multiple normal and pathological processes including wound healing, inflammation and cancer. Our research aims to gain deeper insights into molecular mechanisms that regulate the behavior and function of these cells. This may provide innovative approaches for target-directed therapeutical intervention.

microRNAs (miRNAs) represent a group of small non-coding RNA molecules which are expressed in all cell types at different quantities. Based on sequence complementarity, miRNAs specifically bind to mRNAs and thereby target more than 60% of all human genes. miRNAs are involved in the normal functioning of cells, so has dysregulation of miRNA been associated with disease.

Sulphur mustard (SM) is an extremely toxic chemical warfare agent that after exposure to the skin evokes severe inflammation, extensive blistering and delayed wound healing. We hypothesize, that SM might disturb the homeostatic balance of miRNA expression in skin cells resulting in impaired cell functions such as proliferation, migration and differentiation which are essentially required for proper wound healing. Own previous findings demonstrate that SM upregulates miR-203 in primary keratinocytes under normoxia and hypoxia, and augments hypoxia-induced levels of miR-210 in these cells. This contributes to deficiencies in cellular viability, proliferation, and differentiation of keratinocytes. These cellular defects were efficiently counteracted by the application of specific inhibitors of miR-203 and miR-210 (anti-miRs), providing evidence that miRNAs are key regulators in normal and SM-affected keratinocyte functionality.

Our next goal is to deploy next generation sequencing (NGS) in SM-treated keratinocytes. NGS technology allows to record the entirety of all RNA molecules transcribed in a cell population at a defined time point by means of RNA sequencing. This approach yields SM-specific miRNA and mRNA transcriptomes the combined analysis of which may lead to the identification of miRNA key players, cellular pathways influenced by them and molecular networks in skin cells with relevance for SM-induced wound healing deficiencies (funded by DFG RI 808/6-1 and Bundeswehr E/U2AD/ID016/IF559).



Graphical representation of a selection of sulfur mustard-regulated miRNAs with regard to their validated or potential target mRNAs and the cellular processes that might be influenced by them.

Novel antiplatelet agents for atherosclerosis

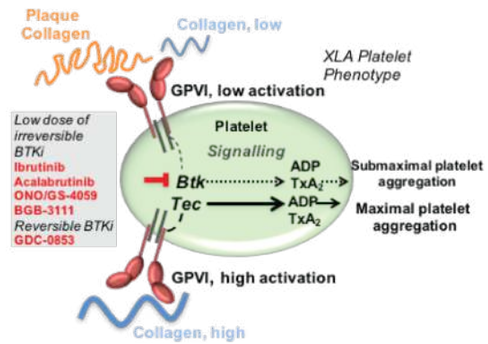
Wolfgang Siess

Our aim is to find novel antiplatelet drugs that inhibit atherosclerotic plaque-induced thrombus formation (atherothrombosis) but not physiological hemostasis.

Prof. Dr. med. Wolfgang Siess - Group Leader
Viola Denzinger, medical student
Mariam Ebrahim, medical student
Luise Goldmann, dentistry student
Joanna Goczyńska, medical student
Danny Zhang, medical student
Kathrin von Oheimb, MTA

Our studies show that irreversible Btk inhibitors may be used as the first orally active platelet inhibitors to selectively inhibit platelet activation triggered by atherosclerotic plaques (atherothrombosis). The inhibition of Btk was sufficient to completely suppress the low GPVI activation stimulated by atherosclerotic plaques. Activation of the second platelet collagen receptor (integrin α2β1) was not inhibited, and collagen-induced thrombus formation under flow was not affected. It was found that low blood concentrations of ibrutinib and the novel Btk inhibitors were sufficient for GPVI selective platelet inhibition relevant for atherothrombosis but they did not impair primary hemostasis. In vitro bleeding times were moderately increased only by 2- to 2.5-fold higher concentrations of the irreversible Btk-inhibitors which is explained by the inhibition of the homologous tyrosine kinase Tec in addition to Btk, and, hence, the complete blockage of the GPVI signaling pathway.

Taking a very low dose of the oral irreversible Btk inhibitor ibrutinib (140mg every other day) inhibited plaque-induced platelet activation effectively and selectively, attributable to the fact that platelets lack nuclei and cannot resynthesize new Btk protein. It was concluded that covalent Btk inhibitors with a high Btk selectivity over other kinases (particularly Tec) have a great potential to be applied in low doses as novel oral antiplatelet drugs for the prevention and therapy of ischemic cardiovascular diseases.
Btk inhibitors could also be used in the therapy of heparin-induced thrombocytopenia (HIT). HIT is the most common drug-associated immunological thrombocytopenia, and 0.2 to 3% of patients receiving heparin develop a life-threatening clinical picture with pronounced thrombocytopenia and venous and / or arterial thrombosis. HIT is caused by antibody formation against heparin and platelet factor 4.
The binding of the IgG immune complexes to the platelet Fc receptor (FcγRIIA) and its activation is critical in the pathogenesis of HIT. Our study shows that both irreversible and reversible Btk inhibitors prevented platelet FcγRIIA activation in blood. Not only platelet aggregation and secretion, but also P-selectin expression (which mediates platelet interaction with monocytes and endothelial cells) and the formation of platelet-neutrophil conjugates were completely inhibited by the Btk inhibitors. Of note, the reversible Btk inhibitor did not increase in vitro bleeding time at all. The work opens up a new therapeutic option for HIT, whereby reversible Btk inhibitors may be more suitable than irreversible Btk inhibitors.
Recent studies claim that platelet GPVI is not only a receptor for collagen but also for fibrinogen and fibrin. Our studies could not confirm these findings. First, recombinant dimeric GPVI-Fc did not bind to any fibrin prepared either from purified fibrinogen, or generated more physiologically by coagulation of plasma or exposing tissue factor -coated surfaces or human atherosclerotic plaque slices to arterially flowing blood. Second, fibrin physiologically formed in plasma had a structure entirely different of fibrin formed from pure or recombinant fibrinogen. Plasma fibrin contained many plasma proteins that probably shielded GPVI activating epitopes, since inhibition of GPVI and GPVI signaling did not reduce platelet adhesion and aggregate formation onto fibrin formed in plasma or blood fibrin.



Model of the selective anti-atherothrombotic effect of reversible and low dose irreversible Bruton's tyrosine kinase inhibitors (BTKi) resembling the XLA platelet phenotype (Figure modified from Busygina et al, Thromb Haemost. 2019 Aug;119(8):1212-1221)

Key Publications

Goldmann et al. *Oral Bruton tyrosine kinase inhibitors block activation of the platelet Fc-receptor CD32 (FcγRIIA): a new option in HIT?* **Blood Adv.** 2019, 3 (23):4021-4033

Busygina et al. *Btk Inhibitors as First Oral Atherothrombosis-Selective Antiplatelet Drugs?* **Thromb Haemost.** 2019 Aug;119(8):1212-1221.

Denzinger et al. *Optimizing Platelet GPVI Inhibition versus Haemostatic Impairment by the Btk Inhibitors Ibrutinib, Acalabrutinib, ONO/GS-4059, BGB-3111 and Evobrutinib.* **Thromb Haemost.** 2019 Mar;119(3):397-406.

Busygina et al. *Oral Bruton tyrosine kinase inhibitors selectively block atherosclerotic plaque-triggered thrombus formation in humans.* **Blood.** 2018 Jun 14;131(24):2605-2616.

Ebrahim et al. *Dimeric Glycoprotein VI Binds to Collagen but Not to Fibrin.* **Thromb Haemost.** 2018 Feb;118(2):351-361.

Vascular Immunotherapy

Oliver Söhnlein

We strive to understand key processes of vascular inflammation driven by neutrophils, the most abundant circulating white blood cells in humans. This knowledge is then applied to develop innovative preclinical interference strategies.

Prof. Dr. Dr. med. Oliver Soehnlein
Group Leader
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Joana Viola, PhD - PostDoc
Almudena Ortega, PhD - PostDoc
Carlos Silvestre-Roig, PhD -PostDoc
Maximilian Mauler, PhD - PostDoc
Kristof van Avondt, PhD - PostDoc
Bartolo Ferraro, PhD - PostDoc
Raphael Chevre, PhD - PostDoc
Pan Chang, MD - PhD student
Celia Borja, Msc - PhD student
Sanne Maas, Msc - PhD student
Ariane Helfrich, Msc- PhD student
Laura Perez, Msc - PhD student
Patricia Lemnitzer - TA
Olga Schengel - TA
Timon Keller - TA
Mohammad Munmun Hasan Mollah - TA

Onset of cardiovascular complications as a consequence of atherosclerosis exhibits a circadian incidence with a peak in the morning hours. Although development of atherosclerosis extends for long periods of time through arterial leukocyte recruitment, we hypothesized that discrete diurnal invasion of the arterial wall could sustain atherogenic growth. Work recently published by our group indicates that myeloid cell recruitment to atherosclerotic lesions oscillates with a peak during the transition from the activity to the resting phase. This diurnal phenotype is regulated by rhythmic release of myeloid cell-derived CCL2, and blockade of its signaling abolished oscillatory leukocyte adhesion. In contrast, we show that myeloid cell adhesion to microvascular beds peaks during the early activity phase. Consequently, timed pharmacological CCR2 neutralization during the activity phase caused inhibition of atherosclerosis without disturbing microvascular recruitment. These findings demonstrate that chronic inflammation of large vessels feeds on rhythmic myeloid cell recruitment, and lay the foundation for chrono-pharmacology-based therapy (Winter et al., Cell Metab, 2019).
Histological analyses of human carotid plaque specimens furnished important insights regarding the possible contribution of neutrophils to plaque destabilization. Abundant lesional neutrophils localized in plaques with a large lipid core, high macrophage numbers, and low collagen levels and smooth muscle cell (SMC) numbers implicating neutrophils in core processes of plaque destabilization, i. e. necrotic core growth and fibrous cap thinning. In agreement with this notion, work recently published by our group established the contribution of neutrophils and in particular NETs to plaque destabilization by promoting precisely these two features (Silvestre-Roig et al., Nature 2019). Mechanistically, modulated SMCs resident in the fibrous cap interact physically with neutrophils resulting in their activation characterized by ROS production and the release of NETs, the latter being mediated by SMC-borne CCL7. Inhibition of NET release by treatment with a PAD inhibitor in mice with pre-existing lesions or those lacking Pad4 exhibited lesions with fewer characteristics of vulnerability, including smaller necrotic cores and higher SMC content compared to control mice.
The striking correlation between neutrophils and NETs on the one hand and dying SMCs, necrotic core sizes and thin fibrous caps in the mouse models on the other hand suggested a direct cytotoxic action of NETs. In fact, ex vivo studies revealed that NETs kill SMCs. This effect did not depend on neutrophil proteins derived of granules or the cytoplasm, but rather on nuclear histones, specifically histone H4, in agreement with earlier reports on cytotoxic activities of NET-borne histones.
Mechanistically, histone H4, a strongly cationic protein, can interact with negatively charged SMC surfaces thereby exerting membrane activity with membrane bending and ultimately pore formation leading to lytic cell death. Smooth muscle cell depletion may promote thinning of the fibrous cap, by removing a source of interstitial collagen synthesis. The importance of histone H4 in promoting features associated with plaque disruption was further corroborated by use of a histone H4 neutralizing antibody and of cyclical histone interference peptides (HIPE) which target the N-terminus of histone H4. Both therapeutic strategies reinforced aspects of plaques associated with plaque stability. In addition, another recent study from our lab showed that the dsDNA backbone of NETs can signal to macrophages through Absent in melanoma 2 (AIM2), a cytosolic non-canonical inflammasome that senses DNA. In mice with advanced atherosclerosis, activation of AIM2 results in a strong production of the pro-atherogenic cytokines IL-1β and IL-18 and lack or neutralization of AIM2 generates plaques with fewer characteristics of propensity to rupture, notably a smaller necrotic core and a thicker fibrous cap (Paulin et al., Circulation, 2018).

Key Publications

Ferraro et al. *Pro-Angiogenic Macrophage Phenotype to Promote Myocardial Repair.* **J Am Coll Cardiol.** 2019 Jun 18;73(23):2990-3002.

Silvestre-Roig et al. *Externalized histone H4 orchestrates chronic inflammation by inducing lytic cell death.* **Nature.** 2019 May;569(7755):236-240.

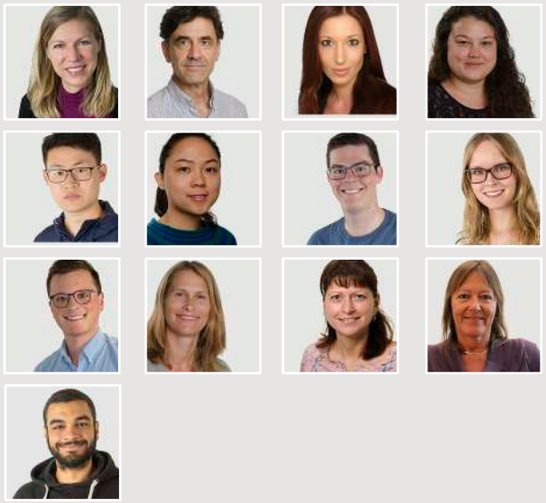
Paulin et al. D*ouble-Strand DNA Sensing Aim2 Inflammasome Regulates Atherosclerotic Plaque Vulnerability.* **Circulation.** 2018 Jul 17;138(3):321-323.

Winter C et al. *Chrono-pharmacological Targeting of the CCL2-CCR2 Axis Ameliorates Atherosclerosis.* **Cell Metab.** 2018 Jul 3;28(1):175-182.e5.

Lipid signaling in cardiovascular disease

Sabine Steffens

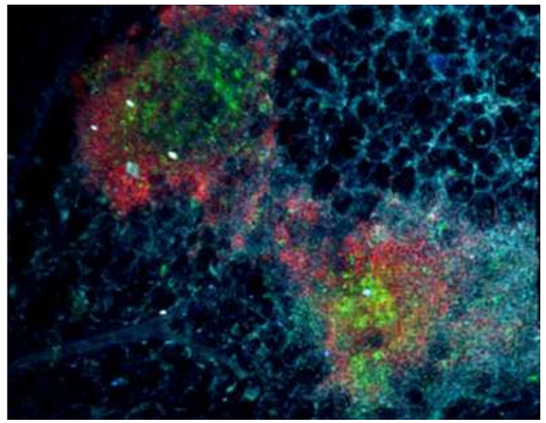
Lipid mediators derived from the essential fatty acid arachidonic acid play pivotal roles in acute inflammatory responses, resolution of inflammation as well as chronic inflammation such as atherosclerosis. Endocannabinoids are one group of arachidonic acid-derived lipid mediators, which bind to cannabinoid receptors CB1 and CB2. We are interested in how lipid mediators and their specific receptors affect acute and chronic cardiovascular disease manifestations.



Prof. Dr. rer. nat. Sabine Steffens - Group Leader
Prof. Dr.rer.nat. Alexander Faussner - Group Leader
Dr. rer. nat. Sarah-Lena Puhl - PostDoc
Dr. Raquel Guillamat-Prats, PhD - PostDoc
Dr. rer. nat. Martina Rami
Yong Wang - PhD student
Bingni Chen - PhD student
Jakob Schindler - PhD student (Vet.med.)
Brigitte Schopohl - cand. med.
Linus Keidel - cand. med.
Harsha Pooveli - cand. med.
Haron Nasiri - cand. med.
Daniela Wagner - TA
Silviya Wolkerstorfer, TA
Cornelia Seidl, TA
Rodrigo Carrasco, TA

Chronic inflammation in atherosclerosis and related metabolic disorders

It is known that tissue and circulating levels of endocannabinoids and fatty acid amide analogues are dysregulated in atherosclerosis and its related cardiovascular risk factors, obesity, dyslipidemia, diabetes and endothelial dysfunction. However, the pathophysiological effect of this dysregulated tone in cardiovascular disease is not well understood. Our group aims to clarify the precise pathophysiological relevance of these receptors and ligands in cardiovascular disease. This might open new avenues for biomarker research and therapeutic interventions. In this context, we recently found that palmitoylethanolamide (PEA) which is an endogenous fatty acid mediator and synthetized from membrane phospholipids, promotes not only anti-inflammatory responses but also efferocytosis capacity of macrophages. These properties of PEA translated into significant therapeutic benefits in a mouse model of atherosclerosis (Rinne et al. 2018). In a different study, we investigated the role of the endocannabinoid 2-AG metabolizing enzyme MAGL in atherosclerosis. Genetic Magl deficiency or pharmacological blockade of MAGL resulted in an atheroprotective phenotype. Mechanistically, blocking the MAGL pathway during atherosclerosis onset led to CB1 desensitization, which translated into an atheroprotective B lymphocyte B1a-IgM phenotype. The atheroprotective effect was dependent on CB2 signaling, as confirmed in Cnr2-/- mice (Guillamat-Pats et al. Thrombosis Hemostasis 2019).



Pericardial fat lymphoid cluster, showing B lymphocytes (red), T lymphocytes (green) and adipose tissue/collagen (blue). [Image provided by Mariaelvy Bianchini & Michael Horckmans]

Myocardial infarction and repair

Myocardial infarction induces an inflammatory response, which is required for the induction of cardiac repair processes. Various cell types, including neutrophils and macrophages, are involved at different stages of infarct healing, ultimately leading to scar formation and adaptive remodeling to preserve cardiac function. The inflammatory response after MI needs to be well-balanced in order to limit infarct expansion and progressive loss of cardiac function. In this regard, our research aims at better understanding the signaling pathways and local (lipid) regulators in the cardiac microenvironment promoting resolution of inflammation and favorable healing responses. Past research investigating the underlying inflammatory mechanisms and cellular key players of cardiac repair has mainly focused on cells within the heart. However, the potential relevance of adipose tissue in the context of MI has been largely neglected so far. Adipose tissue is the largest endocrine organ in the human body and has a role in the development of cardiometabolic disorders such as insulin resistance, cardiovascular disease, type 2 diabetes and many other complications. Perivascular adipose tissue comprises, amongst others, the epicardial adipose tissue (EAT) surrounding coronary arteries as well as pericardial adipose tissue (PAT) overlying the pericardium. EAT thickness, which can be assessed by echocardiography, correlates with acute coronary events and has been proposed as a diagnostic tool for acute coronary risk stratification. It is remarkable that the murine PAT and EAT in humans contains a high density of immune cell clusters, suggesting a role in immune surveillance to protect the

heart from pathogens. These clusters, which are mainly composed of lymphocytes, have been designated as fat-associated lymphoid clusters (FALCs). We recently found that the murine PAT is a crucial regulator of post-myocardial infarction immune responses. We identified the pericardial FALCs as a preferential site for innate-adaptive immune cell cross talk and lymphocyte activation, with important consequences for cardiac healing. Using two-photon laser scanning microscopy and flow cytometry, we observed an expansion of lymphoid clusters in the PAT of mice subjected to MI. We also examined lymphoid clusters in EAT of humans with or without coronary artery disease (CAD) and found larger B cell clusters in EAT of CAD patients compared to controls without CAD (Horckmans et al. Circulation 2018).
We also identified an important role of endocannabinoid lipid signaling in myeloid cell mobilization and cardiac recruitment in response to myocardial infarction. In particular, we found that the endogenous lipid ligand 2-arachidonoylglycerol (2-AG) promotes leukocyte release into the circulation and cardiac leukocyte recruitment after ischemia. We could link the enhanced circulating 2-AG levels to a modulation of endocannabinoid 2-AG biosynthesis and breakdown in the bone marrow and myocardium in response to MI. In addition, we found that mice lacking the CB2 cannabinoid receptor have lower expression levels of CXCL12 and adhesion molecule VCAM1 in the bone marrow (Schloss et al. Cardiovascular Research 2019).

Key Publications

Sager et al. T*ime-of-day at symptom onset was not associated with infarct size and long-term prognosis in patients with ST-segment elevation myocardial infarction.* **J Transl Med.**2019;17(1):180

Bianchini et al. *CD274/PD-L1 marks non-classical monocytes to unveil new features of their origin and immunoloregulatory function.* **Sci Immunol.** 2019;4(36). pii: eaar3054

Yin et al. *ApoE attenuates unresolvable inflammation by complex formation with activated C1q.* **Nature Med.** 2019;25(3):496-506

Guillamat-Prats et al. *Deficiency of monoacylglycerol lipase enhances IgM plasma levels and limits atherogenesis in a CB2-dependent manner.* **Thromb Haemost.** 2019; 119(2):348-351

Schloss et al. *2-arachidonoylglycerol mobilizes myeloid cells and worsens heart function after acute myocardial infarction.* **Cardiov Res.** 2019;115(3):602-613

Horckmans et al. *Pericardial adipose tissue regulates granulopoiesis, fibrosis and cardiac function after myocardial infarction.* **Circulation.** 2018;137(9):948-960

Rinne et al. *Melanocortin 1 Receptor Deficiency Promotes Atherosclerosis in Apolipoprotein E-/- Mice.* **Arterioscler Thromb Vasc Biol.** 2018;38: 313-323

Rami et al. *Chronic intake of the selective serotonin reuptake inhibitor fluoxetine enhances atherosclerosis.* **Arterioscler Thromb Vasc Biol.** 2018;38: 1007-1019

Rinne et al. *Palmitoylethanolamide Promotes a Proresolving Macrophage Phenotype and Attenuates Atherosclerotic Plaque Formation.* **Arterioscler Thromb Vasc Biol**. 2018;38(11):2562-2575.

Soluble mediators of Inflammation

Philipp von Hundelshausen

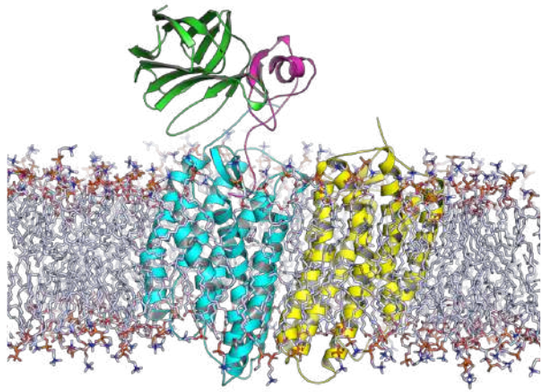
Cardiovascular events that are based on atherosclerosis are still the leading cause for mortality worldwide but in Germany, too. Otimizing prevention and treatment options will have a large impact in socioeconomic and health aspects. Current effective strategies lower LDL-cholesterol levels, or blood pressure and reduce blood glucose. Targeting the inflammatory component of this chronic inflammatory disease is not yet clinically implemented. Several clinical trials such as CANTOS or LoDoCo-2 provided promising perspectives for anti-inflammatory drugs and could become reality in the near future. In this context we are investigating basic principles of the regulation of inflammation, more specifically mechanisms that depend on soluble effectors that guide immune cells to inflammatory lesions

Dr. med. Philipp von Hundelshausen - Group Leader
Dr. rer. nat Xavier Blanchet - PostDoc
Veit Eckardt - PhD student
Julian Leberzammer - MD student
Rundan Duan - graduate student
Tomasz Lakomiec - PhD student
Ya Li - student - graduate student
Sabine Streicher - CTA
Lusine Saroyan - TA

Platelets are a rich source of a few selected chemokines (CXCL4, CXCL4L1, CCL5, CXCL7, CXCL12) and we have elucidated in the past that platelets have proatherogenic properties because they release chemokines that are deposited on glycosaminoglycans of endothelial cells and leukocytes and contribute to the recruitment of immune cells to atherosclerotic lesions. Some of these chemokines such as CCL5 and CXCL4 form heterodimers with synergistic effects on monocyte recruitment.

Under inflammatory conditions soluble mediators organize the coming and going of immune cells thereby positioning these cells according to their task. As many mediators are known to emerge simultaneously contact is inevitable and in some cases complex formation between soluble effector molecules will occur and this could be an important regulatory principle. In this respect we have previously mapped the chemokine interactome and have selected among the more than 200 partnerships, heterodimers with the crucial inflammatory chemokine CCL5 that form distinct types of heterodimer and each of these has a different mechanism.

In the last two years we explored another class of soluble mediators that play a role in inflammation, galectins. Until now, these effector molecules have been considered to function independently. Here, we tested the hypothesis that they form molecular hybrids. By systema-tically screening chemokines for their ability to bind galectins-1 and -3, we identified several interacting pairs, such as CXCL12 and galectin-3. Based on NMR and MD studies of the CXCL12/ galectin-3 heterodimer, we identified contact sites between CXCL12 β-strand-1 and Gal-3 F-face residues. Mutagenesis of galectin-3 residues involved in heterodimer formation resulted in reduced binding to CXCL12, enabling to test functional activity comparatively. Galectin-3, but not its mutants, inhibited CXCL12-induced chemotaxis of leukocytes and their recruitment into the mouse peritoneum. Moreover, galectin-3 attenuated CXCL12-stimulated signaling via its receptor CXCR4 in a ternary complex with the chemokine and receptor, consistent with our structural model. This first report of heterodimerization between chemokines and galectins reveals a new type of interaction between inflammatory mediators that can underlie a novel immunoregulatory mechanism in inflammation. Thus, further exploration of the chemokine/galectin interactome is warranted.



Galectin-3 attenuates CXCL12-stimulated signaling via its receptor CXCR4 in a ternary complex. The contact of the heterodimer between the CRD of Gal-3 (green) and CXCL12 (magenta) with the homodimer of CXCR4 (subunits colored in cyan and yellow) has been calculated based on structural insights from NMR and variants of Gal-3.

Key Publications

Nording, et al. *Platelets mediate ischemia-induced revascularization through C5aR1-induced secretion of CXCL4.* **Acta Physiologica.** 2019; 227: p. 10-10.

Kornhuber et al. *Hemostatic abnormalities in adult patients with Marfan syndrome.* **Cardiovasc Diagn Ther.** 2019: 9(Suppl 2): p. S209-S220.

Goldmann et al. *Oral Bruton tyrosine kinase inhibitors block activation of the platelet Fc receptor CD32a (FcgammaRIIA): a new option in HIT?* **Blood Adv.** 2019. 3(23): p. 4021-4033.

Eckardt et al. *Glycans and Glycan-Binding Proteins in Atherosclerosis.* **Thromb Haemost.** 2019; 119(8): p. 1265-1273

Vajen et al. B*locking CCL5-CXCL4 heteromerization preserves heart function after myocardial infarction by attenuating leukocyte recruitment and NETosis.* **Sci Rep.** 2018: 8(1): p. 10647.

Non-coding RNAs in atherosclerosis and cardiovascular disease

Christian Weber

Deciphering the relevance of cell-specific non-coding RNAs in susceptibility, progression and prevention of atherosclerosis and cardiovascular diseases.



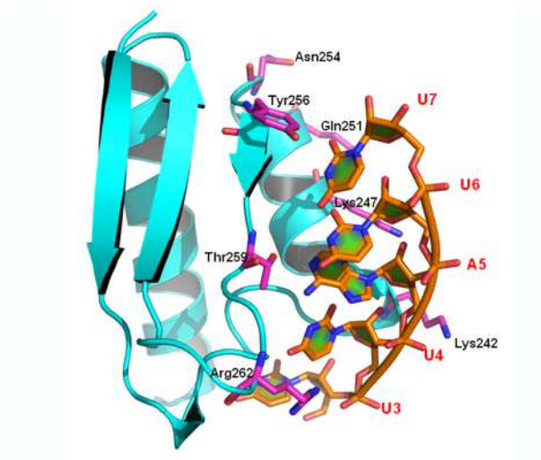

Prof. Dr. med. Christian Weber - Group Leader
Dr. Lucia Natarelli, PhD - PostDoc
Dr. rer. biol. hum. Kiril Bidzhekov - PostDoc
Dr. Ismail Cimen - PostDoc
Dr. Donato Santovito - PostDoc
Zahra Abedi Kichi - PhD student (visiting)

Interactions between non-coding RNAs in atherosclerosis

We aimed to study how miRNA regulate lncRNAs function in atherosclerosis. RNA-sequencing and single transcript-sequencing (i.e.. RACE and nested PCR) in cell specific miRNAs deficient transgenic mice models, enabled us to identify lncRNAs targeted by miRNAs. We found that the novel lncRNA, lncWDR59 regulated endothelial cell proliferation in a Notch-dependent manner while limiting aberrant endothelial cell proliferation through the Wnt/β-catenin signalling pathway. We identified β-catenin to limit the proliferation-related DNA damage, which accumulates in small extranuclear chromatin structures named micronuclei. In vivo, disruption of lncWDR59:miRNA interaction using specifically designed target site blockers protected against atherosclerosis by restoring endothelial cell proliferation while limiting hyperlipidaemia-mediated increase of DNA damage in endothelial cells. Promisingly, the efficacy of this targeting strategy was homologous in humans (Natarelli L et al. Nat Commun 2018). Ongoing research is exploring additional lncRNA:miRNAs candidates involved in micronuclei formation and cardiovascular diseases.

Homeostasis of endothelial miR-126

A second line of research focused on a unique mechanism regulating strand homeostasis of the most abundant endothelial miRNA, miR-126. While the majority of miRNAs show single functional strand, we described both starnds to exert complementary



miRNA126-5p interacting with Caspase 3

bioogica processes. We found the 3p strand to be prone to autophagy and degradation, whereas the 5p strand was preserved and translocated to a nuclear reservoir. We further identified nuclear shuttling motifs, which interacted with the RNA-binding protein Mex3a on the extraluminal surface of autophagosomes. The nuclear translocated 5p strand controlled apoptosis mediators both at RNA and protein level and thus preserved EC viability. In vivo we confirmed nuclear enrichment of miR-126-5 together with enhanced endothelial autophagy at non-predilection sites for atherosclerosis. Conversely, we generated a novel CRISP-Cas9 mouse model with constitutional deletion of Mex3a, which was associated with reduced nuclear enrichment of miR-126-5p in endothelial cells and higher apoptosis (unpublished).

miRNA regulation of CXCL12/CXCR4 axis

As a third line of research, we are investigating how miRNA regulate the chemokine system CXCL12/CXCR4 in a cell-specific context. We identified two specific miRNAs able to target both CXCL12 and CXCR4. We are presently determining their cell-specific expression as well as their functional and therapeutic relevance in atherosclerosis.

Key Publications

Cimen et al. *Double bond configuration of palmitoleate is critical for atheroprotection.* **Mol Metab**. 2019; 28: 58-72.

Natarelli et al. *Next-Generation Therapeutic Concepts for Atherosclerosis: Focus on Cell Specificity and Noncoding RNAs.* **Thromb Haemost.** 2019;119(8):1199-1201

Onat et al. *Intercepting the Lipid-Induced Integrated Stress Response Reduces Atherosclerosis.* **J Am Coll Cardiol.** 2019; 73(10):1149-1169.

Di Francesco et al. *MicroRNA signatures in cardiac biopsies and detection of allograft rejection.* **J Heart Lung Transplant.** 2018; 37(11):1329-1340.

Natarelli et al. *miR-103 promotes endothelial maladaptation by targeting lncWDR59.* **Nat Commun.** 2018; 9 (1):2645.

Wei et al. *Dicer in Macrophages Prevents Atherosclerosis by Promoting Mitochondrial Oxidative Metabolism.* **Circulation.** 2018;138(18):2007-2020.

Cardiovascular Imaging

Remco Megens



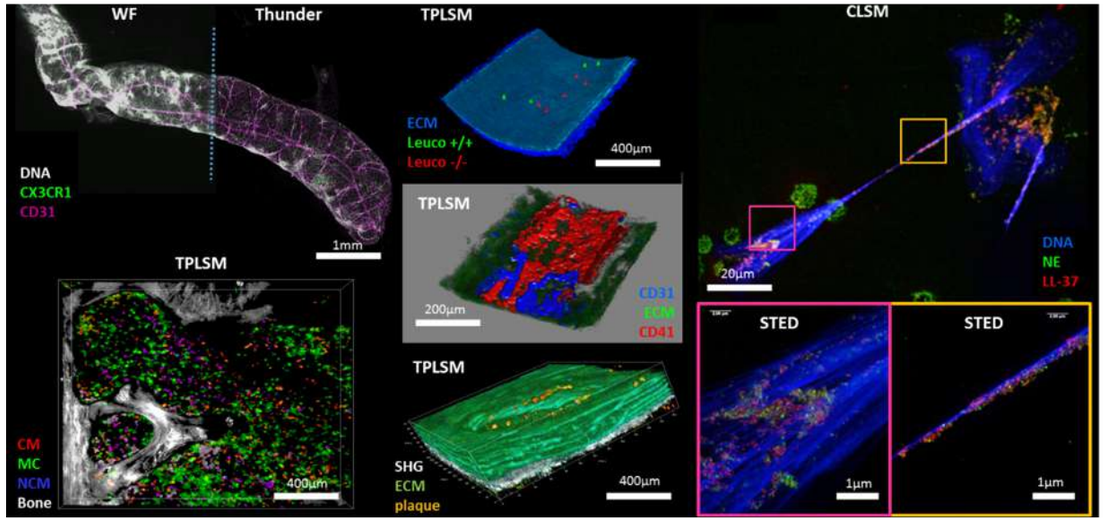
Dr. rer. nat. Remco TA Megens - Group Leader
Mariaelvy Bianchini - PhD student
Yvonne Janssen - TA

To further elucidate the processes involved in initiation and progression of atherosclerosis, insight in cardiovascular structure and function is essential. Histology has provided a detailed insight in various aspects of human and experimental cardiovascular disease. However, the utilized preparation methods in histology limit studying structure and function under physiologically relevant circumstances. In order to study the origin and contribution of various inflammatory cell subsets to the disease, it is a prerequisite to visualize these processes at a (subcellular) resolution level in a (viable) physiological setting.

Our imaging core facility offers the researchers of our Institute as well as external collaborators technology, expertise, and training. We strive to apply and develop state-of-the-art imaging technologies for thoroughly investigating cardiovascular structures. We successfully used technologies such as confocal laser scanning microscopy to facilitate 3D microscopic imaging of thin samples or isolated/cultured cells at sub micrometer and highly specific resolution. Stimulated Emission Depletion Nanoscopy allowed us improving nanometer resolution and comprehensively studying intracellular processes. We took advantage of two-photon laser scanning microscopy for studying biological structures and processes directly at sites of occurrence: i.e. in whole mount tissues or even in vivo. Improved acquisition speed, depth penetration, and optical sectioning properties of this technology enabled four dimensions deep tissue structure imaging. Triggered on the heart and respiration cycle of the animal under investigation or tissue stabilization, two-photon laser scanning microscopy allowed us to circumvent the impact of tissue movement on imaging for successful in vivo imaging of atherosclerosis. We also exploited instant computational clearing technology for bridging between microscopic and mesoscopic imaging enabling fast 3D of classical widefield microscopy over larger areas (up to 5x5cm, 10-50µm thick).

The described microscopic methodologies have been successfully applied in various studies (Figure) that have been conducted over the years by IPEK members, CRC1123 partners, and other collaborators. Moreover, the Megens group will continue to develop applications for imaging in (diseased) cardiovascular targets and apply them for projects studying vessel wall morphology and functionality as well as the dynamics and recruitment of various inflammatory cell subsets in ex vivo or in vivo models. In addition, we aim at expanding the imaging facility with novel imaging modalities and methods with nanoscopic resolution for detailed visualization of subcellular structures and processes involved in cardiovascular disease.

Besides Facilitating and advancing imaging methodologies, our group aims to better understand the morphology and functions of bone marrow and unravel the role of monocyte subsets and monocyte conversion in steady state and cardiovascular disease (in collaboration with the Duchene Group).



Examples of optical imaging in mouse (cardiovascular) tissue and isolate human neutrophils: top left; adipose tissue, overview of whole mount CX3CR1/eGFP+/+ Omentum stained for endothelium and DNA recorded in widefield (WF, left part) and instant computationally clearing (Thunder, right part) modes. Lower left; myeloid cells (MC), classical (CM) and non-classical (NCM) monocytes distribution in whole mount bone marrow (Bianchini et al., Sci Immunol. 2019). Top middle: flow adhesion assay in ex vivo mounted mouse carotid artery of leucocytes derived from control (+/+) or genetically modified (-/-) mice (van der Vorst et al., Bioprotoc. 2017). Center middle; in vivo platelet adhesion (CD41) visualized in an ex vivo mounted mouse carotid artery after (partial) mechanic endothelial (CD31) denudation (Zhao et al., J Cell Mol Med. 2017). Lower middle; optically cleared (TDE) Thoracic aortic section revealing all layers of the wall. Top right; in vitro generated neutrophil extracellular trap formation demonstrating the distribution of DNA, granule derived neutrophil elastase and LL37 as visualized with either confocal (top) or at nanoscopic resolution using STED microscopy (pink and yellow outlines).

Shared Ressource Labs

Transgenic and Gene Targeting Technology

Dr. rer. biol. hum. Kiril Bidzhekov

The Transgenic and Gene Targeting Shared Resource Lab is dedicated to generating mouse transgenic and knockout models for researchers within our Institute. Technologies based on both classical transgenesis (via homologous recombination) and gene editing (via CRISPR-Cas9) are exploited to generate mouse models. Genes can then either be expressed or inactivated in a development- and tissue-specific manner to understand specific gene function and regulation. Genetic mouse model generation goes from engineering targeting vectors to introducing foreign genetic material into the recipient's genome through homologous recombination. In the last two years we successfully implemented the CRISPR-Cas9 technology in mouse transgenesis. Diverse genetic models have been generated and are being exploited by a panel of research groups in our Institute.

Cell Sorting and Flow Cytometry

Dr. med. habil. Michael Hristov

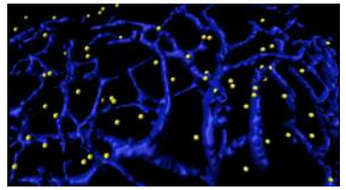
The Cell sorting and Flow Cytometry Shared Resource Lab offers expertise and technology for analytical multicolor flow cytometry and cell sorting to all researchers within our Institute. Expertise with BD FACSAria III high-end cell sorter allows optimal instrument setup and offers state-of-the art and experiment-tailored sorting services. The service spans from aseptic bulk to single-cell sorting. A panel of cell subtypes can be isolated with well-preserved viability encompassing a variety of immune cell subtypes including neutrophils, monocytes, dendritic cells, NK-, T- and B-cells, hematopoietic stem cell subsets (LSK, GMP, CMP and MEP), platelets and megakaryocytes, cells from tissue/organ homogenates but also cell fragments including endothelial cell-derived nuclei and apoptotic bodies.

12/2019
Hitting HIT

Heparin is widely used as an anticoagulant, but evokes in some patients a potentially life-threatening condition called HIT. A study directed by IPEK Professor Wolfgang Siess demonstrated that this hazardous side-effect can be effectively prevented in vitro by the inhibition of a specific enzyme. The discovery provides a new option for the treatment of type II HIT. The study was carried out in collaboration with research groups led by Professor Michael Spannagl (LMU Medical Center) as well as IPEK members Christian Weber and Philipp von Hundelshausen .

Goldmann L et al., Oral Bruton tyrosine kinase inhibitors block activation of the platelet Fc receptor CD32a (FcgammaRIIA): a new option in HIT? **Blood Adv** 2019;3:4021-4033.

06/2019
Not just supporting actors



Non-classical monocytes were long thought to play a purely surveillance role in the immune system. IPEK scientists led by Johan Duchêne, Mariaelvy Bianchini, Remco Megens and Christian Weber identified PD-L1 as a specific marker for these cells and showed in a mouse experimental model, that non-classical monocytes also play a direct regulatory role in the adaptive immune response.

Bianchini M et al., PD-L1 expression on nonclassical monocytes reveals their origin and immunoregulatory function. **Sci Immunol** 2019;4.

06/2019
Self-healing after heart attack

IPEK researchers from the Söhnlein Lab have shown that a protein, which stimulates the resolution of inflammatory reactions, enhances cardiac repair following heart attack in both mice and pigs. They set out to develop a therapeutic approach, which makes use of the endogenous processes that enable the inflammation to be turned off.

Ferraro B et al., Pro-Angiogenic Macrophage Phenotype to Promote Myocardial Repair. **J Am Coll Cardiol** 2019;73:2990-3002.

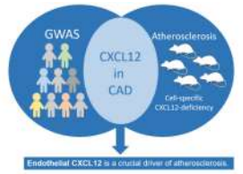
News Research

05/2019
Induced cell death and plaques

IPEK researchers from the Söhnlein Lab showed that neutrophils exacerbate atherosclerosis by inducing a previously unrecognized type of induced cell death. They designed a peptide that could bind to free histones released by neutrophils and neutralize their toxic effect. The peptide may have the same effect on other chronic inflammatory disorders, which prompted a patent application.

Silvestre-Roig C et al., Externalized histone H4 orchestrates chronic inflammation by inducing lytic cell death. **Nature** 2019;569:236-240.

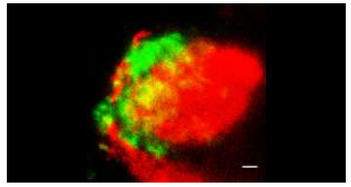
03/2019
CXCL12 and Atherosclerosis



IPEK researchers among whom Yvonne Döring, Emiel van der Vorst and Christian Weber further elucidated the role of the chemokine CXCL12 and its involvement in coronary artery disease (CAD). They identified an intergenic single nucleotide polymorphism (rs2802492), near CXCL12, associated with CXCL12 plasma levels and increased risk for CAD. Endothelial CXCL12 was found to be a crucial driver of atherosclerosis and contributor to CXCL12 levels.

Döring Y et al., CXCL12 Derived From Endothelial Cells Promotes Atherosclerosis to Drive Coronary Artery Disease. **Circulation** 2019;139:1338-1340.

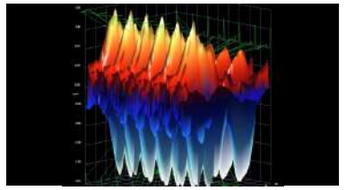
01/2019
Central Regulator



Researchers led by Changjung Yin, Andreas Habenicht and Christian Weber, in cooperation with the Leibniz Institute for Natural Products and Infection Biology in Jena and other partners, have demonstrated that ApoE is a key checkpoint regulator of a central signaling cascade that directly interferes in inflammation. Interfering with this cascade, could dampen diseases as diverse as atherosclerosis and Alzheimer-associated inflammation, providing a novel and promising therapeutic target for chronic inflammatory diseases.

Yin C et al., ApoE attenuates unresolvable inflammation by complex formation with activated C1q. **Nat Med** 2019;25:496-506.

10/2018
Two sides of the same leaf



IPEK researchers led by Sabine Steffens have elucidated the influence of the endocannabinoid 2-arachidonoylglycerol (2-AG) on cardiac healing after acute myocardial infarction (MI). They identified the 2-AG/cannabinoid receptor CB2 axis as a crucial regulator of the homeostatic bone marrow hematopoiesis and leukocyte release after MI. These novel finings raise concerns to the use of plant-derived or synthetic cannabinoids, which facilitate bone marrow haematopoiesis and leukocyte release in MI patients.

Schloss MJ. et al, 2-Arachidonoylglycerol mobilizes myeloid cells and worsens heart function after acute myocardial infarction. **Cardiovasc Res** 2019;115:602-613.

07/2018
RNA-RNA interactions

IPEK researchers led by Andreas Schober and Lucia Natarelli provided further evidence that a specific micro-RNA, called miR-103, could stimulate the development of atherosclerosis. Specific inhibition of the miR-103/lncWDR59 interaction in a mouse experimental model delayed the development of atherosclerosis, which was mirrored by similar mechanisms in the human vasculature, opening avenues for potential therapeutic candidates.

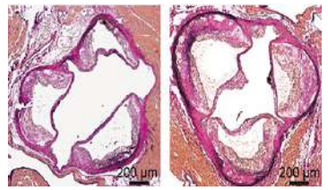
Natarelli L et al., miR-103 promotes endothelial maladaptation by targeting lncWDR59. **Nat Commun** 2018;9:2645.

05/2018
Stopped on time

The internal clock controls all vital functions in the body. Body temperature as well as blood pressure or the release of certain enzymes are subject to oscillations throughout the day, the so-called circadian rhythm. For the first time, a team led by Oliver Söhnlein has now shown the influence of circadian rhythms on atherosclerosis, which could be crucial for improving therapeutic approaches.

Winter C et al., Chrono-pharmacological targeting of the CCL2-CCR2 axis ameliorates atherosclerosis. **Cell Metab** 2018;28:175-182.e5.

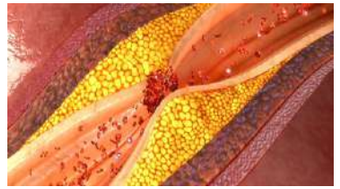
05/2018
Dicer cuts down on fats



The enzyme Dicer cleaves long precursors into short RNA molecules called microRNAs. A team of IPEK researchers, led by Andreas Schober, has now shown that the enzyme Dicer plays an important role in the breakdown of triglycerides in alternatively activated macrophages, enhancing energy metabolism while reducing levels of fat storage in macrophages, thus slowing the progression of atherosclerosis.

Wei Y et al., Dicer in macrophages prevents atherosclerosis by promoting mitochondrial oxidative metabolism. **Circulation** 2018;138:2007-2020.

04/2018
Jamming the signal



Wolfgang Siess and his colleagues showed that Bruton's tyrosine kinase (Btk) inhibitors, which are used for the treatment of certain forms of leukemia, specifically inhibit the formation of atherosclerotic plaque-triggered thrombus formation more effectively than do the agents currently employed for this purpose. These results should encourage more research on the application of Btk inhibitors for the prevention and therapy of cardiovascular disease.

Busygina K et al., Oral bruton tyrosine kinase inhibitors selectively block atherosclerotic plaque-triggered thrombus formation. **Blood** 2018;131:2605-2616.

News Research

C. Silvestre-Roig,
Q. Braster
O. Söhnlein
Rolf Becker Prize 2019
IPEK scientists Carlos Silvestre-Roig, Quinte Braster and Oliver Söhnlein together with scientists from the Department of Anaesthesiology, and Cardiac Surgery Clinic and Polyclinic were awarded the prestigious Rolf Becker Prize 2019 from the LMU Medical Faculty and the "Rufzeichen Gesundheit!" Foundation.The scientific work of the three winners, was published in Nature in early May 2019.

J. M. Jamasbi
PhD award Munich University Society 2019
Janina Maria Jamasbi, was awarded a PhD award from the Munich University Society for her PhD thesis on (the): "Comparison of known and development of new therapeutic approaches to inhibit the interaction of thrombocytic glycoprotein VI with atherosclerotic plaque". Janina Jamasbi's work in the group of Wolfgang Siess was acknowledged as an important contribution to the potential improvement in current antiplatelet therapies for cardiovascular disease.

M. Mauler, Edith von Kaulla Prize 2019
Maximilian Mauler was awarded the Edith von Kaulla Preis Prize for his thesis "Platelet Serotonin Aggravates Myocardial Ischemia/ Reperfusion Injury via Neutrophil Degranulation". The prize, is awarded to young researchers for outstanding doctoral theses and research work in the field of vascular and coagulation disorders.

M. J. Schloss
Doctoral Prize Dr. Hildegard and Heinrich Fuchs Foundation 2019
Maximilian J. Schloss was awarded the LMU medical faculty doctoral Prize from the Dr. Hildegard and Heinrich Fuchs Foundation for his doctoral thesis on (the):"Influence of neutrophilic granulocytes and the circadian rhythm on wound healing after myocardial infarction." As part of his medical doctorate at the IPEK in the group of Sabine Steffens, M. J. Schloss found that the time of the day when an infarction takes place influences the extent of the inflammatory reaction.

O. Söhnlein
Albert-Frankel-Prize 2019
Oliver Söhnlein received the Albert-Fraenkel-Prize for its research on the inflammatory arm of Athersoclerosis. The Prize is awarded to German-speaking scientists who have qualified through publications in the field of physiology, pharmacology, pathology, clinic or therapy of the circulation.

C. Yin
Bayer Thrombosis Research Award 2019
The Scientific Committee of the Bayer Science and Education Foundation has awarded the Bayer Thrombosis Research Award to IPEK scientist Changjun Yin. He was chosen in recognition of his research on Atherosclerosis and Alzheimer's disease as inflammatory conditions with high risks to develop thrombosis-related diseases.

Prizes and Awards

A. Bartelt
Schering Foundation Friedmund Neumann Prize 2018
The activation of brown adipose tissue appears as a promising therapeutic option for the treatment of metabolic diseases. IPEK junior group leader Alexander Bartelt developed and greatly advanced the concept underlying this therapy. For his outstanding individual academic profile Alexander Bartelt was awarded the Friedmund Neumann Prize from the Ernst Schering Foundation.

E. Lutgens
ESC Outstanding Achievement Award 2018
With this award, the ESC Council for Basic Cardiovascular Science (CBCS) honours basic researchers with outstanding accomplishments in the early stage of their career. The award was presented to Esther Lutgens at the ESC Congress 2018 in Munich. Prof Lutgens is the fourth consecutive PI/Professor from the IPEK to receive this award.

C. Winter
Hermann Rein Award 2018

Carla Winter was awarded the Hermann Rein Award by the German Society for Microcirculation and Vascular Biology (GfMVB) sponsored by SERVIER Deutschland for her published work „Chrono-pharmacological targeting of the CCL2-CCR2 axis ameliorates atherosclerosis" (Cell Metab. 2018).

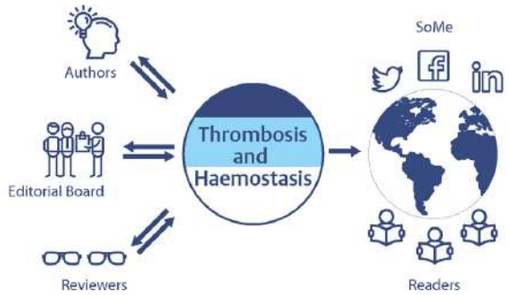
Y. Döring
DGAF W. H. Hauss-Prize 2018
Yvonne Döring was awarded the W.H. Hauss Prize from the DGAF, which supports scientific work in the field of atherosclerosis research. The work entitles "Vascular CXCR4 Limits Atherosclerosis by Maintaining Arterial Integrity: Evidence from Mouse and Human Studies" (Circulation 2017).

Journal Aims and Scope

Thrombosis and Haemostasis publishes reports on basic, translational and clinical research dedicated to novel results and highest quality in any area of thrombosis and haemostasis, vascular biology and medicine, inflammation and infection, platelet and leukocyte biology, from genetic, molecular & cellular studies, diagnostic, therapeutic & preventative studies to high-level translational and clinical research. The journal provides position and guideline papers, state-of-the-art papers, expert analysis and commentaries, and dedicated theme issues covering recent developments and key topics in the field. It provides a forum for the exchange of ideas and concepts fostering cross-disciplinary insights in basic and clinical research. It is published monthly in print and online via Thieme E-Journals. It is covered in the main abstracting and indexing services worldwide.
Thrombosis and Haemostasis is accompanied by TH Open, an Open Access journal for original basic research and clinical studies, review articles, letters to the editor, and case reports in vascular biology and medicine.

2018-2019

The Impact factor and CiteScore have maintained a stable trend in comparison to others in the field, specifically reflected by the CiteScore Percentile in the category hematology, which matched near 90th, over the past 5 years.
The full retro-digitalization now lets readers browse through issues dating back to he first published issue in 1957 (then under the name Thrombosis et Diasthesis Haemorrhagica)
TH Open, the open access companion journal of Thrombosis and Haemostasis launched in 2017, is now



listed on PubMed Central and the Directory of Open Access Journals. Its unique “pay-what-you-want” policy gives everyone a chance to submit open access. As such, all articles in TH Open are freely available at www.thieme.com/tho.
With the successful move to the Thieme Publisher group, Thrombosis and Haemostasis got a new cover design visually matching the very distinct look from Thieme, a very strong brand which is known worldwide for high-quality medical publishing.

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Thrombosis and Haemostasis

Teaching (Selection)

Atzler D - M4/Pharma/Rezeptierkurs
Atzler D - M23g/Pharma/Dosierübungen (DANI)
Bartelt A - Anleitung zum selbstständigen wissenschaftlichen Arbeiten auf dem Gebiet der experimentellen Stoffwechselforschung und Endokrinologie (7C0386)
Bartelt A- Seminar: Molekulare Grundlagen kardiometabolischer Erkrankungen (7C0387)
Bartelt A - Journal Club: Novel molecular pathomechanisms of obesity, diabetes and cardiovascular disease (7C0389)
Bartelt A, Steffens S- Lecture - Cardiovascular, Lung and Metabolism, Master of Science Program: Human Biology - Principles of Health and Disease Lectures: Heart, Lung and Metabolism: From basic Physiology to Pathophysiological Processes and advanced Therapies (19475)
Bidzhekov K - Classical and modern strategies in mouse transgenesis (7C0482)
Bidzhekov K, Duchêne J, Megens R, Steffens S, Weber C - BioImaging (19184)
Döring Y, Ries C - Biochemische Grundlagen der Arteriosklerose (7C0301)
Döring Y, Megens R, Weber C - Research School Vascular Biology / Immunology (7C0322)
Döring Y, Megens R, Weber C - Immune cell crosstalk in inflammation (7C0702)
Döring Y - The adaptive immune system in inflammatory disease, vascular biology and atherosclerosis (7C0705)
Duchêne J, Megens R - Flow Cytometry & Optical Imaging – Seeing is Believing (7C0741)
Duchêne J - Flow Cytometry in Clinical Practice (7C4071)
Ries C - Kolloquium über die neuesten Forschungsergebnisse zu molekularen Mechanismen der Zellmigration und Differenzierung (7C0478)
Ries C - Anleitung zum experimentellen wissenschaftlichen Arbeiten auf dem Gebiet der Molekular- und Zellbiologie im Rahmen von Doktor- und Masterarbeiten (7C0479)
Schober A - Anleitung zum selbstständigen wissenschaftlichen Arbeiten auf dem Gebiet der experimentelle Gefäßmedizin (7C0365)
Schober A - Interdisziplinäre Vorlesung (7M1380)
Schober A - Klinisch-Pharmakologische-Konferenz im Kardiovaskuläres System, Medical Faculty (7M1296)
Schober A - Kursus Repetitorium Pharmakologie: Multimorbidität (7M3409)
Schober A, Faussner A- Lecture - Cardiovascular, Lung and Metabolism (19475)
Schober A - Literaturseminar: Experimentelle Gefäßmedizin (7C0366)
Schober A - Macrophage biology in atherosclerosis (7C0462)
Schober A - MicroRNAs in der vaskulären Pathogenese (7C0461)
Schober A - Molekulare Grundlagen des vaskulären Remodellings (7C0363)
Schober A - Experimentelle Gefäßmedizin (7C0364)
Schober A - Seminar: Biochemische Grundlagen der Arteriosklerose (7C0301)
Schober A - Cannabis in der Medizin (7C0379)
Steffens S - Cardiovascular Research – from preclinical models to human studies (19186)
Steffens S, Faussner A - Cardiovascular Lung Metabolism Module (3rd semester (19482, 19483)
Faussner A - Übungen und Seminare der Klinischen Chemie und Laboratoriumsdiagnostik (7M0813)
Von Hundelhausen P - Echokardiographie (7M3410)
Von Hundelhausen P - Ausgewählte Kapitel aus der Pathophysiologie vaskulärer Erkrankungen (7C0302)
von Hundelshausen P - Master Lecture Series SFB1123, (7C0438)
von Hundelshausen P - Struktur-Funktionsanalyse von Protein-Proteininteraktionen. (7C0434)
BioImaging - Practical course und Seminar (19199)

Teaching

Graduate School

The aim of the Integrated Research Training Group (IRTG) is to train doctoral researchers to highly qualified scientists. We provide a structured curriculum and mentoring program specifically tailored to the needs of the doctoral researchers within our CRC. Our curriculum is carried out in the framework of the respective LMU and Tum Medical Faculty PhD programs, the Munich Medical Research School (MMRS) and TUM Medical Graduate Centre (MGC). The training includes lecture series to introduce the scientific background, networking meetings, talks from external and internal experts as well as soft skill courses and methods courses on advanced scientific techniques. Every PhD student is assigned a thesis advisory committee, which supervises the scientific work, its feasibility and milestones and advises the student in his/hers career planning and scientific network.

Doctoral researchers enrolled in the IRTG program are offered a three-year structured PhD program, allowing the students to collect the necessary ECTS points to obtain their PhD in Medical Research. MD students are welcome to join the study program for the duration of their medical thesis research project in the lab. IRTG1123 students are located at LMU, TUM and Helmholz and are encouraged to choose individual seminars, lectures or courses offered by other organizations and graduate schools.

In 2019, about 20 students were enrolled in the IRTG1123 while an additional 20 students were associated to us, working on related topics in participating CRC research groups. In addition to our biweekly IRTG1123 seminar series, we also offered two methods courses about GraphPad Prism and FACS. The 2019 annual retreat took place in Hotel am Badersee in beautiful Grainau in October. During two oral presentation sessions, 10 students presented and discussed their work, chaired by two senior PhD students. More than 20 posters were presented in two poster sessions with three PhD students chairing the discussions. As a guest speaker, we invited Ingo Hilgendorf from the University Heart Center Freiburg, who held an inspiring talk about macrophage kinetics in atherosclerosis. During the first evening the students were playing escape games while enjoying a drink as our social activity. In a Student Representative Election, the students voted for three new speakers as well as one Technical Support.

Theses

PhD candidates

M. Lacy, Atzler Lab, started 2017
Y. Wu, Atzler Lab, started 2019
I. Lemmer, Bartelt Lab, started 2019
A Ofoghi, Bartlet Lab, started 2019
N. Willemsen, Bartelt Lab, started 2019
C. Neideck, Bartelt Lab, completed 2018
S. Gencer, Döring Lab, started 2017
M. Aslani, Duchêne Lab, started 2018
M Bianchini. Megens Lab, started 2014
B. Brumec, Schober Lab, started 2018
I. Baatsch, Schober Lab, started 2015
S.S. Maleki, Schober Lab, started 2018
A. Popal, Schober Lab, started 2018
R. Mohibulla, Schober Lab, started 2015
C. Winter, Söhnlein Lab, completed 2018
N. Paulin, Söhnlein Lab, completed 2019
Q. Braster, Söhnlein Lab, completed 2019
M. Rami, Steffens Lab, completed 2018
Y. Wang, Steffens Lab, started 2018
B. Chen, Steffens Lab, started 2019
J. Schindler, Steffens Lab, started 2019
T. Lacomiec, von Hundelshausen Lab, started 2019
Z. A. Kichi, Weber Lab, started 2018

MD candidates

S. Kotschi, Bartelt Lab, started 2019
T. Greve, Ries Lab, started 2010
L. Zhang, Ries Lab, started 2016
S. Waas, Schober Lab, completed 2018
G. Feische, Siess Lab, completed 2018
A-K. Mojica Muñoz, Siess Lab, completed 2019
V. Denzinger, Siess Lab, started 2018
K. Busygina, Siess Lab, started 2013
M. Schloss, Steffens Lab, completed 2018
M. Deininger, Steffens Lab, started 2014
M. Hilby, Steffens Lab, started 2016
D. Hering, Steffens Lab, started 2016
M. Volz, Steffens Lab, started 2017
B. Schopohl, Steffens Lab, started 2018
H. Pooveli, Steffens Lab, started 2018
H. Nasiri, Steffens lab, started 2018
L. Keidel, Steffens lab, started 2019
V. Eckardt, von Hundelshausen Lab, started 2012
J. Leberzammer, von Hundelshausen, started 2019

Project	Sponsor *Reference*	Principal Investigator *Collaboration Partner*	Time frame
Cxcl12 and Cxcr4/7 in atheroscleoris	DFG *CRC1123, A1*	Y. Döring C. Weber	2018-2022
Physical and functional interactions of chemokines with potent inflammatory effectors in atherosclerosis: focus on galectins	DFG *CRC1123, A2*	P. von Hundelshausen	2018-2022
Masterswitches of T cell reactivity in atherosclerosis	DFG *CRC1123 A5*	D. Atzler E. Lutgens	2018-2022
Circadian control of atheroprogression	DFG *CRC1123 A6*	O. Soehnlein C. Silvestre-Roig	2018-2022
Role of ACKR1/DARC in the myeloid pathogenesis of atherosclerosis	DFG *CRC1123, A10*	J. Duchene C. Weber	2018-2022
miRNA-regulated energy metabolism in macrophage-derived foam cellsmiRNA-regulated energy metabolism in macrophage-derived foam cells	DFG *CRC1123, B4*	M.Nazari-Jahantigh A. Schober	2018-2022
Role of NETs in atherogenesis	DFG *CRC1123, B5*	O. Söhnlein Y. Döring *L. Maegdefessel* *S. Massberg*	2018-2022
Lysophosphatidic acid and autotaxin in atherosclerosis	DFG *CRC1123, B8*	W. Siess A. Schober	2014-2018
Peripheral CB1 receptors in atherosclerosis	DFG *CRC1123, B9*	S. Steffens	2018-2022

Third Party Funding

Project	Sponsor *Reference*	Principal Investigator *Collaboration Partner*	Time frame
Role of the cholesterol sensor Nfe2l1 for adipose inflammation and atherogenesis	DFG *CRC1123, B10*	A. Bartelt	2019-2022
Macroscopic, microscopic, and nanoscopic (label free) imaging of atherosclerosis	DFG *CRC1123, Z1*	R. Megens	2018-2022
Integrated Research Training Group	DFG *CRC1123*	S. Steffens	2018-2022
Peripheral endocannabinoid system in atherosclerosis	DFG *STE1053/3-1*	S. Steffens	2014-2018
Endocannabinoid system and circadian rhythm in MI	DFG *STE1053/5-1*	S. Steffens	2015-2018
Role of GPR55 in atherosclerosis	DFG *STE1053/6-1*	S. Steffens	2018-2021
The role of microRNAs in HIF-1alpha-mediated regulation of macrophage energy metabolism during atherosclerosis	DFG *KA 4209/2-1*	E. Karshovska L. Natarelli	2016-2019
Alarmins induce acute neutrophil mobilization	DFG *CRC914 B8*	O. Söhnlein	2019-2023
Neutrophils and platelets cooperate in monocyte recruitment	DFG *CRC914, B8*	O. Söhnlein C. Weber	2015-2018
Munich Cluster for Systems Neurology (Synergy)	DFG *EXC 2145*	C. Weber	2019-2026
Structural basis and mechanisms of strand-specific microRNA trafficking and function in cardiac disease	DFG *CRCTRR267, A2*	C. Weber M. Sattler	2019-2023
The role of miR-10a and let-7b in cellular energy metabolism during macrophage polarization and atherosclerosis	DFG *WE 6160/1-1*	Y. Wei A. Schober	2016-2020

Project	Sponsor *Reference*	Principal Investigator *Collaboration Partner*	Time frame
Neutrophils fatten atherosclerotic lesions	DFG *OE465/1-1*	A. Ortega-Gomez	2018-2022
B Cell Autoimmunity in ApoE-deficient (ApoE-/-) Mice	DFG *YI133 /3-5* *HA1083/15-5*	C. Yin A. Habenicht	2019-2022
microRNA-regulated processes in keratinocytes after exposure to sulfur mustard: modulation by mimics and antagomirs	DFG *RI 808/6-1*	C. Ries	2019-2022
Immunotherapy of Vascular Disease	DZHK	O. Söhnlein C. Weber	2015-2018
Late pre-clinical development of CD40-TRAF6 inhibitors (TRAF-STOPs) part I: Go - No Go project	DZHK *High Risk High Volume Late Translational Project*	E. Lutgens C. Weber D. Atzler	2017-2019
Elucidation of a novel mediator of monocyte recruitment: the calcium-sensing receptor	DZHK	E. van der Vorst U. Wagner	2018-2019
Nfe2l1-mediated proteasomal activity in heart function and cardiovascular disease	DZHK	A. Bartelt	2018-2023
CARDIOMETABOLISM	DZHK	A. Bartelt *S. Herzig*	2019-2020
PostDoc Start up – late career	DZHK	Y. Döring	2019-2020
Promotion of women scientists	DZHK	Y. Döring	2019-2020
Immunotherapy of Vascular Disease	DZHK	O. Söhnlein	2019-2020

Project	Sponsor *Reference*	Principal Investigator *Collaboration Partner*	Time frame
Genetic discovery-based targeting of the vascular interface in atherosclerosis	DZHK-BHF	J. Duchene C. Weber	2019-2022
Endocannabinoid lipidomics	BMBF DZHK Shared Expertise	S. Steffens	2018
Fighting Atherosclerotic Plaques in Coronary Artery Disease Via Targeting Neuroimmune Interfaces	BMBF *ERA-CVD PLAQUEFIGHT*	A. Habenicht	2018-2021
Pericardial immune cell cross talk in cardiac repair and remodeling	BMBF *DZHK 81Z0600205*	S. Steffens	2019-2020
NEMO-IMMUNE	BMBF *ERA-CVD*	S-L. Puhl	2019-2022
AtheroInside	BMBF *ERA-CVD*	R. Megens *B. Slütter* *K. Raemdonck*	2019-2022
Modulation of microRNA-regulated processes in skin and inflammatory cells as a therapeutic option for sulfur mustard-induced wound healing disorders.	BAAINBw *E/U2AD/ID016/ IF559*	C. Ries	2019-2022
Proteasomal protein quality control in muscle activity and metabolic fitness	LMUexcellent	A. Bartelt	2018
CODEX machine	LMUexcellent	O. Söhnlein	2019
LMU Excellent Junior Research Fund	LMUexellent *867949-0*	C. Yin	2019-2020

Project	Sponsor *Reference*	Principal Investigator *Collaboration Partner*	Time frame
Elucidating the interaction of Neutrophil extracellular traps (NETs) and smooth muscle cells during atherosclerotic plaque destabilization	Else-Kröner-Fresenius Foundation	C. Silvestre-Roig	2017-2019
Hypercholesterolemia-induced extramedullary hematopoiesis generates neutrophil subsets	Else-Kröner-Fresenius Foundation	O. Söhnlein	2018-2021
Role of Mir21 in endothelial regeneration during atherosclerosis	Else-Kröner-Fresenius Foundation *2015_A183*	M. Nazari-Jahantigh	2019
Optoacoustic imaging of atherosclerosis	Visualsonics	O. Söhnlein	2019-2020
Resolution of myocardial infarction	Thyssen Krupp Stiftung	G. Leoni O. Söhnlein	2016-2018
Immune-Lipid Crosstalk Research Group	Aachen Interdisciplinary Center for Clinical Research	E. van der Vorst	2019-2021
Circadian plaque destabilization	Swedish Heart Lung Foundation	O. Söhnlein	2019-2020
Targeting immune-lipid crosstalk in leukocytes: focus on HDL dependent regulation of chemokine-receptor signaling	NWO-ZonMw Veni	E. van der Vorst	2019-2021
Importance of formyl peptide receptor 1 in emergency neutrophil mobilization	Vetenskapsrådet	O. Söhnlein	2017-2021
Targeting epigenetic REPROGRamming of innate immune cells in Atherosclerosis Management and other chronic inflammatory diseases	REPROGRAM	E. Lutgens	2016-2019

Project	Sponsor *Reference*	Principal Investigator *Collaboration Partner*	Time frame
Cell-specific vascular protection by CXCL12/CXCR4 PROVASC	ERC	C. Weber	2016-2022
PROTEOFIT Adapting protein fate for muscle function and fitness	ERC	A. Bartelt	2019-2024
ITN European Vascular Interventions and Therapeutic Innovation Network	European Union	O. Söhnlein	2016-2019
Molecular mechanisms linking the CXCL12 pathway to atherosclerosis	NIH *1R01HL122843*	Y. Döring C. Weber *D. Saleheen*	2017-2020
Clonal hematopoiesis and atherosclerosis	Leducq foundation	O. Söhnlein	2019-2023

Research Networks

Leducq Transatlantic Network of Excellence

The Foundation Leducq Scientific Advisory Committee has selected four new Transatlantic Networks of Excellence for funding. These networks were chosen based on the quality of the research plan, the strength of the international collaboration, and the commitment to the development of young investigators. Each research network will receive $6,000,000 over five years to support a collaborative research program involving European and North American investigators. Among the selected networks is the following:

Molecular mechanisms of novel genes associated with plasma lipids and cardiovascular disease

It has long been known that blood levels of lipids like cholesterol are important risk factors for atherosclerotic cardiovascular disease. Lipid levels and atherosclerosis both run in families, but how these traits are genetically determined is poorly understood. Genome-wide association studies (GWAS) represent one approach to identifying the relevant genes. In a typical GWAS, genetic variations throughout the entire genome are compared between two groups of individuals, those with and those without the trait of interest, such as high cholesterol levels or atherosclerosis. Genetic variations that are more frequent in one group are considered to indicate the regions of the genome (loci) that are likely responsible for the presence or absence of the trait. In recent years, GWAS for atherosclerotic disease have identified multiple loci of interest, but thus far very few have been adequately characterized to determine the exact mechanisms of how the specific genes at these loci influence disease risk. This network will study 6 loci found to be associated with atherosclerotic disease in previous GWAS. Three of these loci appear to affect blood lipid levels. This multidisciplinary team includes experts in epidemiology, human genetics, molecular and cell biology, and animal physiology. In addition to identifying new potential therapeutic targets, this research program will also establish an infrastructure for the systematic evaluation of future GWAS results.

National Institute of Health

Together with Prof S. Saleheen from the University of Pennsylvania, Prof C. Weber was awarded a grant in the amount of $733.396 from the Institute of The National Instiute of Health (NIH) to further investigate novel genetic associations in cardiovcascular disease. The earlier genomic and mechanistics studies strongly suggested that CXCL12 and its major receptor CXCR4 are involved in the development of Coronary heart disease (CHD). Funding will be awarded for a period of four years (from 2017 until 2020) for the project: *Molecular mechanism linking the CXCL12 pathway to atherosclerosis.*

Munich Heart Alliance

The Munich Heart Alliance Centre (MHA Centre) is part of the German Cardiovascular Research Centre. Coronary heart disease (CHD) is the leading cause of death worldwide. According to the WHO at least half of the deaths and isabilities resulting from CHD could be avoided by improved primary or secondary prevention. Improved prevention of CHD requires a better understanding of the athomechanisms and a faster and more efficient translation of novel leads into clinical application. We propose the establishment of the Munich Heart Alliance (MHA) Centre as a node of the German Center for Cardiovascular Research (GCRC). The mission of the MHA Centre is to accelerate the development of strategies to prevent and treat CHD. To fulfil this mission, the MHA Centre will focus on the following scientific objectives, each addressed by a distinct research program:

1. to identify on a population level risk factors predisposing to CHD
2. to model CHD in order to dissect the underlying mechanisms
3. to develop novel therapeutic strategies against CHD

The **Munich research area** is the ideal site to address these goals, as it combines excellent basic and clinical research on the disease mechanisms and interventions to prevent and treat CHD. In particular, Munich provides the nation's leading cardiovascular framework to conduct large clinical phase III/IV trials.

Built on this expertise, the MHA Centre aims to accelerate the translation of mechanistic findings into clinical application. Through the foundation of the MHA Centre, we will achieve the following structural goals:

- to focus the broad local cardiovascular expertise onto the common topic CHD
- to establish research groups at the interface of basic and clinical science
- to join the forces of these interdisciplinary groups under the roof of the MHA Centre.

As a node in the GCRC, the MHA Centre will contribute its unique epidemiological resources (e.g. KORA) and its leading clinical trial infrastructure and serve as a platform for the efficient translation of novel therapeutic concepts in CHD.

DFG Sonderforschungsbereich 914

Trafficking of Immune Cells in Inflammation, Development and DiseaseTrafficking of immune cells is a key prerequisite for immune surveillance under physiological steady state conditions and during disease states. Proper immune surveillance is of utmost importance in mammalian homeostasis as it ensures defense against pathogen intruders, but also because it guarantees tissue integrity through the continuous removal of dying cells. In order to be both functional and efficient, the migration and trafficking behaviour of immune cells has to be precisely controlled and fine-tuned on demand. This critical task is complicated by the fact that trafficking of immune cells does not follow a uniform process. Indeed, different types of immune cells are rather endowed with unique machinery allowing them to chase subset-specific trafficking routes in order to fulfill their individual tasks within their individual target tissues. To date, the molecular and cellular signatures that control and organize this complex process of mammalian immune cell trafficking are still incompletely understood. It will therefore be the mission of the collaborative research centre (CRC) 914 to dissect the signals and mechanisms that regulate the migratory responses of distinct leukocyte subsets during inflammation, development and in disease states. An Integrated Research Training Group entitled “Leukocyte Trafficking” will flank our scientific efforts. As a long-term perspective, the CRC aims to contribute to the development of innovative concepts for therapeutic interventions during acute and chronic infectious and non-infectious inflammatory diseases by specifically and selectively targeting the identified migratory patterns of distinct leukocyte subsets.

VIAgenomics
BHF-DZHK Partnership

PIs from the UK and from Germany among whom IPEK director Christian Weber, joined forces to successfully obtain over 2.4 Mi Euros Partnership Funding from the British Heart Foundation (BHF) together with the German Centre for Cardiovascular Research (DZHK). Partnership between the BHF and DZHK funds innovative cardiovascular research projects to encourage international collaborations between cardiovascular researchers in the UK and Germany. The scientists aim to find new targets of the vascular interface in atherosclerosis, based on gene discovery. In particular, they propose to understand the role of coronary disease risk genes at the vascular interface and identification of key tagets for therapies. Contributing PIs include Hugh Watkins (Oxford), Jeannette Erdmann (Lübeck), John Danesh (Cambridge), Shu Ye (Leicester), Heribert Schunkert (München) and Christian Weber (München).Studies involving large groups of people with and without heart disease, have identified changes in the DNA code that are more frequent in people with the disease. The scientists found that many of these DNA changes are in genes involved in the wall of our blood vessels, an important biological system in the development of heart disease.

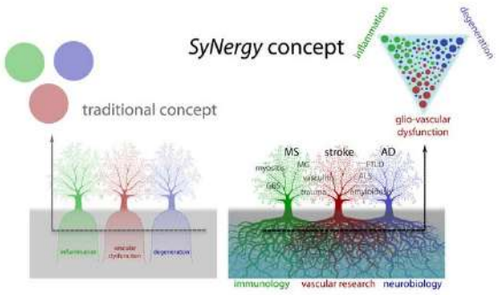
The researchers plan to combine innovative computational and experimental methods to understand the role of these risk genes at the vascular interface and to identify novel drug targets for therapies.

DFG Collaborative Research Centre
Transregio TRR 267

The field of ncRNA is rapidly developing and probably most – if not all – key processes in cells are directly or indirectly controlled by these molecules. TRR 267 contributes to decipher the function of ncRNAs in the cardiovascular system thereby gaining important insights into the regulatory mechanisms of CV disease. This may – in the long-term – also open novel therapeutic avenues. Our research program addresses fundamental questions on the regulation and mechanism of action of ncRNAs, their roles in development and their disease relevance:
1) How are ncRNA biogenesis and transport controlled in CV cells?
2) Through which mechanisms do ncRNA control CV signaling and infer with e.g. epigenetic control, transcription and mRNA processing?
3) How do ncRNAs govern disease processes and regeneration, and can this be exploited by manipulating their expression or activity?
These questions will be addressed by combining outstanding and complementary expertise in a collaborative manner, making use of an excellent infrastructure and state-of-the art technology at our sites, and by educating young scientists in an interdisciplinary environment.

Munich Cluster for Systems Neurology

Traditional nosology holds that neurological diseases can be separated into mechanistically distinct families, including neurodegenerative, inflammatory and vascular conditions. Underlying this classification is the assumption that disease manifestations relate in a categorical fashion to a discernible mechanism. As a result, research efforts have traditionally reflected this categorization, and are mostly focussed on one or another of these mechanisms. However, recent insights have revealed a more complex relationship between different disease mechanisms and prompt a rethinking of the relationship between disease entities and their underlying mechanisms. Such reassessment suggests that distinct disease manifestations can not be explained in isolation but instead all root in an intricate network of shared pathomechanisms (Figure).



Schematic comparison of the traditional nosological concept (left) and the SyNergy approach to neurological diseases (right).

To appropriately address these entangled "network" relationships, novel research tools and integrated approaches are needed. One approach that has been developed in basic life sciences to decipher such complex interactions and the resulting "emerging properties" is systems biology. Systems approaches have proven their power to analyse simple model organisms and the physiology of small neuronal networks, yet are only beginning to be applied to questions of immediate medical relevance.
Neurological diseases meet the central theoretical tenet that motivates systems approaches: they affect one of the most complex biological systems, the human nervous system. While not all aspects of systems biology and systems neuroscience can be directly transferred into the realm of disease-oriented biomedical research, we believe that many of the tools that enable comprehensive quantitative study of dynamic systems are of direct relevance to the investigation of neurological disease. The application of such tools and concepts to neurological diseases is currently emerging – a new field that we call "systems neurology".

Large-scale Project Funding

ERC Advanced Grant PROVASC

Professor Dr. med. Christian Weber, Director of IPEK and Chair in Vascular Medicine at LMU has been awarded his second ERC Advanced Grant. This ERC Grant entitled PROVASC is an exceptional distinction for Weber, who is one of the few researchers to receive the honor of a second award in the course of his career to date. Atherosclerosis is a major cause of morbidity and premature death in modern societies, and the principal goal of all of Christian Weber's research is to contribute to our understanding of this condition and to identify new drug targets opening up new routes more effective and personalized treatment. Weber analyzes the molecular mechanisms involved in the pathogenesis and progression of the disorder. Commonly known as hardening of the arteries, atherosclerosis is primarily characterized by the development of fatty deposits on the inner surfaces of major blood vessels, which provoke chronic inflammation that leads to obstruction of blood flow. In his first ERC Advanced Grant, entitled "Atheroprotect", he studied the role of pro-inflammatory signal proteins which control the immune response that initiates the inflammation process and hampers its timely resolution. The title of his new ERC project is PROVASC, which will be devoted to elucidating the mechanisms responsible for "cell-specific vascular protection by CXCL12/CXCR4". CXCL12 is a signal protein which binds to the receptor CXCR4, which in turn activates a particular homeostatic signal pathway. Moreover, studies of genetic variation in human populations have indicated that this pathway can

protect the vasculature against atherosclerosis. Weber plans to characterize the downstream signal relay and elucidate the basis for its ability to reduce the risk of developing atherosclerosis. To this end, he will investigate the
effects of defined genetic risk variants on the activity of the CXCL12/CXCR4 pathway, and explore ways of modulating its action in a targeted fashion.
Interestingly, so-called microRNAs – short RNA fragments that are involved in regulating the synthesis of specific proteins – have been implicated in the pathway and offer possible targets for new therapies.

DFG Collaborative Research Centre 1123

Atherosclerosis - Mechanisms and Networks of Novel Therapeutic Targets

Academic profile of the Collaborative Research Centre
Vascular disease including coronary artery disease (CAD) and stroke remains the leading cause of death and morbidity worldwide despite significant advances in interventional and medical treatment. As impressively illustrated by the global burden of disease study, cardiovascular disease, which is overwhelmingly caused by atherosclerosis as the underlying pathology, is the global killer number one, claiming 15.6 million lives in 2010. Compared with other entities, this prevalence will continue to dominate,owing to an increasing life expectancy in Western but also emerging societies. In the EU, CAD represents the most frequent cause of death, accounting for 40% or 2 million per year. The enormous socio-economic costs imposed by CAD on European healthcare systems are estimated at 110 billion Euro per year and continue to rise. This dilemma could be limited by improving vascular prevention and therapy based on a more refined mechanistic pervasion of atherosclerosis, prompting a more efficient and reliable identification and validation of new targets for potential translation to drug development. The latter is mandated by declining success rates for transition beyond clinical phase II and numerous recent failures in clinical phase III, which illustrate inherent pitfalls of cardiovascular drug development. Hence, it is the mission of the planned collaborative research center (CRC) to improve the in-depth mechanistic understanding of molecular networks in atherogenesis, atheroprogression and atherothrombosis as the pathological sequence of CAD, leading to the identification and verification of worthwhile targets for treating atherosclerosis.
Atherosclerosis is characterized by a delicate continuum of early atherogenesis amenable to prevention and a progression to vulnerable plaques. This can either lead to stabilization and remodeling or to destabilization with plaque rupture, atherothrombosis and occlusion, giving rise to stroke or myocardial infarction. We will limit our focus to the spectrum of arterial pathology, which is accessible to specific targeting, but we will not cover myocardial damage by infarction or ischemia/reperfusion. The latter area has benefited from recent advances in interventional therapy and is a central topic of various other research initiatives. In contrast, atherosclerosis requires chronic treatment, which carries a considerable risk of side effects. The stagnation in therapeutic development and multiple failures in clinical validation e.g. due to off-target effects, are less surprising when considering the complex levels of pathophysiological regulation and interactions of potential targets. This predicament also explains the tendency of the pharmaceutical industry to resort to known therapeutics and why no specific cardiovascular therapeutic has been introduced recently. We thus plan to adequately map the pathogenic complexity and to

discover novel mechanisms, their interactions and targets with a better predictable efficacy and safety. Atherogenesis is driven by a disturbed equilibrium of lipid accumulation, maladaptive immune responses and their clearance, entailing chronic inflammation of the artery wall, crosstalk with pro-coagulant pathways and culminating in plaque rupture and thrombosis. New atherogenic and/or protective pathways mutually linking lipid, inflammation and coagulation biology have been discovered, and profiling studies, namely genome-wide association studies (GWAS), unveiled risk genetic variants and epigenetic factors for CAD. This multitude of variables gives rise to complex network effects creating specific signatures for this disease. Bioinformatics analysis, next generation sequencing (NGS) and omics tools will be instrumental for the discovery of biologicals for vascular disease, which will gain importance over classical drug candidate or high-throughput approaches, since their structure-function relationship can be more readily probed, while off-target effects and toxicity can be better anticipated. An identification of worthwhile targets within such networks requires unbiased screening of different targets, a thorough pathogenic basis and analysis of their interactions in relevant model systems in vivo. We aim to systematically elaborate such intricately linked molecular mechanisms for different target families (cytokines, signal proteins, nucleic acids and lipid mediators), some of which have been verified in relevance by GWAS, allowing for a sufficiently broad yet coherent spectrum. We will propagate their validation by molecular imaging technologies in human tissue or animal models, e.g. using an array of transgenic and knockout mouse models of cell-specifically inducible gene deletion, knocking insertion of mutants and/or fluorescent labeling. We will further aim to extend the boundaries of subcellular visualization by implementing newly developed methods of optoacoustic imaging and super-resolution nanoscopy. Primary goal of the planned CRC 1123 will be to improve and accelerate the identification and validation of novel targets to treat the pathogenetic sequence of atherosclerosis culminating in plaque rupture and/or atherothrombosis. The disturbed equilibrium between lipid metabolism and immune reactivity entailing chronic inflammation of the arterial wall is shaped by leukocyte trafficking and homeostasis governed by guidance cues, e.g. chemokines or lipid mediators. The chronic inflammatory reaction and maladaptive immune response features effector cells of both innate and adaptive immunity, for instance neutrophils, dendritic cells and their interactions identified by our group members. The growing appreciation of the inflammatory processes and mediators involved has uncovered an intriguing diversity of targetable mechanisms that could be exploited to complement lipid-lowering therapies. In the planned CRC, we aim to implement harmonized model systems and standardized protocols and to employ bioinformatic network analyses, which reflect the multifactorial and complex nature of this disease, to identify the cross-talk and interaction of the molecular mechanisms and individual targets. In particular, we see an important triad emerging that links chronic inflammation to lipid mediators and metabolism, to procoagulative/ thrombogenic pathways and to genetic/epigenetic risk factors. These pathways are represented in two target areas with signal proteins and cytokines (area A) and nucleic acids and lipid mediators (area B), wherein multiple projects exemplify the cross-talk of inflammation with lipid biology or with coagulation and thrombogenicity (Fig. 1). We envision that the planned CRC, by assembling an internationally leading group of scientists, will contribute to a significant conceptual advance in the field of atherosclerosis research by introducing harmonized protocols, bioinformatic network analysis and interactive modeling of a complex disease, and implementing state-of-the-art transgenic and novel molecular imaging technology. This may help to redefine the Summary
Vascular disease including coronary artery disease

(CAD) and stroke remains the leading cause of death and morbidity worldwide despite significant advances in interventional and medical treatment. The enormous socio-economic costs imposed by CAD on European healthcare systems continue to rise. This dilemma could be limited by improving vascular prevention and therapy based on a more refined mechanistic pervasion of atherosclerosis as the underlying pathology, prompting a more efficient and reliable identification and verification of new targets for potential translation to drug development. Hence, it is the mission of the planned CRC 1123 to improve the in-depth understand-ing of molecular networks in atherogenesis, atheroprogression and atherothrombosis as the patholo-gical sequence of CAD, leading to the identification of worthwhile targets for treating atherosclerosis. An identification of worthwhile candidates within such networks requires an unbiased screening of different targets on a thorough pathogenic basis and analysis of their interactions in relevant model systems in vivo. We aim to systematically elaborate such intricately linked molecular mechanisms for different target families (cytokines, signal proteins, nucleic acids and lipid mediators), allowing for a sufficiently broad yet coherent spectrum. We will propagate their validation by employing novel technologies for optoacoustic and super-resolution imaging and an array of transgenic and knockout mouse models of conditional gene deletion, knockin insertion of mutants and/or fluorescent labeling. We aim to implement harmonized model systems and standardized protocols and to employ bio-informatics network analyses to adequately map the pathogenic complexity and to identify the cross-talk and interaction of new molecular mechanisms and individual targets. This will help to redefine the standards of target discovery and validation and to open new therapeutic options.standards of target discovery and validation and to open desired therapeutic options.

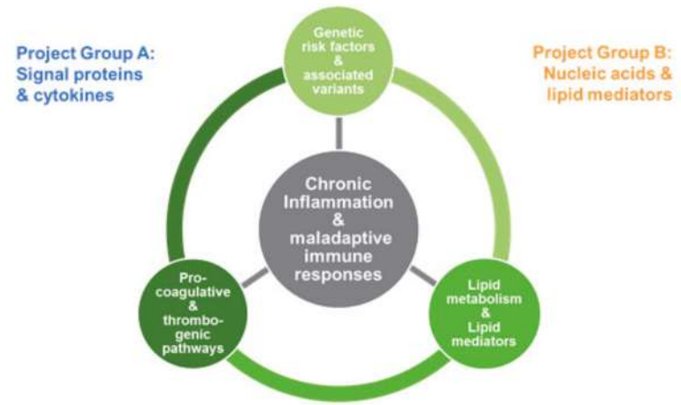


Figure: Pathogenesis of atherosclerosis: creating mechanistic links between target families/pathways

Performance Report 2018

Number of budget-funded scientific employees: 27
Number of budget-funded non-scientific employees: 21
Number of all externally funded employees: 80

Third party funds spent (in €):

Source	Number of projects	Funds spent 2018
DFG	38	3 160 984
BMBF, StMWFK	16	1 179 857
EU	6	966 735
Foundations (Humboldt, Foundation Leducq, etc...)	19	340 272
Total external third party funding		**5 647 850**

Source	Number of projects	Funds spent 2018
FöFoLe	1	25 400
Lebmit (Invest.)	17	25 867
PhD Fellowship	2	15 081
Total internal third party funding		**66 348**
Total third party funding spent		**5 714 198**

Performance Report 2019

Number of budget-funded scientific employees: 25
Number of budget-funded non-scientific employees: 18
Number of all externally funded employees: 80

Third party funds spent (in €):

Source	Number of projects	Funds spent 2019
DFG	38	3 957 574
BMBF, StMWFK	16	1 415 996
EU	6	643 389
Foundations (Humboldt, Foundation Leducq, etc...)	12	372 172
Total external third party funding		**6 389 131**

Source	Number of projects	Funds spent 2019
FöFoLe	3	1248
PhD Fellowship	3	14 337
Total internal third party funding		**15 585**
Total third party funding spent		**6 404 716**

The staff key figures are divided into the budget-funded and third party funded personnel.

Position	Total	Budget funded 2018-2019	Third-party funded 2018-2019
Institute Director	1	1	
Professors	13	12	1
Research Group Leaders	10	6	4
Postdoctoral Researchers	26	5	21
PhD candidates	34		34
Non-scientific Staff	49	22	27
Total	133	46	87

Due to overlapping distribution of tasks mainly in basic science and partly in clinical science staff, the total number of employees amounts to **133 persons**. This number also includes staff members who are funded by grants and/or work 50-75% part-time at IPEK.

Key Figures

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Winter, Janine
Wolkerstorfer ,Silviya

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Yildirim, Tugce Mercan

Zhang, Chuanaki
Zhang, Xi
Zhu, Mengyu, MSc

2018

	n	IF Sum	IF Average
Total	86	754.2	8.8
First/Last Authorship IPEK	38	289.2	7.6

	n	IF Sum	IF Average
Original articles	53	489.1	9.2
First/Last Authorship IPEK	15	138.6	9.2

	n	IF Sum	IF Average
Reviews and commentaries	33	265.1	8
First/Last Authorship IPEK	23	150.6	6.5

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2019

	n	IF Sum	IF Average
Total	100	1037.0	10.4
First/Last Authorship IPEK	54	642.8	11.9

	n	IF Sum	IF Average
Original articles	58	605.9	10.4
First/Last Authorship IPEK	21	238.4	11.3

	n	IF Sum	IF Average
Reviews and commentaries	42	433.7	10.3
First/Last Authorship IPEK	33	404.4	12.3

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