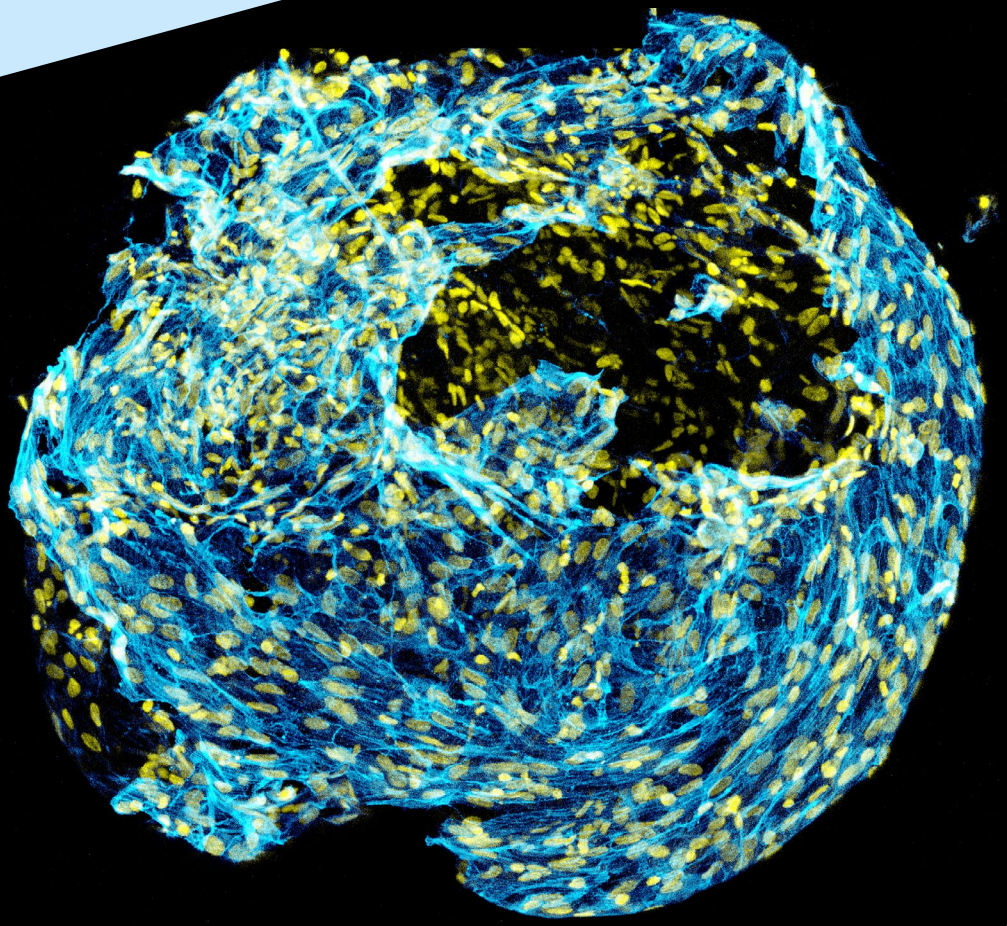
ANNUAL REPORT 2022-2023



LMU KLINIKUM

ipek Institute for CARDIOVASCULAR PREVENTION

ON THE VIRTUES OF CONSERVATISM AND FREEDOM

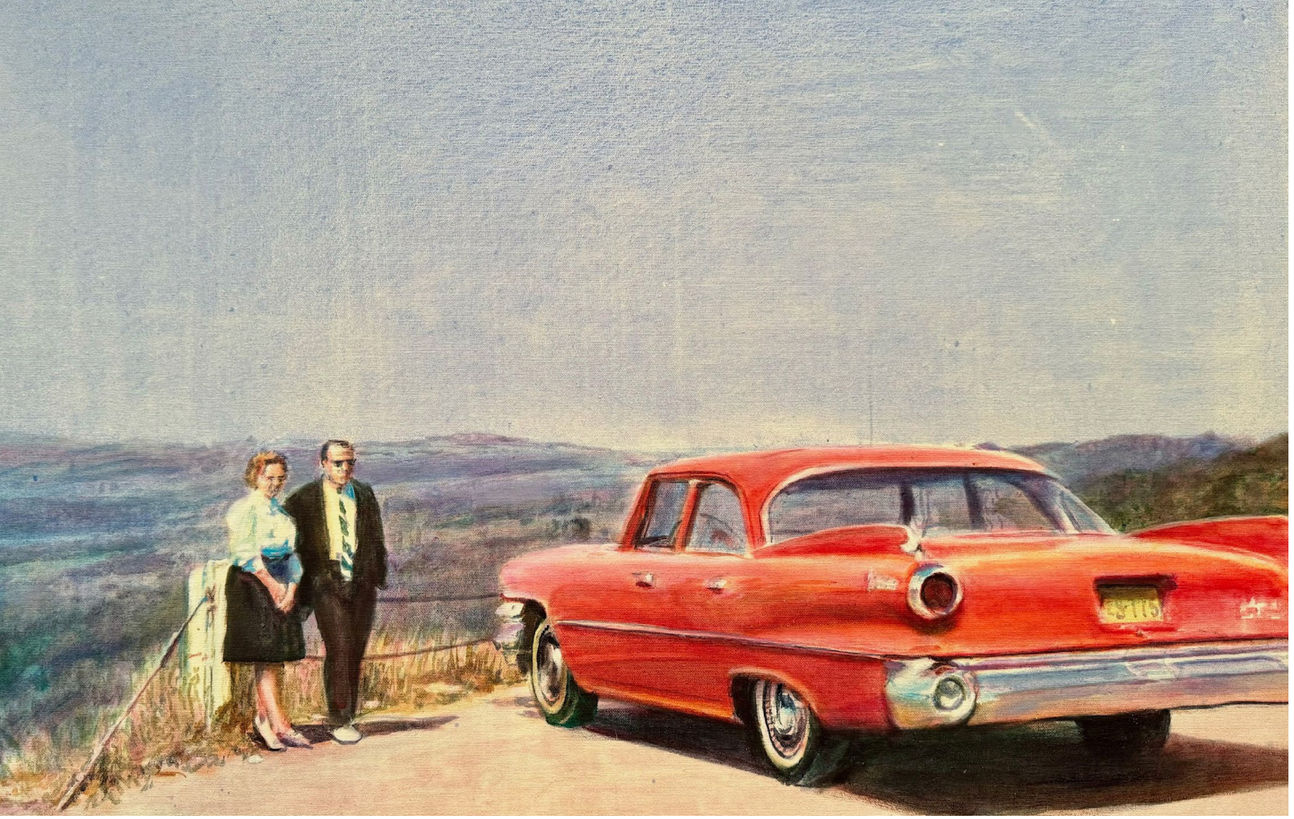
Following up on the preceding editorial inspired by Hannah Arendt, who coined the statement "One day after the revolution, even the most radical revolutionary becomes a conservative", I wish to take this year's opportunity to elaborate a little on the virtues of conservatism (and freedom), given that "Those who marry the Zeitgeist will soon be widowed." (Sören Kierkegaard). Whereas the "Zeitgeist" frequently attempts to escape into utopia, the prematurely deceased philosopher Roger Scruton contemplated on the abandoned present in his publication "Confessions of a Heretic". In his forays, we are allowed to look back, not for evading towards an obsolete direction, but as a reminder of the old measures of a community of responsible individuals capable of taking action. Instead of the global anywhere-and-nowhere, this community operates in a manageable, coherent territory, to which it feels existentially connected. Past, present and future form an organic connection; ancestors, contemporaries and future generations are in touch with each other, and aligning their best interests is defined as the ideal form of government, or as G.K. Chesterton puts it: "Tradition is democracy for the dead". This cohesion also remains vital with regard to the freedom of a society: "Because it simply represents the other side of freedom, that which must be there for freedom to be possible at all". In fact, anyone who maintains the much-cited freedom to dissent can now be promptly accused of heresy and hastily excommunicated. Inversely stated: "Joy arises when we do something that is not simply a means to an end, but has an end in itself, and we come together around this end with others, who feel as attached to it as we do. This shared sense of connectedness shows respect for our rational nature and strengthens us in the sense of our freedom."

Scruton compiles seven features as essential pillars of our civilization. Firstly, citizenship, implying a willingness to obey law and order. Western societies consist of citizens, religiously dominated societies mostly of subjects, because law and justice are not understood as deliberate agreements, but as God-given, demanding absolute obedience. The second feature is a sense of nationality perceived as a language- and culture-based system of solidarity. In the West, we practice an obligation to the community, while family, tribe or faith are less important. National identity enables citizens of Western societies to live together with shared loyalty and respect each other's rights, unlike in archaic communities. Without this identity, no political order is stable, nor will there be loyalty to society as a whole. The third feature is Christianity, often defined as a synthesis of Jewish metaphysics and Greek ideals of political freedom. Centuries of Christian supremacy have created the basis for such national loyalty. Christ was already caught between the legalism of his Jewish heritage and accepting the concept of secular government. Paul then interpreted the faith to be embedded in the Roman Empire without challenging secular power. The fourth feature to be emphasized is irony. The Hebrew Bible already encourages a sense of irony, later mirrored in Christian rhetoric as well: "Let he who is without sin cast the first stone". Irony should thus be perceived as a virtue, as a figurative form of acknowledging the unique distinctiveness of everyone, including oneself.

The fifth feature introduced is the ability to be self-critical. It has become natural for us to allow dissenting voices and thereby to exercise true freedom of opinion. The habit of letting critics have their say and honoring their opinion even in dissent is a special characteristic of Western culture and an important indicator of freedom. The sixth key feature is the representation of interests. Western civilization has a long tradition of associations, societies, clubs, companies, which do not require permission from higher authorities. These associations provide spokespersons and public representatives of interests, whose negotiation outcomes are recognized. Finally, what is the fabric that makes the Western way of life work? Scruton's answer may appear astounding: drinking together. At any party, the ice breaks immediately between complete strangers, when they pour each other a glass and toast. Social drinking has led to the enormous flexibility of Western societies and always helped to cope with major changes and differences. The resulting lightness of being may of course ignite resentment among its opponents.

We have two options in the firm defense of our heritage and freedom: on a societal level, making no concessions to those who want us to trade civil rights for submissiveness, individualism and national characteristics for conformity, secular for religious law, irony for sacred seriousness, self-criticism for dogmatism, advocacy for sub-ordination and cheerful drinking for abstinence. "In the private sphere, we should follow the path laid down for us by Christ and that means looking soberly and in a spirit of forgiveness on the hurts that we receive, and showing by our example that these hurts do nothing save to discredit the one who inflicts them." By various means, structural conservatism as outlined enables and preserves freedom of thought and expression, and perhaps likewise freedom and creativity in science that is not following predominant dogma. Whereas the virtues of such conservatism are hard to question, the benefit of transformative and disruptive components brought about by such freedom should also be appreciated and invigorated, as they will allow and stimulate a further evolutionary improvement of well-balanced working systems. In this dialectic sense as well as for scientific perspective and experimental prescription, I may wish to close with Jean Cocteau's bon-mot: "Originality is trying to do things like everyone else, but failing."

EDITORIAL



Florian Thomas – Couple with red sedan (invasive art II)

IF – RUDYARD KIPLING

If you can keep your head when all about you
    Are losing theirs and blaming it on you;
If you can trust yourself when all men doubt you,
    But make allowance for their doubting too:
If you can wait and not be tired by waiting,
    Or being lied about, don't deal in lies,
Or being hated don't give way to hating,
    And yet don't look too good, nor talk too wise;

If you can dream—and not make dreams your master;
    If you can think—and not make thoughts your aim,
If you can meet with Triumph and Disaster
    And treat those two impostors just the same:
If you can bear to hear the truth you've spoken
    Twisted by knaves to make a trap for fools,
Or watch the things you gave your life to, broken,
    And stoop and build 'em up with worn-out tools;

If you can make one heap of all your winnings
    And risk it on one turn of pitch-and-toss,
And lose, and start again at your beginnings
    And never breathe a word about your loss:
If you can force your heart and nerve and sinew
    To serve your turn long after they are gone,
And so hold on when there is nothing in you
    Except the Will which says to them: 'Hold on!'

If you can talk with crowds and keep your virtue,
    Or walk with Kings—nor lose the common touch,
If neither foes nor loving friends can hurt you,
    If all men count with you, but none too much:
If you can fill the unforgiving minute
    With sixty seconds' worth of distance run,
Yours is the Earth and everything that's in it,

    And—which is more—you'll be a Man, my son!

CONTENTS

Christian Weber is Chair in Vascular Medicine and the Director of the Institute for Cardiovascular Prevention (IPEK) at LMU Munich 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 Van de Laar-Professor of Atherosclerosis at Maastricht University. An outstanding scientist and physician, Dr. Weber has made ground-breaking contributions to understanding the pathogenesis of atherosclerosis towards new therapeutic avenues. For example, he 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) committed to the topic of atherosclerosis and its therapeutic targets. He also coordinates the partner site Munich Heart Alliance in the German Centre for Cardiovascular Research (DZHK). So far, his pivotal findings have led to 436 original publications (126 as first/senior author, 310 as co-author) and been cited more than 57,000/85,000-times to yield an h-index of 129/154 (Scopus/GoogleScholar). He has received the distinction of being named Highly Cited Researcher 2018, 2020-23 by Clarivate Analytics. In science-wide citation metrics of all authors, his ranking of #3163 (Cardiovascular #148; Biochemistry #232) indicates his influence and impact, and on research.com he was ranked #9/#24 in Biochemistry/Medicine in Germany. The innovations of Dr. Weber are reflected in numerous patents, which have formed the basis for spin-off companies such as Carolus Therapeutics Inc. and Cartesio Therapeutics B.V. for further preclinical development. His efforts have been honoured with the GlaxoSmithKline Science Prize, Paul Martini Prize, Arthur Weber Prize, Alexander Schmidt Prize, Outstanding Achievement Award and William Harvey Lecture of the ESC, ATVB Special Recognition Award of the AHA and the Galenus von Pergamon Prize. Dr. Weber has received the honour to be elected as a member of the National Academy of Science Leopoldina and is currently Editor-in-Chief of Thrombosis & Haemostasis and Associate Editor of Circulation. Funded until 2026. He has been instrumental for introducing new technologies, e.g. 2-photon and super-resolution imaging, an array of conditional mouse models, structural and bioinformatics analysis to map the pathogenic complexity and identify individual mechanisms and targets. At the international level, Dr. Weber has received two consecutive European Research Council (ERC) Advanced Grants (Atheroprotect 2010, PROVASC 2016). From 2011 to 2016, he coordinated the Leducq Transatlantic Network of Excellence CVGeneF(x). All of this demonstrates his outstanding ability to bring together world-leading experts at national and international levels to engage in interdisciplinary research cooperation with extraordinary synergy. Beyond his research, Dr. Weber is dedicated to educating the next generation of researchers. He has promoted >20 PhD/MD students and 17 postdoctoral fellows and many have received honour degrees and awards. His mentorship has helped talented junior scientists to excel in atherosclerosis research internationally with many obtaining associate professorships and Chairs, e.g. Profs. Y. Döring, N. Gerdes, E. Lutgens, D. Santovito, A. Schober, O. Söhnlein, S. Steffens, and A. Zernecke. He co-established the international DFG graduate school IRTG 1508 on Arterial Remodeling, the (CRC 1123) IRTG on atherosclerosis and teaches curriculum and electives in Medicine and Biology. He serves his research field with distinction having key leadership roles in several organizations, e.g. the EAS and the ESC Council for Basic Cardiovascular Science.

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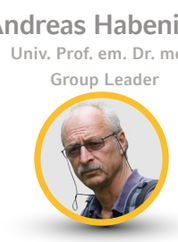

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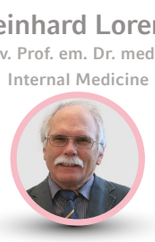

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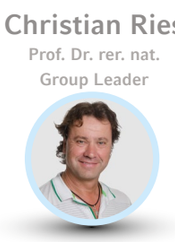

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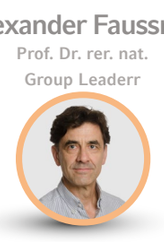

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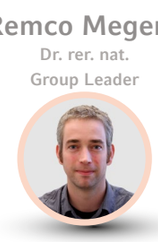

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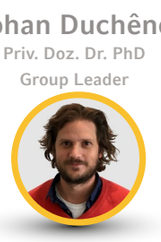

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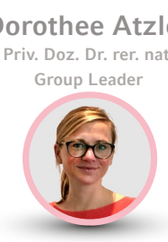

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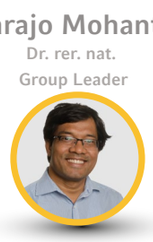

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Hintergrund

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.

AUGUST LENZ STIFTUNG

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 MedizinProfessoren-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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NEWS

05 / 2022

2022 LMU Medical Scientist

Dr. Nazari Jahantigh received the 'LMU Medical Scientist of the Year 2022" award from the Board of the LMU Munich Faculty of Medicine.

05 / 2022

CRC 1123 third period

We were awarded a funding extension from the DFG for our Collaborative Research Centre 1123 “Atherosclerosis: Mechanisms and Networks of Novel Therapeutic Targets”.

09 / 2022

New DZHK W2 Professor

Prof. Santovito was appointed new DZHK W2 Professor for Translational Vascular Therapy.

09 / 2022

Galenus and Becht Prizes

Dr. Mohanta awarded two Prizes: the Galenus von Pergamon Prize and the August Wilhelm and Lieselotte Becht Research Prize.

04 / 2023

Arthur Weber Prize

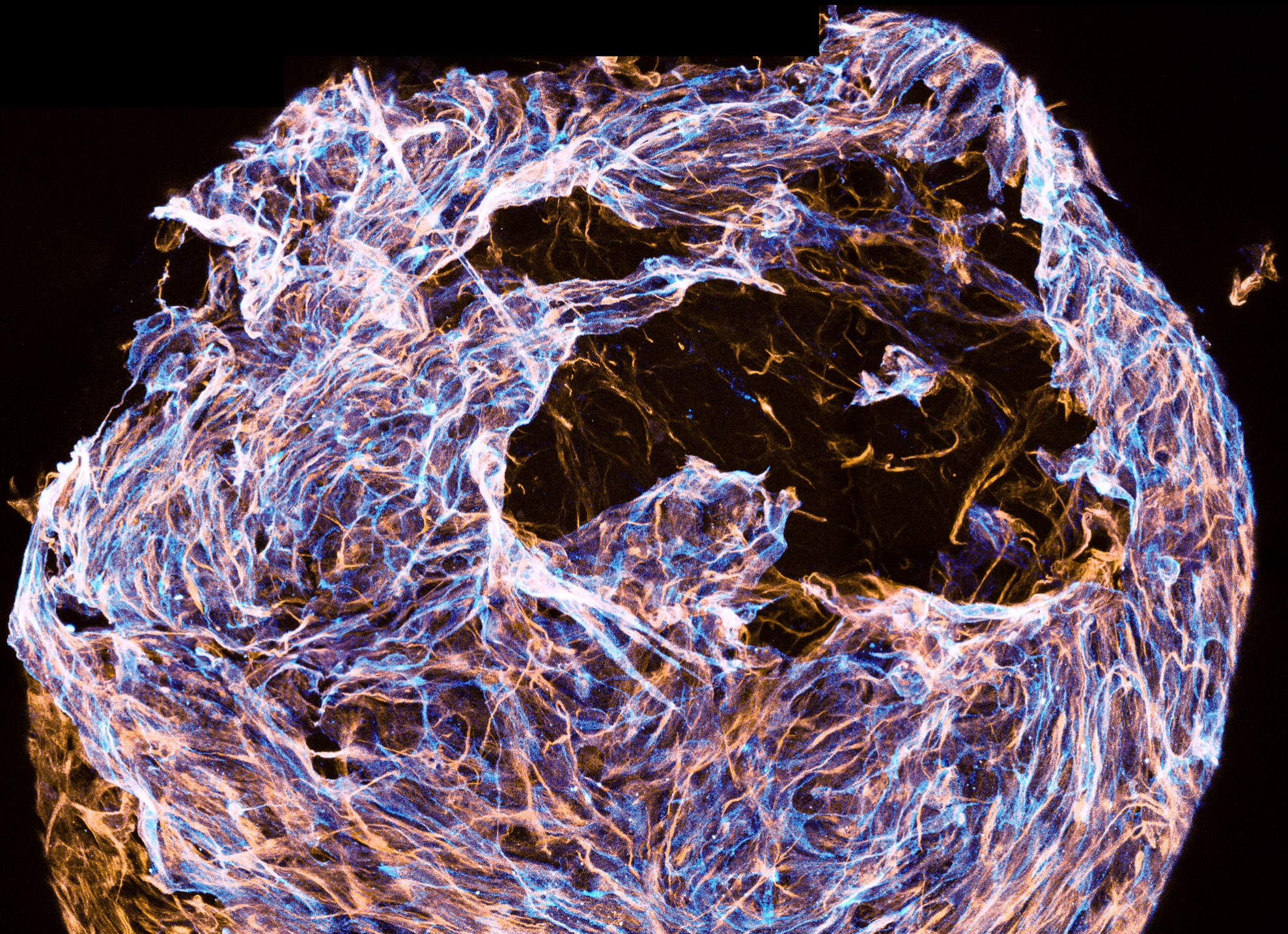
Prof. Steffens received the Arthur Weber Prize, endowed by the Arthur Weber Foundation with the motto "Researching to help."

11 / 2023

Highly cited

Prof. Weber has received the honour of being named Highly Cited Researcher for 2022 and 2023 by Clarivate Analytics.

RESEARCH



IMMUNITY MASTER SWITCHES IN ATHEROSCLEROSIS

Dorothee Atzler, Esther Lutgens

We investigate T cell regulation in atherosclerosis. Our aim is to study how intracellular metabolically and environmentally induced changes in T cell co-stimulation regulate atherosclerosis. Our goal is to discover novel drug targets for the development of powerful therapeutics in cardiovascular disease and atherosclerosis.

The interplay of different immune cells determines the progression of atherosclerosis and the propensity to cause clinical symptoms, such as a myocardial infarction or stroke. Immune checkpoint regulators, including co-stimulatory and co-inhibitory molecules, are important modulators of immune responses in atherogenesis. Previously, we have uncovered how co-stimulatory CD40L-CD40, CD27-CD70 and GITR-GITRL interactions drive atherosclerosis. We found that the CD40L-CD40-TRAF6 axis is crucial in atherosclerosis, and we could develop small molecule inhibitors targeting CD40-TRAF6 interactions, named TRAF-STOPs. TRAF-STOP treat-ment successfully blocked (established) atherosclerosis and is currently being tested and optimized for human administration. In a current `Translational Research Project' grant obtained from the German Center of Cardiovascular Research (DZHK) we focus on the development of novel TRAF-STOP compounds in order to pass the late pre-clinical pipeline to progress towards first in human administration.

Under atherosclerotic condition, both immune and non-immune cells display distinct dysfunctions, which are related to intracellular pathways. In addition to the classical metabolic traits (e.g., glycolysis, TCA cycle, mitochondrial fatty acid ß-oxidation and oxidative phosphorylation), also certain amino acids, such as L-arginine and homoarginine (HA) and their metabolism play a pivotal role in the progression of atherosclerosis. We recently found that HA-supplementation protects against atherosclerosis in Apolipoprotein E (Apoe)-deficient mice. We uncovered that HA-supplementation modulates the spatial organization of the actin cytoskeleton in CD4+ T cells, impeding T cell mobility, migration, activation and proliferation via inhibition of the actin-binding protein Myh9 (Myosin heavy chain 9, non-muscle myosin heavy chain IIA). This was associated with a reduction of effector CD4+ T cells and an attenuation of atherosclerosis.

Key Publications

van Os BW, Vos WG, Bosmans LA, van Tiel CM, Lith SC, den Toom MS, Beckers L, Levels JHM, van Wouw SAE, Zelcer N, Zaal EA, Berkers CR, van der Lest CHA, Helms JB, Weber C, Atzler D, de Winther MPJ, Baardman J, Lutgens E. *Hyperlipidaemia elicits an atypical, T helper 1-like CD4+ T-cell response: a key role for very low-density lipoprotein.* **Eur Heart J Open**. 2023;3(2):oead013.

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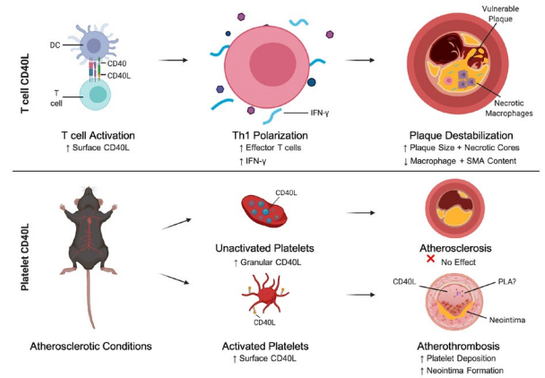

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CARDIOVASCULAR METABOLISM

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.

Adipose tissue inflammation and metabolic disease

Adipocytes are key regulators of metabolic health: healthy white adipocytes are essential as in the complete absence of white adipose tissue in mice and humans systemic metabolic homeostasis is compromised. In the very different condition of obesity, excess accumulation of white adipocytes leads to the same phenotypic alterations of metabolic disease. Obesity is a chronic inflammatory disease and adipocytes are actively recruiting professional immune cells with chemokines when they are stressed. Our goal is to define molecular mechanisms of adipocyte health that direct the nature of adipose inflammation and associated systemic pathologies such as diabetes and atherosclerosis.

Brown fat thermogenesis and metabolic health

Thermogenic adipocytes are UCP1-expressing cells that activated by cold and use energy-dense nutrient such as fatty acids, carbohydrates, and derived carbohydrates for producing heat to maintain body temperature homeostasis. Activation of thermogenic adipocytes has been shown to improve metabolic health in regular rodents, preclinical animal models of metabolic disease and humans. The thermogenic activity greatly varies from warmer to colder season as well as differs from mice to men. Our goal is to understand how thermogenic adipocytes adapt their metabolism to the extreme challenges of high metabolic flux, high oxidative activity, as well as synthesis of new organelles and cellular structural remodeling.

Cardiomyocyte adaptation in myocardial infarction

The heart is a fascinating and dynamic organ essential for human life. However, its metabolic flexibility is compromised in many critical medical conditions such as cardiohypertrophy, heart failure and during myocardial infarction. Both physiological changes in heart rate as well as the very distinct condition of heart disease require special mechanisms of adaptation. Our goal is to understand the molecular adaption of a trained heart versus dysfunctional heart, particularly after myocardial infarction. A detailed molecular understanding of cardiomyocyte-immune cell interaction would be transformative for designing new therapeutic strategies of myocardial infarction outcomes.

Key Publications

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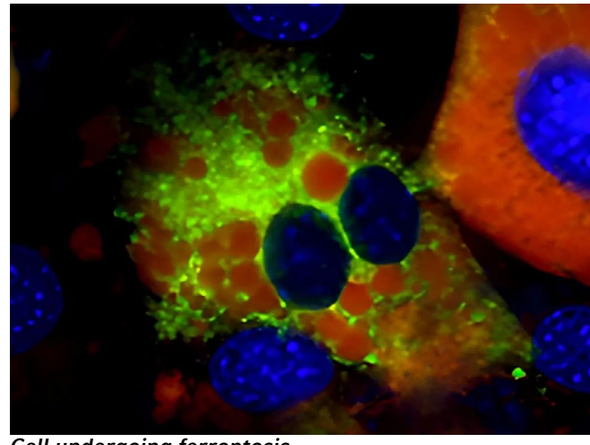

Cell undergoing ferroptosis

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CHEMOKINE-(RECEPTOR) GUIDED CELL CROSSTALK

Yvonne Döring

We focus on chemokine(-receptor) crosstalk with leukocytes and vascular cells in cardiovascular diseases. In particular, we examine the roles of CXCL12 and its receptors CXCR4 and ACKR3 in chronic arterial vascular inflammation. Furthermore, we are interested in ChemR23-mediated vascular immune responses in cardiovascular disease and we dissect the function of chemokine receptor CCR8 in guiding anti-inflammatory immune cell-crosstalk in atherosclerosis.

Recently, we identified a novel interaction of CCR8 expressed on CD4+ T cells and CCL17 in driving atherosclerosis. Specifically, we showed that CCR8-CCL17 interaction restraints Treg suppressive function via CCL3 release binding to CCR1 on Tregs. Conversely, blockade of CCR8 decreased CCL3 levels and attenuated atherosclerotic lesion development concomitant with an increase in Treg numbers (PMID: 39044999).

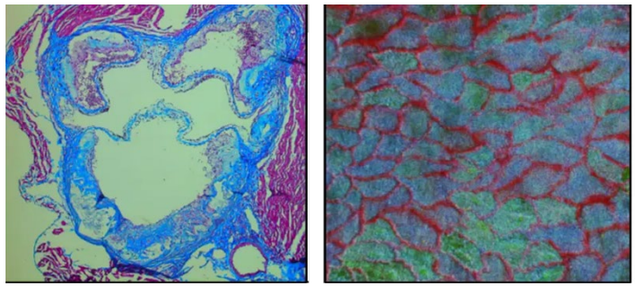
Importantly, CCR8 is also highly expressed on ILC2s. Therefore, we are examining the role of CCR8 on ILC2s in chronic vascular inflammation. In particular, we are interested in (adipose-)tissue crosstalk of ILC2s via chemokines and their receptors in atherosclerosis (PMID: 38179045; doi: 10.3389/fcell.2024.1473616).

We further just recently described a proatherogenic role of the CXCL13-CXCR5 dyad in atherosclerosis, an effect that is likely attributable to its impact on B1 cells and their IgM production.

Similarly, we could show that expression of the chemokine receptor CXCR4 on B1 cells controls IgM titers and thereby mediated atheroprotection underlining the importance of B1 cell–derived IgM in atheroprotection.

In addition, we now further evaluate the role of CXCR4+ in CD4+ T cells and the role of endothelial ACKR3 in atherosclerosis (PMID: 35674847).

Furthermore, we are exploring the role of microRNA26b in various cardiometabolic diseases, like atherosclerosis, myocardial infarction, metabolic dysfunction-associated steatohepatitis (MASH) and thrombosis.



Left side: aortic root (trichrome staining). Right side: mouse aortic endothelial cell. CD31 (green), VE Cadherin (red).

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Baretella O, Buser L, Andres C, Haberli D, Lenz A, Doring Y, Baumgartner I, Schindewolf M. *Association of sex and cardiovascular risk factors with atherosclerosis distribution pattern in lower extremity peripheral artery disease.* **Front Cardiovasc Med** 2023; 10: 1004003.

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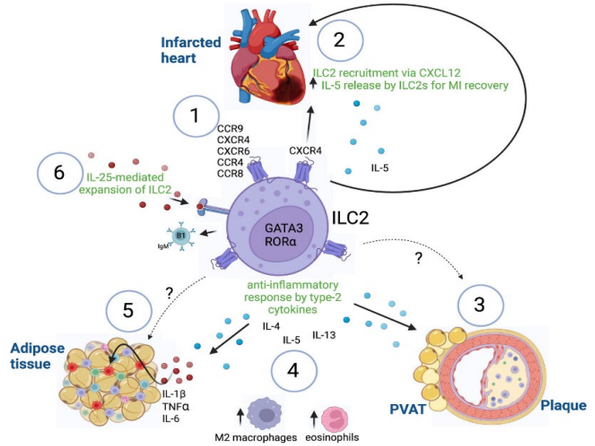

ILC2-mediated crosstalk via different chemokine receptor signalling in chronic (vascular) inflammation.

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MOLECULAR INFLAMMATION

Johan Duchêne, Remco Megens

The main objective of our research is to uncover novel molecular mechanisms that regulate inflammation and immune responses. We focus on the chemokine system, a critical player in leukocyte recruitment during inflammation. Our experimental work primarily investigates the biology of the atypical chemokine receptors (ACKRs), which modulate chemokine bioavailability. By doing so, we aim to identify new pathways to control inflammation, potentially leading to innovative therapies for inflammatory diseases.

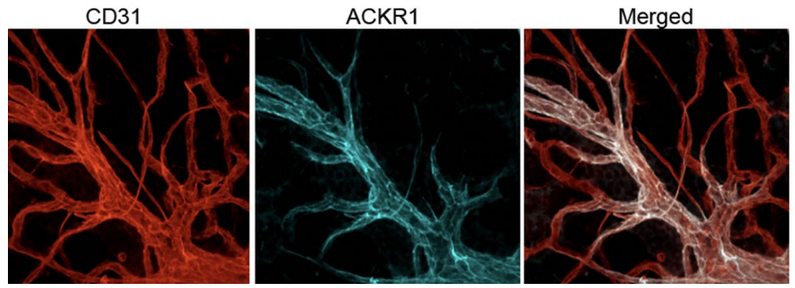
Inflammation is a natural immune response triggered by harmful stimuli, such as infections or injuries. Its primary function is to protect the body against potential threats and to promote the healing of damaged tissue. However, dysregulated inflammation that become chronic can contribute to many diseases. A key component of inflammation is the recruitment of leukocytes to inflamed sites, which is governed by chemokines. The effects of chemokines are mediated by G-protein coupled receptors (GPCRs), which are expressed in a wide range of immune cell types. Chemokines also bind to atypical chemokine receptors (ACKRs) that are mainly expressed by non-hematopoietic cells. ACKRs regulate chemokine bioavailability and thus influence immune cell behavior.

ACKR1 in Immune Response

ACKR1, also known as Duffy antigen, binds over 20 inflammatory chemokines and is expressed in red blood cells, venular endothelial cells, and neurons. A genetic variant (rs2814778(G)) in individuals of African ancestry results in the absence of ACKR1 on red blood cells, causing the Duffy-negative phenotype. Our lab generated a mouse model carrying the equivalent polymorphism, and we are investigating the role of erythroid-ACKR1 in inflammatory diseases.

CXCL12-ACKR3 in Cardiovascular Disease

Genome-wide association studies (GWAS) have linked CXCL12 expression to cardiovascular disease. However, its role in atherosclerosis, a chronic inflammatory disease of the arterial wall, is not fully understood. Using human atherosclerotic plaques in culture and transgenic mouse models, we investigate the properties of CXCL12 and its receptors, CXCR4 and ACKR3, in atherosclerosis.



Immunostaining showing ACKR1 expression on venular endothelial cells.

Western Diet and Hematopoiesis

Diet impacts health and even a short-term consumption of a Western diet can have harmful effect. It disrupts arterial homeostasis and hematopoiesis, the process of immune cell production. Using transgenic mouse models and human bone marrow organoid systems, we explore how a short-term Western diet alters hematopoiesis and aim to uncover the molecular mechanisms involved.

Key Publications

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TARGETING CHEMOKINE-HETEROMERS IN ATHEROSCLEROSIS/THROMBOSIS

Philipp von Hundelshausen

We are investigating how chemokines influence platelet function, with a focus on their role in atherosclerosis and thrombosis. An additional key area of interest is the formation of chemokine oligomers, where chemokines interact with themselves or other soluble molecules, leading to changes in their functional behavior. Our ultimate aim is to clarify the contribution of chemokines to atherosclerosis and thrombosis, with the goal of identifying new therapeutic targets and developing innovative treatments.

Atherosclerotic Vascular Disease (ASCVD) and Inflammation

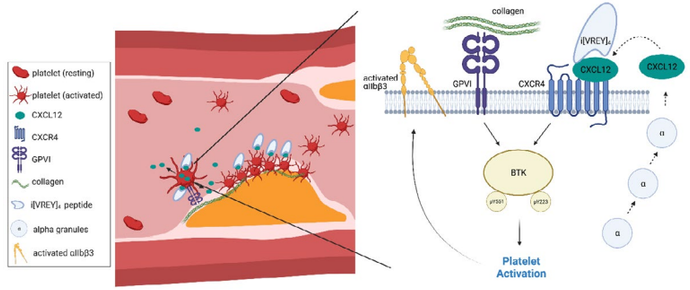
Atherosclerotic vascular disease (ASCVD) is a chronic inflammatory condition affecting the arterial wall and serves as the underlying cause of plaque erosion and rupture, which can lead to acute coronary syndromes and ischemic strokes. These conditions are major contributors to global mortality and disability. Several clinical trials targeting inflammatory mediators, such as IL-1 , have demonstrated the therapeutic potential of targeting inflammation. However, these treatments must be more specific to minimize immune-related side effects and maintain effectiveness. This highlights the need for continued research into immunomodulatory pathways to treat atherosclerosis and thrombosis more safely and effectively.

Chemokines and Galectins: Modulating Inflammation Through Heterodimers

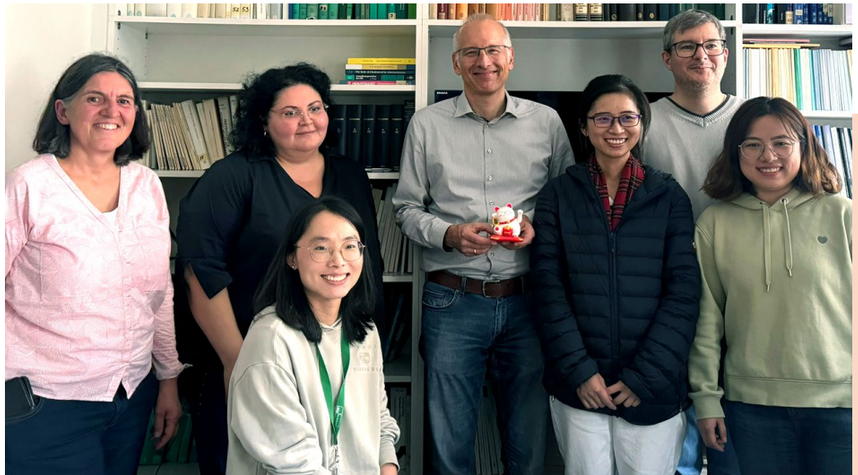
Chemokines and galectins are both upregulated during inflammation and play key roles in leukocyte recruitment. While they have traditionally been studied as independent molecules, our research investigates whether they can form functional molecular hybrids. Through systematic screening, we identified several chemokines that interact with galectins-1 and -3, including the CXCL12/galectin-3 pair. Using NMR and molecular dynamics studies, we mapped the contact sites between CXCL12 and galectin-3. We found that galectin-3 can attenuate CXCL12-mediated signaling through the CXCR4 receptor in a ternary complex with both the chemokine and the receptor. This discovery of chemokine-galectin heterodimerization reveals a novel immunoregulatory mechanism in inflammation, offering new insights into how inflammatory mediators interact to regulate immune responses.

Btk as a Target in Atherothrombosis

Bruton tyrosine kinase (Btk) is a critical signaling molecule in platelets and is involved in platelet activation pathways. Given its role in immune cell function, Btk inhibitors (BTKi) are used in the treatment of B-cell malignancies and are being explored for autoimmune diseases. Since Btk also regulates platelet activation, particularly through pathways like GPVI/GPIb-mediated atherothrombosis and FcgRIIA-dependent immune responses, Btk inhibitors could potentially be used to target platelet-driven thrombosis. However, BTKi treatment is often associated with mild bleeding events, possibly due to off-target effects on Tec kinase. In our research, we compared the platelet effects of two novel Btk inhibitors, remibrutinib and rilzabrutinib, which differ in their selectivity for Btk over Tec.



Our findings show that both inhibitors reduce platelet aggregation in response to GPVI, VWF/GPIb, and FcgRIIA activation, with remibrutinib demonstrating a stronger and more favorable profile for inhibiting Btk-dependent platelet activation without compromising hemostasis. These results suggest that remibrutinib may be a promising candidate for further development as an antiplatelet therapy.



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NEUROIMMUNE CARDIOVASCULAR INTERFACE

Sarajo Mohanta, Andreas Habenicht

Our group focuses on five areas of the immunology and neuroimmunology of cardiovascular diseases during aging: i. Define atherosclerosis as a bona fide autoimmune disease; ii. examine tolerance dysfunction in atherosclerosis; iii. identify the impact of artery tertiary lymphoid organs (ATLOs) on atherosclerosis; iv. delineate neuroimmune cardiovascular interfaces (NICIs) and artery-brain circuits (ABCs); and v. study the choroid plexus as a major gateway for circulatory immune cells to enter the brain.

Atherosclerosis 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. We have begun to isolate B-2 cells from diseased arteries, sequence their B cell receptors, clone and express the autoimmune antibodies and examine their role in atherosclerosis progression.

Tolerance dysfunction in atherosclerosis

Tolerance dysfunction as a driver of atherosclerosis progression is poorly understood. Using single cell RNA sequencing coupled with T cell receptor or B cell receptor profiling, we aim to identify abnormal tolerance checkpoints as disease drivers.

Artery tertiary lymphoid organs (ATLOs) in atherosclerosis

ATLOs belong to a large group of tertiary lymphoid organs that are found in cancer, autoimmune diseases, and atherosclerosis. Clinical correlation studies of the incidence of TLOs have shown beneficial associations in most cancers and infectious diseases but unfavorable outcomes in most autoimmune diseases, transplant rejection, and atherosclerosis. We aim to define the specific roles of ATLOs in cardiovascular diseases using a cross-tissue and cross-genotype approach using single cell RNA sequencing and spatial transcriptomics.

Neuroimmune cardiovascular interfaces (NICIs)

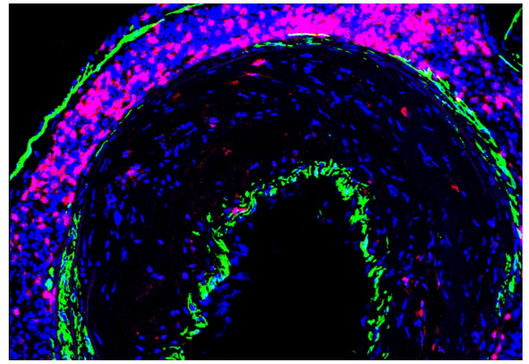
As plaques lack innervation, the impact of neuronal control on atherosclerosis remains unknown. Because the peripheral nervous system uses the adventitia as their principle conduit to reach distant targets, we postulated that the peripheral nervous system may directly interact with diseased arteries. Surprisingly, wide-spread neuro-immune-cardiovascular interfaces (NICIs) arose in murine and human atherosclerosis: adventitia segments showed extensive axon networks which form an artery-brain-circuit.

The choroid plexus

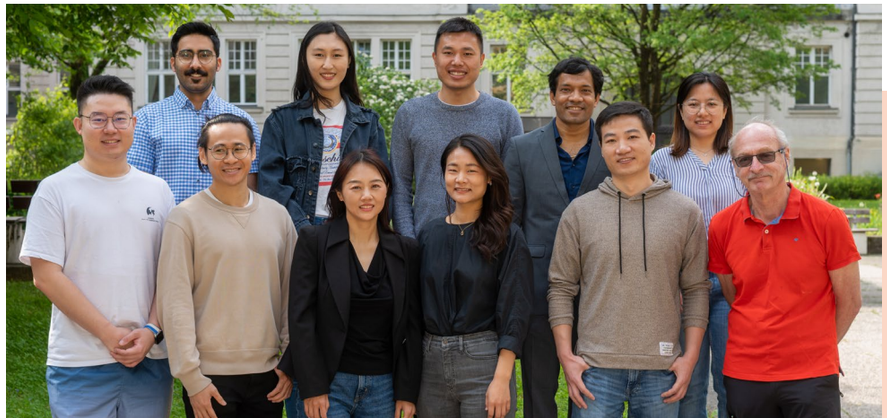
The choroid plexus is the principal gateway for blood-borne leukocytes to infiltrate the central nervous system in inflammatory and degenerative brain diseases. We identified a hitherto unrecognized choroid plexus pathology consisting of lipid and leukocytes. Demented Alzheimer Disease patients have higher lipid content in choroid plexus versus non-dementia cases.

Artery-brain-circuit (ABC)

Murine NICIs established the ABCs to regulate cardiovascular functions. Abdominal-adventitia nociceptive afferents forms afferent artery-brain projection through spinal cord termed ABC sensor, which is linked to an efferent arm termed ABC effector forming a brain-artery projection. The brain integrates these peripheral signals and sends compensatory efferent effector signals from the hypothalamus and medulla to arteries.



ATLOs in aged hyperlipidemic mice. T cells (in red) are a major cellular constituent of ATLOs. Green, smooth muscle cells in aortic media and in plaque. Blue, DAPI stained nuclei.



Key Publications

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Xinyi Deng (Graduate student)
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miRNAS IN CELL FUNCTION

Christian Ries

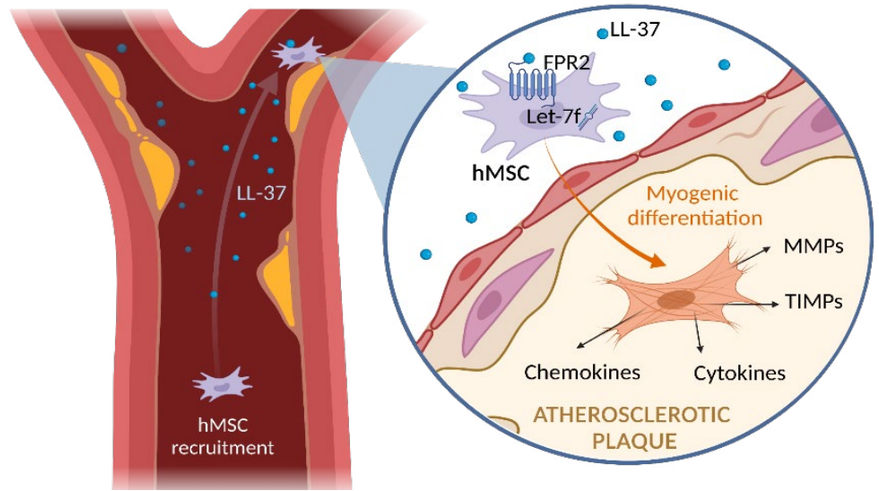
Migrating cells such as human mesenchymal stem cells (hMSCs) and epidermal keratinocytes play key roles in multiple normal processes and inflammatory diseases including atherosclerosis, cancer, and wound healing. Our research aims to gain deeper insights into molecular mechanisms that regulate the behavior and function of these cells. microRNAs (miRNAs) are a group of regulatory RNA molecules. Their dysregulation has been associated with disease. The results of our research may provide innovative approaches for target-directed therapeutical intervention.

miRNA let-7f in atherosclerosis

Human mesenchymal stem cells (hMSCs) are recruited to tissue sites of damage and disease where they contribute to immunomodulation and repair. This multi-step process involves chemokine-directed migration of hMSCs and on-site release of factors that influence target cells and tissues. Inflammation plays a crucial role in every stage of atherosclerosis from initial onset of the plaque to rupture. LL-37 is an antimicrobial peptide abundantly expressed in plaques. We discovered that hMSCs are recruited to atheromas by a mechanism involving the chemoattractant LL-37 and its cellular receptor FPR2, a process promoted by elevated levels of endogenous let-7f. hMSCs exposed to human plaque respond by increased secretion of multiple immunomodulatory cytokines and chemokines as well as matrix metalloproteinases and their natural inhibitors. Moreover, human plaque induced differentiation of hMSCs into myogenic cells suggesting a potentially plaque-stabilizing effect (see Figure). Hence, let-7f is a key promotor of hMSC tropism to atheromas enhancing the athero-protective potential of these cells (Egea et. al, Cardiovascular Research, 2023).

miRNAs in sulfur mustard-affected skin cells

Sulfur mustard (SM) is a cytotoxic chemical warfare agent. Exposure of the skin to SM evokes severe inflammation, extensive blistering and impaired wound healing. The precise pathomechanisms in the affected skin, however, are still unclear. To date, there are no effective treatments available. We hypothesize that SM might disturb the homeostatic balance of miRNA expression in skin cells causing dysregulation of cellular processes such as proliferation, migration and differentiation which are essential in wound healing. In our current project funded by DFG and Bundeswehr, we deployed next generation sequencing followed by experimental studies in human keratinocytes and ex vivo human skin biopsies. By this approach, miRNA key players have been identified and demonstrated for their impact on cell functions relevant in SM-induced wound healing deficiencies (manuscript submitted).



Elevated expression of let-7f facilitates LL-37-mediated recruitment of hMSCs to atherosclerotic plaques involving up-regulation of FPR2. Upon arrival in plaques, hMSCs release various bioactive molecules and differentiate into myogenic cells with a potentially athero-protective signature. Picture taken from Egea V. et al., Cardiovascular Research, 2023.

Key Publications

Egea V, Megens RTA, Santovito D, Wantha S, Brandl R, Siess W, Khani S, Soehnlein O, Bartelt A, Weber C, Ries C. *Properties and fate of human mesenchymal stem cells upon miRNA let-7f-promoted recruitment to atherosclerotic plaques.* **Cardiovas. Res.** 2023. 119(1):155-166

Ebert S, Zang L, Ismail N, Otabil M, Fröhlich A, Egea V, Ács S, Hoeberg M, Berres ML, Weber C, Moreira JMA, Ries C, Bernhagen J, El Bounkari O. *Tissue Inhibitor of Metalloproteinases-1 interacts with CD74 to promote AKT signaling, monocyte recruitment responses, and vascular smooth muscle cell proliferation.* **Cells** 2023. 12(14):1899

Christian Ries, Prof. Dr. rer. nat. (Group Leader)
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TRANSLATIONAL VASCULAR THERAPY

Donato Santovito

We investigate the contribution of epigenetics and non-coding RNAs (ncRNAs) in cardiovascular physiology and pathology. We focus on the interplay of multiple epigenetic regulatory layers, molecular mechanisms behind canonical and noncanonical functions of microRNAs, and how they control the development of vascular diseases, such as atherosclerosis.Our goal is to shed light on the role of epigenetics and ncRNAs in cardiovascular disease and unveil their possible exploitation as therapeutic or diagnostic/prognostic tools in patients with cardiovascular diseases.

Non-canonical functional paradigms of microRNAs.

While microRNAs traditionally repress target RNA through the RNA-induced silencing complex (RISC), a significant quota of microRNAs reside in low-molecular-weight complexes devoid of the machinery for effective repression. The functional relevance of these microRNAs remains largely unexplored. We revealed that functional biophysical interactions of microRNAs with proteins and DNA could influence cell function and homeostasis. Ongoing studies investigate these atypical mechanisms, focusing on their impact on cardiovascular biology.

Cell-specific therapeutic targeting via epigenetic interference.

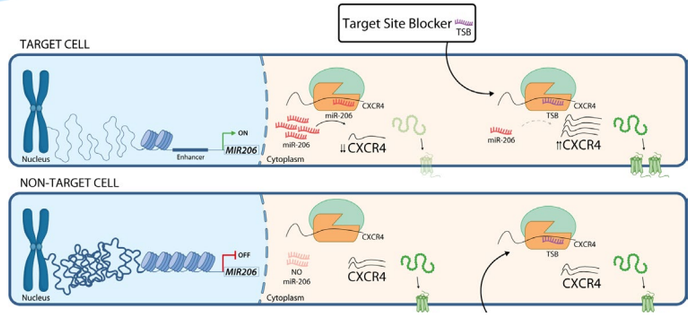
We explored cell-targeted therapeutic strategies leveraging the unique epigenetic landscape of each cell type. Specifically, microRNAs exhibit high cell-specificity due to the proximity of their genes to cell-specific super-enhancers and provide an opportunity for selective gene regulation. We developed a therapeutic approach to enhance gene expression cell-specifically by blocking microRNA interactions with target transcripts using target-site blockers (TSBs). As proof of concept, we used a systemically administered TSB to selectively increase CXCR4 expression in endothelial and vascular smooth muscle cells without affecting myeloid cells.

Epigenetic mechanisms in vascular biology.

Epigenetic mechanisms - such as DNA methylation, histone modification, and microRNA-mediated transcript suppression - shape the transcriptional landscape of every cell, influencing homeostasis and disease states. We investigate the crosstalk of these layers of regulation within cells in the arterial wall to understand how they regulate vascular function and mediate communication with immune cells, especially in atherosclerosis.

Role of autophagy in cardiovascular disease.

Autophagy maintains cellular homeostasis and resilience under stressful environmental conditions by recycling damaged components and supporting adaptive, non-degradative functions. Critical cardiovascular stimuli, including shear stress, hypoxia, and lipoproteins, modulate autophagy in a cell-specific manner, affecting vascular homeostasis. Our ongoing studies aim to elucidate the role of autophagy in cell types implicated in atherosclerosis, examining its impact on disease progression.



Synopsis of the miRNA-disengagement approach: Some MIRNA genes map in the proximity of cell type-specific enhancers/ super-enhancers. Target site blocker (TSB) oligonucleotides preventing the interaction of cell-specific miRNAs with ubiquitously expressed transcripts offer the opportunity for cell-specific gene enhancement. By this approach, a TSB averting miR-206 from repressing CXCR4 in the cells of the vessel wall (i.e., endothelial and smooth muscle cells) to promote antiatherogenic features without off-target effects in myeloid cells that do not express miR-206.

Key Publications

Cimen I, Natarelli L, Kichi ZA, Henderson JM, Farina FM, Briem E, Aslani M, Megens RTA, Jansen Y, Mann-Fallenbuchel E, Gencer S, Duchêne J, Nazari-Jahantigh M, van der Vorst EPC, Enard W, Döring Y, Schober A, Santovito D, Weber C. *Targeting a cell-specific microRNA repressor of CXCR4 ameliorates atherosclerosis in mice.* **Sci Transl Med**. 2023;15:eadf3357.

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Santovito D, Weber C. *Non-canonical features of microRNAs: paradigms emerging from cardiovascular disease.* **Nat Rev Cardiol.** 2022;19:620–638.

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James M. Henderson, Dr., PhD (PostDoc)
Rhoda Anane Karikari, Dr., PhD (PostDoc)
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ENDOTHELIAL AND MACROPHAGE microRNAS AND AUTOTAXIN IN NECROTIC CORE FORMATION

Andreas Schober

We investigated how microRNAs, autotaxin, and lipopolysaccharide (LPS) affect atherosclerosis and obesity. We are particularly interested in determining the cell-specific roles of miR-147, Dicer, and let-7b, in endothelial cells and macrophages. To this end, we developed a 3d live imaging approach to investigate the function of these cells in atherosclerosis and adipose tissue.

Endothelial autotaxin promotes atherosclerosis.

Our results show that endothelial cells contribute to atherosclerosis by secreting the enzyme autotaxin (ENPP2), which generates lysophosphatidic acid (LPA) from mildly oxidized LDL-derived lipid precursors. The effect of LPA depends on the length and saturation of the fatty acyl chains at the glycerol backbone. We found in mice that endothelial autotaxin promotes the recruitment of monocytes and the proliferation of macrophages in atherosclerotic plaques. This effect was associated with generating LPA16:0 and LPA18:1, which upregulate the expression of inflammatory chemokines, such as Cxcl1, in endothelial cells.

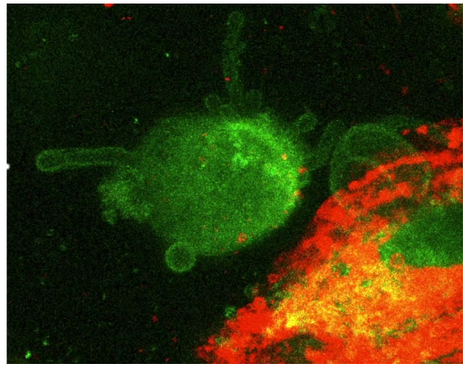
MicroRNAs regulate cell death and efferocytosis in atherosclerotic plaque.

Increased lesional cell death and impaired phagocytic removal of dead cells by macrophages contribute to necrotic core formation. MicroRNAs are produced by the endonuclease Dicer and negatively regulate post-transcriptional gene expression. MicroRNAs in macrophages play a crucial role in lesional cell death and phagocytosis by controlling mitochondrial energy production. We developed a 3D live plaque confocal imaging approach using myeloid cell-specific miR-147, let-7b, and Dicer knockout mice to study how miRNAs regulate the balance between apoptosis and efferocytosis in necrotic core formation. Moreover, we aim to identify the targets of the miRNAs in plaque macrophages by cell-specific overexpression of a tagged Ago2 protein.

Role of lipopolysaccharides (LPS) in obesity and atherosclerosis

Low LPS levels in the bloodstream trigger chronic low-grade inflammation and may thus increase obesity and atherosclerosis. We explored whether blocking LPS using neutralizing antibodies ameliorates high-fat diet-induced obesity and atherosclerosis in mice. LPS neutralization improved insulin sensitivity and lipid profiles and reduced adipose tissue inflammation, weight gain, and atherosclerosis. Multi-omics analysis showed that blocking LPS induced an anti-inflammatory gene expression profile related to improved mitochondrial function, especially in adipose tissue macrophages. Thus, anti-LPS antibodies are a potential therapeutic strategy for metabolic syndrome and atherosclerosis.

4D Plaque Imaging



Key Publications

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Yanyi Zhou, M.Sc. (PhD student)
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ENDOCANNABINOIDS AND CARDIOVASCULAR DISEASE

Sabine Steffens

We are studying the role of innate and adaptive immunity in cardiovascular disease and the role of lipid mediators in this context. We are particularly interested in the pathophysiological mechanisms of atherosclerosis, myocardial infarction and cardiac remodelling that may lead to heart failure. Our goal is to dissect underlying molecular disease mechanisms, which may eventually help identifying new therapeutic targets

Lipid signaling in cardiovascular disease

Lipid mediators derived from the arachidonic acid play pivotal roles in acute inflammatory responses as well as chronic inflammation such as atherosclerosis. Endocannabinoids – a group of arachidonic acid-derived lipid mediators – bind to cannabinoid receptors CB1 and CB2. GPR55 has been (controversially) proposed as a novel cannabinoid receptor, although lysophosphatidylinositols are more potent endogenous GPR55 ligands than endocannabinoids. We are investigating how lipid mediators and their specific receptors affect acute and chronic cardiovascular disease manifestations.

Chronic inflammation in atherosclerosis and related metabolic disorders

Tissue and circulating levels of endocannabinoids and fatty acid amide analogues are dysregulated in atherosclerosis and its related cardiovascular risk factors. However, their pathophysiological effect in cardiovascular disease is not well understood. Our group aims to clarify the precise pathophysiological relevance of these receptors and ligands in cardiovascular disease.

Myocardial infarction and repair

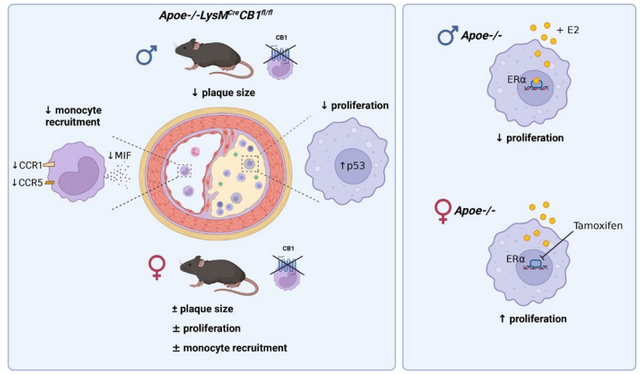
Myocardial infarction (MI) induces an inflammatory response required for cardiac repair processes. Various cell types are involved at different stages of infarct healing, leading to scar formation and adaptive remodeling. We aim to elucidate the signaling pathways and local (lipid) regulators in the cardiac microenvironment promoting resolution of inflammation and healing responses. We recently discovered that pericardial adipose tissue plays a crucial role in regulating post-MI immune responses by serving as a preferential site for innate-adaptive immune cell interaction and lymphocyte activation.

Adverse cardiac remodeling and heart failure

Heart failure is a chronic inflammation state characterized by heightened levels of proinflammatory cytokines promoting pathological left ventricular remodeling. Chronic heart failure can be associated with poor prognosis and high mortality rate and can have multiple causes including ischemic injury and molecular changes acting on the myocardium. We aim to clarify the role of the pericardial adipose tissue lymphoid clusters and underlying cues for immune cell activation in this condition.

Key Publications

Wang Y, Li G, Chen B, Shakir G, Volz M, van der Vorst EPC, Maas SL, Geiger M, Jethwa C, Bartelt A, Li Z, Wettich J, Sachs N, Maegdefessel L, Nazari Jahantigh M, Hristov M, Lacy M, Lutz B, Weber C, Herzig S, Guillamat Prats R, Steffens S. *Myeloid cannabinoid CB1 receptor deletion confers atheroprotection in male mice by reducing macrophage proliferation in a sex-dependent manner.* **Cardiovasc Res** 2024. (BioRxiv 2023)



In this study we could show that male mice with myeloid-specific CB1 deficiency on atherogenic background develop smaller lesions and necrotic cores than controls, showing reduced arterial monocyte recruitment and macrophage proliferation with less inflammatory phenotype. On the contrary, only minor genotype differences were observed in females. The sex-specific differences in proliferation were dependent on estrogen receptor (ER) -estradiol signaling. Overall, impaired macrophage CB1 signaling is atheroprotective by limiting their arterial recruitment, proliferation and inflammatory reprogramming in male mice. The importance of macrophage CB1 signaling appears to be sex-dependent. Cardiovasc Res 2024

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Sarah-Lena Puhl, Dr. rer. nat. (PostDoc)
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Bingni Chen (PhD student)
George Shakir (PhD student)
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CARDIOVASCULAR MOLECULAR SIGNATURES

Christian Weber

We are studying molecular mechanisms involved in atherosclerosis and metabolic diseases. We are particularly interested in epigenetic signatures and non-coding RNAs (ncRNAs) characterizing the susceptibility and progression to atherosclerosis and metabolic sindromes. Our goal is to dissect the mechanisms involved in the susceptibility and progression of vascular diseases and dissect novel therapeutic approaches.

DNA damage and mutations affecting cells of arterial vessels

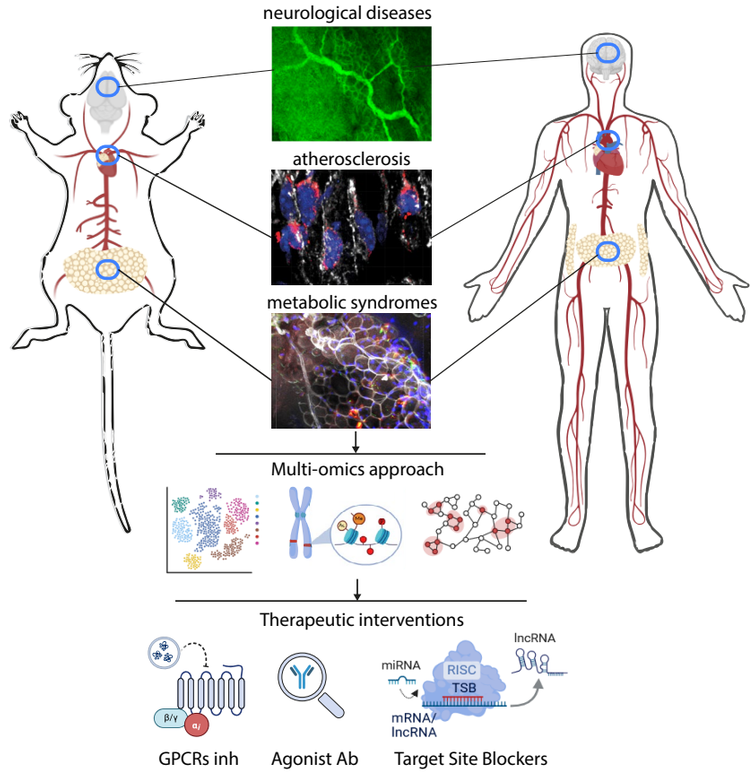
Chromosomal aberrations and DNA damage in proliferating cells can result in the formation of micronuclei (MN), which are extranuclear structures linked to genomic instability. We investigate the molecular mechanisms underlying MN formation, focusing on micro and long non-coding RNA molecules, as well as on epigenetic signatures relocated in MN, like those deriving from atherogenic loci. By studying the impact of atherogenic stimuli and the relocation of genetic signatures, we aim to understand how these factors contribute to endothelial dysfunction and atherosclerosis, with the goal of identifying strategies to preserve genomic stability and vascular health.

Epigenetic modulation of ncRNAs

Long non coding (Lnc) RNAs are RNA transcripts longer than 200 nucleotides that do not encode proteins but influence cell biology through epigenetic regulation, miRNA sponging, and direct protein interactions. We identified lncWDR59 as a novel target of atherogenic miR-103-3p, which inhibited endothelial proliferation and promoted DNA damage and plaque development. We highlighted the miR-103:lncWDR59 axis's role in maintaining genomic stability and preventing the anti-to-proatherogenic switch in adipose tissue. We now study how these epigenetic modulation of micro- and long- ncRNAs, may connect arterial vessels, immune system, adipose tissues, and neuronal system to atherosclerosis and metabolic syndromes.

Role of orphan GPCRs in metabolic syndromes and cardiovascular diseases

Diabetes, the ninth leading cause of death, significantly increases the risk of cardiovascular diseases. Hyperglycaemia, a key feature of diabetes, drives inflammation by activating endothelial cells and dysregulating monocyte activity. We identified orphan GPR26 as protective against hyperglycaemic conditions by limiting pro-inflammatory pathway activation in monocytes. We uncovered a non-canonical role for GPR26 in mitochondrial recycling and endothelial metabolism under hyperglycaemic and atherogenic conditions. We now study its localization to the mitochondrial membrane during metabolic stress and its role in regulating endothelial metabolism, aiming to preserve mitochondrial function and prevent endothelial dysfunction.



Key Publications

Cimen I*, Natarelli L*, Abedi Kichi Z, Henderson JM, Farina FM, Briem E, Aslani M, Megens RTA, Jansen Y, Mann-Fallenbuchel E, Gencer S, Duchêne J, Nazari-Jahantigh M, van der Vorst EPC, Enard W, Döring Y, Schober A, Santovito D, Weber *Targeting a cell-specific microRNA repressor of CXCR4 ameliorates atherosclerosis in mice.* ***Sci Transl Med.*** *2023 Nov;15(720):eadf3357.*

Tahamtan A, Samadizadeh S, Salimi V, Natarelli L, Nakstad B. *Editorial: miRNAs and inflammation: from biogenesis to therapeutic option.****Front Immunol.*** *2023* Oct 3;14:1296589.

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Natarelli L, Weber C. *Non-Canonical Link between Non-Coding RNAs and Cardiovascular Diseases.* **Biomedicines**. 2022 ;10(2):445.

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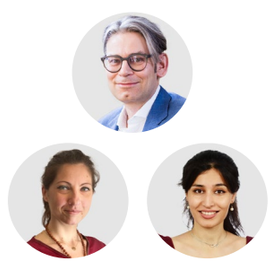

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MICROSCOPIC IMAGING CORE FACILITY

Remco Megens

Our microscope facility supports internal and external collaborators and offers several microscope systems:

- three Leica Thunder microscopes (upright, inverted, organism imager)
- a Leica SP5IIMP Two photon microscope
- a Leica SP8 3X confocal/STED microscope

In collaboration with various IPEK groups, the facility develops and applies imaging applications for studying various processes and structures of the (diseased) cardiovascular system.We are continually expanding the optical imaging facility with the latest microscope technology.

We apply advanced optical fluorescence microscopic and nanoscopic techniques such as the novel instant computational clearing microscopy (Thunder), confocal (CLSM) and two-photon laser scanning microscopy (TPLSM), Stimulated Emission Depletion (STED) for (molecular) imaging of atherosclerotic structures and processes in cardiovascular samples.

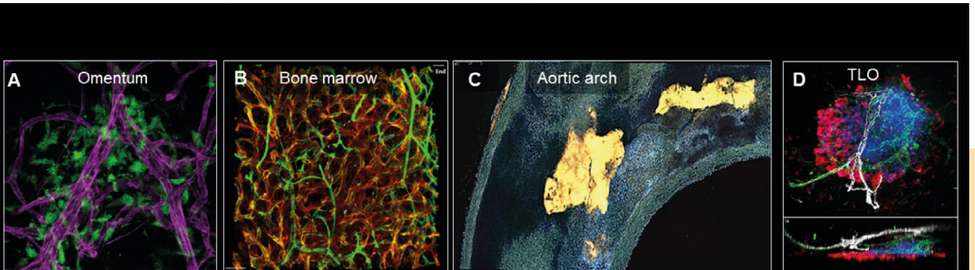
Algorithm supported Thunder imaging vastly improves the image quality of the traditional immunofluorescence microscopy and allows for fast generation of overview images as well as 3D detailed imaging in various samples.

CLSM facilitates true 3D microscopic imaging of thin samples or isolated/cultured cells at sub micrometer resolution and great specificity, whereas STED offers improved nanometer resolution thereby strongly improving our possibilities of studying intracellular, micro- and nanoscopic processes and structures.

TPLSM is perfectly suited for studying of biological structures and processes directly at sites of occurrence: i.e. imaging of structures deep in intact tissues such as the large arteries, myocard, or bone marrow in up to four dimensions.

For in vivo imaging of atherosclerosis, the impact of arterial movement on imaging can be avoided by usage of TPLSM imaging triggered on the heart and respiration cycle of the animal under subject, or artery stabilization.

Examples of preliminary image data conducted at the microscope facility: A) Whole mount Omentum imaged in 3D using Thunder microscopy; B) whole mount and optically cleared bone marrow visualized with CLSM; C) whole mount 3D overview of optically cleared aortic arch with label-free plaque visualization (TPLSM); D) optically cleared TLO including nerves (white) and vessels (green) recorded with CLSM.



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Yvonne Jansen,
(Technician)

TRANSGENIC AND GENE TARGETING

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.

CELL SORTING AND FLOW CYTOMETRY

Johan Duchêne,
Michael Hristov

The Cell sorting and Flow Cytometry Shared Resource Lab provides solid experimental knowledge with high performance technology for analytical multicolor flow cytometry and cell sorting to all research groups within our Institute.

Sustained operator expertise with the BD FACSAria III cell sorter ensures optimal instrument setup and maintenance and offers experiment-tailored, aseptic bulk or single-cell sorting. The sorter is configurated with 3 lasers (488, 633, 405nm) and enables detection of up to 12 parameters. Several cell types with multiple markers at different expression levels can be sorted at high purity and well-preserved viability for downstream experiments. The various efforts inside the Resource Lab include sorting mainly of immune cell subsets like neutrophils, monocytes, macrophages, dendritic cells, NK-, T- and B-cells next to hematopoietic progenitor cells, platelets, cells derived from tissue/organ homogenates, transduced cell lines and cell nuclei or apoptotic microvesicles.

Our institute also offers an access to BD FACSCanto II and BD LSRFortessa X-20 cell analyzers that deliver high performance and multicolor analysis. The BD FACSCanto II is configurated with 3 lasers (488, 633, 405nm) and enables simultaneous detection of up to 8 parameters. The BD LSRFortessa X-20 is configured with 5 lasers (355, 405, 488, 561, 640nm) and enables the detection of up to 20 parameters simultaneously. Thus, BD Fortessa X-20 is a powerful instrument that allows our researchers to detect different hematopoietic cell types and their activation status in tissues.

(EPI)TRANSCRPTOMICS CORE UNIT

Donato Santovito

The (Epi)Transcriptomic core unit in IPEK houses a complete next-generation sequencing (NGS) workflow and bioinformatic expertise supporting a wide range of methods such as transcriptome sequencing, single-cell profiling, and epigenome applications. This unit operates an Illumina NextSeq sequencing system, the 10X genomics Chromium X controller for single-cell resolution, as well as equipment for chromatin/RNA shearing (Bioruptor Pico) and quality-check of input samples and DNA libraries.

The Illumina NextSeq 1000 has recently been acquired and represents the core equipment of the (Epi) transcriptomic unit. It applies next-generation sequencing (NGS) technology to enable sequencing applications, ranging from bulk gene expression profiling to single-cell applications (e.g., scRNAseq, CITE-seq) and complex functional genomic experiments (e.g., ATAC-seq, ChIP-seq).

The main applications include:

- Stranded mRNA sequencing
- Stranded total RNA sequencing
- Small RNA sequencing
- Chromatin Immunoprecipitation and sequencing (ChIP-seq)
- Single-cell genomic applications (e.g., scRNAseq)

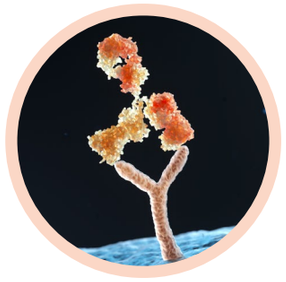
Donato Santovito, Prof., Dr. med.
(Head of Facility)
Vasiliki Triantafyllidou,
(Bioinformatician)

Arterial thromboses: new treatment approach

The Hundelshausen and Weber Labs have shown in an animal model that CXCL12 could be suitable as a target for the treatment of blood-clotting disorders.

BLOOD

04/ 2022

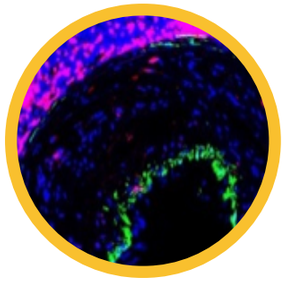


Antibodies get it wrong

The Duchene-Megens and Rot Labs alerted to the wrong use of antibodies in scientific publications. Here they refuted a specific study on localization of immune receptor ACKR1.

CELL STEM CELL

07/ 2022



T cells and atherosclerosis

The Mohanta-Habenicht Lab described how atherosclerosis can lead to disorders of the immune system, similar to those in known autoimmune diseases.

NATURE CARDIOVASCULAR RESEARCH

11 / 2022

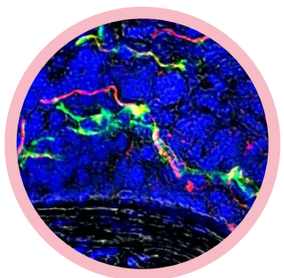
02 / 2023

11 / 2023

Diseased blood vessels communicate with the brain

The Mohanta-Habenicht and Weber Labs have demonstrated for the first time that nerve signals are exchanged between arteries and the brain in atherosclerosis.

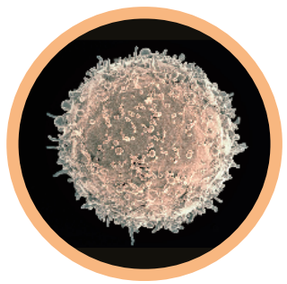
NATURE



Atherosclerosis: B cell activity control

The Steffens Lab described a protective role for GPR55 in the regulation of B cells in the development of atherosclerosis.

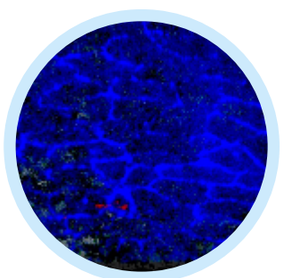
NATURE CARDIOVASCULAR RESEARCH



RNA fragment for atherosclerosis therapies

The Weber and Santovito Labs have identified the role a specific micro-RNA, mir206, in atherosclerosis and in the CXCR4 signaling pathway.

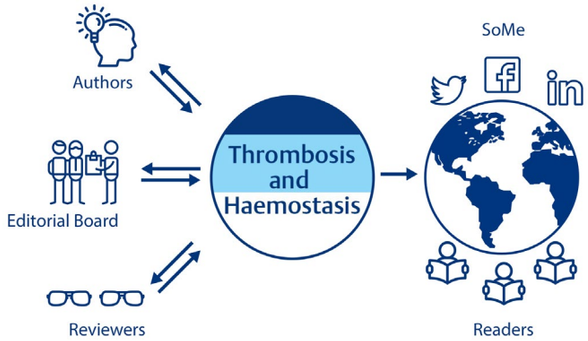
SCIENCE TRANSLATIONAL MEDICINE



RESEARCH NEWS

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, stateof-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.



2022-2023

The Impact Factor has remained stably high at 6.7 even in the postpandemic era and did not experience the same drop as many other cardiovascular or thrombosis journals, reflecting efforts toward a balanced approach in topic selection and commitment to prioritizing scientific quality over quantity. The Open access companion journal, TH Open, has also continued to grow, featuring reliable submissions and high-quality publications, some of which were transferred from its parent journal, Thrombosis & Haemostasis. The journal's new appearance displaying the now mandatory visual summaries helps identifying the most relevant or valuable content amidst the flood of information characterized by our modern era and facilitates information sharing on social media platforms.

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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

IRTG 1123

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 the CRC1123. 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.

Each 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 also welcome to join the study program for the duration of their medical thesis research project in the lab. IRTG 1123 students are located at LMU, TUM and Helmholtz and are encouraged to choose individual seminars, lectures or courses offered by other organisations and graduate schools.

IRTG SPEAKER

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GRADUATE SCHOOL

THESES

Student Name, Lab, Start/Complete Date

Y. Wu, Atzler Lutgens Lab, Started 2019

I. Arigoni, Bartelt Lab, Started 2021

J. Caca, Bartelt Lab, Started 2022

Y. Kechur, Bartelt Lab, Started 2022

S. Kotschi, Bartelt Lab, Started 2020

A. Wallney, Bartelt Lab, Started 2021

S. Fairley, Duchene/Megens Lab, Started 2022

Z. Möller-Ramon, Duchene/Megens Lab, Started 2022

N. Sobczak, Duchene/Megens Lab, Started 2022

X. Deng, Mohanta-Habenicht Lab, Started 2021

M.Hong, Mohanta-Habenicht Lab, Started 2021

Y. Li, Mohanta-Habenicht Lab, Started 2019

M.R. Monjezi, Mohanta-Habenicht Lab, Started 2022

X. Xu, Mohanta-Habenicht Lab, Started 2023

Y. Zhang, Mohanta-Habenicht Lab, Started 2023

X. Zhang, Mohanta-Habenicht Lab, Completed 2022

M. Kumkum, Santovito Lab, Started 2023

B. Avsec, Schober Lab, Completed 2022

I. Baatsch, Schober Lab, Completed 2020

N. Li, Schober Lab, Started 2020

A. Popal, Schober Lab, Started 2018

S. S. Maleki, Schober Lab, Completed 2022

B. Chen, Steffens Lab, Completed 2023

D. Hering, Steffens Lab, Completed 2022

G. Li, Steffens Lab, Started 2021

A. Kaltenbach, Steffens Lab, Started 2021

A. Prabhu, Steffens Lab, Started 2023

G. Shakir, Steffens Lab, Started 2020

S. Yi Xuan, Steffens Lab, Started 2021

Y. Wang, Steffens Lab, Completed 2023

R. Duan, Hundelshausen Lab, Completed 2022

V. Eckardt, Hundelshausen Lab, Completed 2021

J. Leberzammer, Hundelshausen Lab, Completed 2022

T. Lakomiec, Von Hundelshausen Lab, Started 2019

Rui Su, Von Hundelshausen Lab, Started 2023

Ya Li, Von Hundelshausen Lab, Started 2020

Z. Abedi Kichi, Weber Lab, Completed 2022

THESES

Project Title	Sponsor	Principal Investigator *Collaborator*	Time Frame
PROVASC: Cell-specific vascular protection by CXCL12/ CXCR4	ERC Advanced Grant	C. Weber	2016-2023
CD40 goes innate	ERC Consolidator Grant	E. Lutgens	2018-2023
PROTEOFIT: Adapting protein fate for muscle function and fitness	ERC Starting Grant	A. Bartelt	2019-2025
Integrated Research Training Group on Atherosclerosis	DFG CRC 1123, MGK	S. Steffens *V. Paloschi*	2022-2026
CCR8-driven immune functions of group 2 innate lymphoid cells (ILC2s) in atherosclerosis	DFG CRC1123, A01	Y. Döring *C. Weber*	2022-2026
Interactions of chemokines with heterologous effectors in atherosclerosis	DFG CRC1123, A02	P.v. Hundelshausen *J. Bernhagen*	2022-2026
Epigenetic regulation of T-cell activation via the polycomb repressive complex 2 in atherosclerosis	DFG CRC1123, A05	D. Atzler/E.Lutgens	2022-2026
Atypical role of erythroid cells in atherosclerosis	DFG CRC1123, A10	J. Duchêne *C. Weber*	2022-2026
Regulation of necrotic core formation by macrophage miRNAs	DFG CRC1123, B04	A. Schober *M. Nazari-Jahantigh*	2022-2026
Regulatory role of non-coding RNAs and their homeostasis by autophagy in the progression of atherosclerosis	DFG CRC1123, B05	D. Santovito *L.Maegdefessel*	2022-2026
Targeting endocannabinoid receptors in atherosclerosis and metabolic dysfunction	DFG CRC1123, B09	S. Steffens *S. Herzig*	2022-2026
Mechanisms of Nfe2l1-linked inflammation and atherogenesis	DFG CRC1123, B10	A. Bartelt *O. Bruns*	2022-2026
Role of micronuclei-contained DNA and the cytosolic DNA sensor cGAS in atherosclerosis	DFG CRC1123, B12	L. Natarelli	2023-2026

THIRD PARTY FUNDING

Project Title	Sponsor	Principal Investigator *Collaborator*	Time Frame
Label-free microscopic and nanoscopic imaging of atherosclerosis	DFG CRC1123, Z1	R. Megens/S. Mohanta *V. Ntziachristos*	2022-2026
Mex3a-dependent regulation of microRNAs in cardiac disease	DFG TRR 267/2 TP, A02	C. Weber/D.Santovito *M. Sattler*	2019-2027
LMUexcellent Investitionsfonds	DFG	C. Weber	2022
LMUexcellent für CoG	DFG	D. Atzler	2024
LMUexcellent	DFG	D. Santovito	2023
Munich Cluster for Systems Neurologie Grundförderung /Tandemprojekte	DFG Synergy, C5/C6	C. Weber	2019-2025
The role of the arginine/arginase 1 metabolism in atherosclerosis	DFG	D. Atzler	2021-2024
IronBAT: Mechanisms of ferroptosis resistance in brown adipose tissue	DFG SPP2306	A. Bartelt	2022-2024
IRONBAT Mechanismen der Ferroptose-Resistenz im braunen Fettgewebe	DFG	A. Bartelt	2022-2024
Rolle des Orphanrezeptors GPR55 in der Immunzellhomöostase und Atherosklerose	DFG	S. Steffens	2018-2023
Mechanismen der perikardialen Fettaktivierung nach Myokardinfarkt	DFG	S. Steffens	2021-2024
Role of microRNA-147 in adipose tissue macrophages during obesity	DFG	M. Zhu	2020-2023
B Cell Autoimmunität in ApoE-defizienten Mäusen	DFG	A.Habenicht	2019-2022
B Cell Autoimmunity in ApoE-deficient (ApoE-/-) Mice	DFG	C. Yin	2019-2023
MicroRNA-regulierte Prozesse in Keratinozyten nach Expostiion mit S-Lost	DFG	C. Ries	2019-2022
EXERBRAIN - Interaktion zwischen Sport und Lipidstoffwechsel im Gehirn im Zusammenhang der Alzheimer-Erkrankung	BMBF	A. Bartelt	2023-2026
CNATM: Antisense-Oligonukleotide und andere Nukleinsäuretherapeutika (Verbundprojekt 2)	BMBF	C. Weber	2023-2026
Neurale Modulation des Immunsystems bei der Umgestaltung des Herzmuskels infolge permanenten Bluthochdruck	BMBF ERA-CVD	S.L. Puhl	2019-2022

Project Title	Sponsor	Principal Investigator *Collaborator*	Time Frame
AtheroInside. Local immunomodulation of atherosclerosis by CD8+ T cell-based nanomedicines	BMBF ERA-CVD	R. Megens	2019-2023
Fighting Atherosclerotic Plaques in Coronary Artery Disease Via Targeting Neuroimmune Interfaces	BMBF ERA-CVD	A. Habenicht *G. Lembo, Z. Mallat, T. Guzik*	2018-2023
Standortmanagement München	DZHK	C. Weber	2021-2026
DZHK Trainingsprogramm	DZHK	C. Weber	2019-2025
Inflammation - thrombosis crosstalk in patients with high cardiovascular risk	DZHK	Y. Döring *H.Noels*	2023-2024
Lipid nanoparticles containing microRNA-26b as therapeutic approach against atherosclerosis	DZHK	K. Bidzhekov *E. van der Vorst*	2022-2023
The immune checkpoint landscape of the atherosclerotic plaque	DZHK	D. Atzler *H. Winkels*	2023-2024
Genetic discovery-based targeting of the vascular interface in atherosclerosis	DZHK-BHF	J. Duchêne *C. Weber*	2019-2023
Connectivity and Functional Mapping of Cardiovascular Brain Circuits	DZHK Innovation Cluster	S.Mohanta	2023-2026
Nfe2l1-mediated proteasomal activity in heart function and cardiovascular disease	DZHK Nachwuchsgruppe	A. Bartelt	2018-2024
Role of the CXCL 12-CXDR4/ACKR3 axis in atherosclerotic plaque instability	DZHK Post-Doc Start-Up Grant	L. Parma	2022-2023
The role of T cell H3K27 trimethylation on T cell polarization and its effects on atherosclerosis	DZHK Shared Expertise	D. Atzler *M. Lacy/E. Schwedhelm*	2021-2022
Immune Pathogenesis	DZHK Standortprojekt	C. Weber	2019-2025
Molecular determinants	DZHK Standortprojekt	D. Santovito	2019-2025
Pericardial immune cell cross talk in cardiac repair and remodeling	DZHK Standortprojekt	S. Steffens	2019-2025
TRP: Re-screening for novel CD40-TRAF6 interaction inhibitors (TRAF-STOPs 2-0)	DZHK TRP	D. Atzler	2021-2024

Project Title	Sponsor	Principal Investigator *Collaborator*	Time Frame
Development of a novel platelet inhibitor that blocke the CXCL12-CXCR4 axis to prevent and treat atherothrombosis	DZHK TRP Starter Grant	P.v. Hundelshausen	2023-2024
Immuno-metabolic phenotyping of the amino acid homoarginine in atherosclerosis	DZHK women scientist	D. Atzler	2020-2022
Investigating the role of central serotonin in atherosclerosis	DZHK	J. Duchêne *M. Bader*	2022-2023
Flow-depentent regulation of autophagy and miR-126-5p trafficking in endothelial cells	DZHK	D. Santovito *H. Morawietz*	2022-2023
Effects of the erythroid-ACKR1 polymorphism in ANCA-associated vasculitis	DZHK	J. Duchêne *A. Schreiber*	2023-2024
Modulation microRNA-regulierter Prozesse in Haut- und Entzündungszellen als Threapeutische Option bei S-Lost-induzierten Wundheilungsstörungen	Bundeswehr	C. Ries	2019-2023
Epigenitic mechanisms of cardiovascular desease development and progression	Friedrich-Baur Stiftung	F. Farina	2023
Elucidating the cellular and molecular mechanisms behind the pro-atherogenic role of miR-NA-26b	Fritz-Thyssen Stiftung	E. van der Vorst	2021-2023
The role of GITR in atherosclerosis	Novo Nordisk	E. Lutgens	2021-2024
Unravelling consequences of SARS-CoV-2 mediated inflammatory immune responses in heart and vasculature	SNF NRP 78 Project “CoVasc”	Y. Döring *N.Mercander, R.Rieben, B.Engelhardt*	2020-2022
Molecular mechanism and translational relevance of the atypical chemokine receptor ACKR3 in atherosclerosis	SNF Project Grant	Y. Döring	2021-2024
Mapping of Neuroimmune Cardiovascular Interfaces in Murine and Human Atherosclerosis(NICImap)	Corona Stiftung	S.Mohanta	2022-2027

RESEARCH NETWORKS

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 underlyin 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 clinicalphase 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.

RESEARCH NETWORKS PROJECT FUNDING

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:

- How are ncRNA biogenesis and transport controlled in CV cells?
- Through which mechanisms do ncRNA control CV signaling and infer with e.g. epigenetic control, transcription and mRNA processing?
- 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.

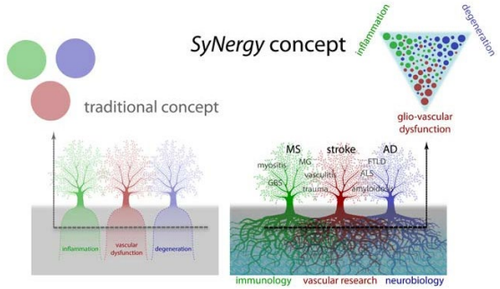
VIAgenomics BHF-DZHK Partnership

PIs from the UK and from Germany among whom IP-EKdirector 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.

SyNergy
Munich Cluster for
Systems Neurology

Munich Cluster for Systems Neurology

Traditional nosology holds that neurological diseases an 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). 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".



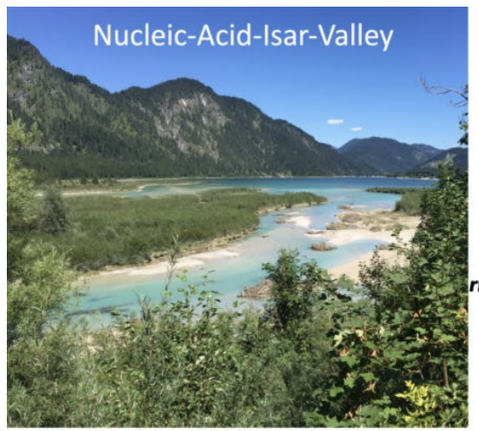
Schematic comparison of the traditional nosological concept (left) and the SyNergy approach to neurological diseases (right).

CNATM
Cluster for Nucleic Acid Therapeutics Munich

Clusters4Future- CNATM

Cluster for Nucleic Acid Therapeutics

CNATM is on of the seven winners of the Clusters4Future initiative of the German Ministry for Education and Research (BMBF). The annual funding amounts to 5 million euro and is provided by the BMBF, the state of Bavaria an the industrial partners. The research consortium consists of research groups from the leading universities LMU and TU, researchers from the universities of Regensburg and Würzburg, as well as the Helmholtz center Munich, and 14 industrial partners from the Munich area.



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

Atherosclerotic complications such as coronary artery disease (CAD) and stroke remain the leading cause of death and morbidity worldwide despite therapeutic advances in lipid lowering management. The high morbidity and medical costs related to cardiovascular disease (CVD) continue to rise with an increasing life expectancy and ageing population in our society. This is associated with an increased prevalence of lifestyle-related metabolic risk factors (e.g. obesity, diabetes) and environmental cardiovascular risk factors (such as air pollution). Thus, improving vascular disease prevention and therapy based on a refined mechanistic understanding of atherosclerosis as the underlying pathology remains a central question in biomedical research to achieve a more efficient and reliable identification of new targets for translation to drug development. A better validation and precision of targets is warranted by limited success rates in the clinical phase and by considerable risks of adverse or off-target effects inherent to the chronic treatment of atherosclerosis. It is the overarching aim of the CRC 1123 "Atherosclerosis – mechanisms and networks of novel therapeutic targets" to provide an in-depth mechanistic understanding of molecular networks in atherogenesis, progression and atherothrombosis. In two target areas, signal proteins and cytokines (A) and nucleic acids and lipid mediators (B), we will continue our mission to map the pathogenic complexity, to discover new mechanisms and their interactions and to identify targets with improved efficacy and safety for treating atherosclerosis. Atherosclerosis is characterized by accumulation of lipid-laden macrophages in arterial lesions upon hyperlipidemia and occurs preferentially at branching points with disturbed flow. Chronic inflammation is driven by a disturbed equilibrium of lipid overload, immune responses and their resolution, leading to crosstalk with procoagulant pathways, plaque rupture, and thrombosis. Major advances in the field have recently been accomplished with bulk or single cell RNA-seq analyses, revealing an unexpected immune cell heterogeneity in atherosclerotic plaques. The concept that inflammatory targets have a major impact in the pathogenesis and treatment of atherosclerosis and atherothrombosis has been confirmed by positive outcomes of the CANTOS and COLCOT trials. Yet, side effects observed, e.g. compromised host defense against infections, underscore a need for safer antiinflammatory therapies by optimizing target specificity. Atherogenic or protective factors linking lipid, inflammation and coagulation biology have been unveiled and genome-wide association studies validated genetic variants and epigenetic factors for CAD. Bioinformatics and omics have been instrumental for discovering specific signatures in vascular disease. An identification of relevant targets in their networks requires unbiased screening, a thorough pathogenic basis, and analysis of interactions in model systems so

that structure function relationships can be readily probed. We persist in elaborating intricately linked molecular mechanisms of different target families in a broad yet coherent spectrum. We use genome editing, conditional mouse models for gene deletion or cell tracking, and extend limits of visualization by new methods, e.g. optoacoustic, nanoscopic or mass spectrometry imaging. With increasing relevance of bulk and single cell RNA sequencing throughout CRC 1123 projects, we opted to expand the scope of expertise by accessible and proprietary prime-seq and barcoding technologies. Likewise, we complement the modalities in our imaging core with Thunder/SWIR imaging and tissue clearing. In the 3rd funding period we will develop studies on the molecular mechanisms of chemokine and cytokine-regulated atherogenic cell recruitment, priming and homeostasis with a specific focus (I) on alternative or atypical chemokine receptors (e.g. CCR8 and DARC), chemokines or alarmins such as MIF, and (II) on specific cellular targets and downstream pathways exerting pathophysiological effects, e.g. neuroendocrine circuits, smooth muscle cell (SMC) and macrophage interplay, or the epigenetic modulation of the immune synapse in atherosclerosis. The role of NETs in atherosclerosis will be extended to hyperglycemia as a comorbidity (area A). Such mechanistic evidence complemented by insights into novel genetic and epigenetic determinants, e.g. a role of the transcriptional repressor REST in regulating the eNOS/sGC/PDE5 pathway, that of HDAC9 in NLRP3 inflammasome activity or interactions of miRNAs/lncRNAa affecting macrophage efferocytosis and endothelial autophagy as regulators of tissue homeostasis and resolution of inflammation. In addition, we will study the consequences of remote injuries on atherosclerosis and the role of lipid mediators as well as the key transcription factor NFE2L1 in the metabolic control of atherogenesis (area B). The overarching task of the central Z projects will be to provide a state-of-the-art multiphoton and super-resolution microscopy core facility, and a high-end transcriptomics and proteomics platform as the basis for a profound bioinformatics interaction and network analysis. This portfolio will be complemented by optoacoustic imaging, tissue clearing technologies, spatial and prime-seq transcriptomics to close methodological gaps and to further advance the current state-of-theart, as one key to the continued overall success of CRC 1123. To accomplish these aims we have consolidated a unique multidisciplinary network of excellent basic and clinical scientists from various Munich research campuses. The implementation of a ded-cated graduate program for CRC 1123 doctoral researchers was instrumental for attracting outstanding junior scientists and providing tailored research training, while fostering interdisciplinary exchange between the project partners. This has led to an extraordinary success of the CRC during its first two funding periods, as exemplified by multiple joint and highimpact publications in excellent journals including NEJM, Cell, Nature and Science families, and many prestigious awards received by CRC 1123 PIs including a total of 7 ERC Advanced grants. In addition, CRC 1123 has attracted outstanding junior scientists with a specific focus on atherosclerosis, including 4 recent ERC Starting grantees and 4 W2 professors to participate in CRC 1123. In turn, its mentoring program facilitated the recruitment of female junior CRC 1123 scientists to international tenure-track positions. Equipped with an excellent scientific infrastructure and collaborative culture, our interdisciplinary discovery-driven approach will continue to decipher the molecular and cellular determinants of atherosclerosis, giving rise to novel links between genetic, inflammatory and metabolic factors. By dissecting their interactions and combined effects in different stages of disease, CRC 1123 will provide valuable targets for future therapeutic options to treat atherosclerosis with minimal side effects on immune responses or homeostatic activities.

CRC1123 International Symposium at the Nymphemburg Palace, Munich, 2022

PERFORMANCE REPORT 2022

Number of budget-funded scientific employees: 24

Number of budget-funded non-scientific employees: 19

Number of all externally funded employees: 58

Source	Number of projects	Fund spent 2022
DFG	33	3,937,089
BMBF, StMWFK	23	1,464,579
EU	5	746,610
Foundations, Industry, etc.	7	380,682
TOTAL EXTERNAL THIRD PARTY FUNDING	**68**	**6,528,960**

Source	Number of projects	Fund spent 2022
PhD Fellowship	3	10,036
Total internal third party funding	3	10,036
TOTAL THIRD PARTY FUNDING SPENT		**6,538,996**

PERFORMANCE REPORTS

PERFORMANCE REPORT 2023

Number of budget-funded scientific employees: 22

Number of budget-funded non-scientific employees: 12

Number of all externally funded employees: 53

Source	Number of projects	Fund spent 2023
DFG	29	3,969,551
BMBF, StMWFK	24	1,429,804
EU	3	341,912
Foundations, Industry, etc.	6	299,499
TOTAL EXTERNAL THIRD PARTY FUNDING	**62**	**6,040,766**

Source	Number of projects	Fund spent 2023
PhD Fellowship	3	14,727
Total internal third party funding	3	14,727
TOTAL THIRD PARTY FUNDING SPENT		**6,055,493**

STAFF KEY FIGURES

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

Position	Total	Budget funded 2022-2023	Third Party funded 2022-2023
Institute Director	1	1	
Professors	15	14	1
Research Group Leaders	16	15	1
Postdoctoral researchers	30	7	23
PhD candidates	34		34
Non scientific Staff	32	16	16

Due to overlapping distribution of tasks mainly in basic science and partly in clinical science staff, the total number of employees amounts to 175 persons. This number also includes staff members who are funded by grants and/or work 50-75% part-time at IPEK.

STAFF FIGURES

Aaldijk, Alexandra Sonia
Abedi Kichi, Zahra
Abraham, Kevin
Ambrosius, Laura
Anak, Seray
Antal, Rot
Ashyralyyev, Annageldi
Atzler, Dorothee
Auer, Theresa
Avcilar Kucukgoze, Irem
Barkin, Ergün
Bartelt, Alexander
Bayer, Batoul
Bayasgalan, Soyolmaa
Bazioti, Venetia
Bährens, Esther
Berger, Johanna
Bidzhekov, Kiril
Bici, Ana
Bindl, Damaris
Blaas, Lukas
Blanchet, Xavier
Bonetti, Matteo
Bonfiglio, Cecilia
Boroja, Slobodan
Buric, Hannah
Buller, Emma
Caca, Jan Philipp
Capodiferro, Brigitta
Chen, Bingni
Chowdhury, Niti
Deng, Xinyi
Derle, Abishek
Dobler, Melanie
Döring, Yvonne
Duan, Rundan
Duchene, Johan
Duong, Thanh Van
Ebert, Katharina
Ebrahim, Martrez Nabil Zaki
Egea Alonso, Virginia
Ettenhuber, Anna
Fairley, Savannah
Farina, Floriana
Faußner, Hans Alexander
Freire Soares Marques, Yonara Maria
Fusco, Anja Elena
Geiger, Martina
Geißler, Claudia
Gencer, Selin
Gjika, Ejona
Gimpfl, Christiane
Gokay, Asli
Guerra, Joel
Guillamat-Prats, Raquel
Grouls, Annabelle
Gunczi, Catherine
Haberbosch, Markus
Habenicht, Andreas
Habenicht, Livia
Hariri, Hana
Hayrapetyan, Nane
Heimann, Laura
Henderson, James
Henver, Brunetta
Hong, Mingyang
Igl, Marcus
Jacob, Katharina
Jain, Tanishq
Jansen, Yvonne
Jeevanandan, Sree Priyanka
Jethwa, Carolin
Jodeleit, Henrika
Jung, Anna Simone
Kaltenbach, Anna
Karikari, Rhoda Anane
Kechur, Yurii
Kern-Matschilles, Stefanie
Khani, Sajjad
Kichi, Zahra
Kolobas, Daniel
Kotschi, Stefan
Krishna, Kupa
Kral, Maria
Kumkum, Mahadia
Lakomiec, Tomasz
Lemmer, Imke
Li, Guo
Li, Nan
Li, Xinwei
Li, Yutao
Limoncu, Özge
Lorenz, Reinhard
Lu, Shu
Lutterberg, Karina
Lutgens, Esther
Ma, Zhe
Mahmoud Badr, Passant Ayman
Mann Fallenbuchel, Elizabeth
Mao, Min
Martin-Liew, Charlotte
Matta Pereira, Leonardo

STAFF MEMBERS

Megens, Remco
Mena Gomez, Alba
Merchant, Kevin
Migheli, Roberta
Mohanta, Sarajo
Möller Ramon, Zoe Carmen
Monjezi Rafiee, Mohammad
Nagarajan, Yoghalakshmi
Nasiri, Haron
Natarelli, Lucia
Nazari-Jahantigh, Maliheh
Nitz, Kathrin
Ofoghi, Anahita
Oliaeimotlagh, Mohammad
Özdem, Doruk
Parikh, Shipra
Parma, Laura
Peng, Li
Pitsch, Thomas
Polla, Anna
Popal, Aamoun
Pooveli, Harsha
Prabhu, Aishvaryaa
Puhl, Sarah-Lena
Ramanathan, Srishti
Rauser, Sandra
Ridder, Julius
Rigby, Anne
Ries, Christian
Röß, Katja
Rossiter, Michael
Santovito, Donato
Saroyan, Lusine
Sekhar, Avinash
Shaikh, Saima
Shakir, George
Shia, Yi Xuan
Silla, Lukas
Simoni, Ambra
Siess, Wolfgang
Sobczak, Nikola
Sommer, Katja
Stamataki, Maria
Steffens, Sabine
Streicher, Sabine
Stremlau, Marleen
Subramanian, Narayani
Su, Rui
Sun, Ting
Taherdangkoo, Khadijeh
Thiemann, Ellen
Triantafyllidou, Vasiliki
Van der Vorst, Emiel
Vatovci, Iliriana
Veselinov, Olivera
von Hundelshausen, Philipp
von Oheimb, Kathrin
Wallney, Aurora Julia
Wang, Yong
Wang, Zhihua
Weber, Christian
Weidner, Silvia
Willemsen, Nienke
Winiger, Kilian Johannes
Wu, Yuting
Yin, Changjun
Yanyi, Zhou
Zahran, Hala
Zakaria, Zeina Ihab Seifeldin
Zhang, Chuankai
Zhang, Xi
Zhang, Yixin
Zhu, Mengyu

2022

	n	IF Sum	IF Average
Original Articles	49	596.7	12.2
Reviews, Editorials	28	418.3	14.9
TOTAL NUMBER OF ARTICLES	**77**	**1015**	**13.2**

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7. Daugherty A, Hegele RA, Lu HS, Mackman N, Rader DJ, Weber C. Web of Science's Citation Median Metrics Overcome the Major Constraints of the Journal Impact Factor. Arterioscler Thromb Vasc Biol. 2022;42:367-371. (IF: 10.5)

8. Evans BR, Yerly A, van der Vorst EPC, Baumgartner I, Bernhard SM, Schindewolf M, Doring Y. Inflammatory Mediators in Atherosclerotic Vascular Remodeling. Front Cardiovasc Med. 2022;9:868934. (IF: 5.8)

9. Evans PC, Davidson SM, Wojta J, Back M, Bollini S, Brittan M, Catapano AL, Chaudhry B, Cluitmans M, Gnecchi M, Guzik TJ, Hoefer I, Madonna R, Monteiro JP, Morawietz H, Osto E, Padro T, Sluimer JC, Tocchetti CG, Van der Heiden K, Vilahur G, Waltenberger J, Weber C. From novel discovery tools and biomarkers to precision medicine-basic cardiovascular science highlights of 2021/22. Cardiovasc Res. 2022;118:2754-2767. (IF: 13.1)

10. Farina FM, Santovito D, Weber C. Two-Faced Janus: CCR2-Expressing Macrophages and Their Dual Role in Allograft Rejection of the Transplanted Heart. Circulation. 2022;146:639-642. (IF: 39.9)

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13. Ferdinandy P, Koller A, Weber C, Wojta J, Waltenberger J. Frontiers in CardioVascular Biomedicine (FCVB) 2022 Budapest is on in person! The excellent programme proves that scientists won against COVID-19. Cardiovasc Res. 2022;118:e59-e61. (IF: 13.1)

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15. Ganesh N, van der Vorst EPC, Spiesshofer J, He S, Burgmaier M, Findeisen H, Lehrke M, Swirski FK, Marx N, Kahles F. Gut immune cells-A novel therapeutical target for cardiovascular disease? Front Cardiovasc Med. 2022;9:943214. (IF: 5.8)

16. Gencer S, Doring Y, Jansen Y, Bayasgalan S, Yan Y, Bianchini M, Cimen I, Muller M, Peters LJF, Megens RTA, von Hundelshausen P, Duchene J, Lemnitzer P, Soehnlein O, Weber C, van der Vorst EPC. Endothelial ACKR3 drives atherosclerosis by promoting immune cell adhesion to vascular endothelium. Basic Res Cardiol. 2022;117:30. (IF: 12.4)

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18. Giroud M, Jodeleit H, Prentice KJ, Bartelt A. Adipocyte function and the development of cardiometabolic disease. J Physiol. 2022;600:1189-1208. (IF: 6.2)

19. Guillamat-Prats R, Hering D, Derle A, Rami M, Hardtner C, Santovito D, Rinne P, Bindila L, Hristov M, Pagano S, Vuilleumier N, Schmid S, Janjic A, Enard W, Weber C, Maegdefessel L, Faussner A, Hilgendorf I, Steffens S. GPR55 in B cells limits atherosclerosis development and regulates plasma cell maturation. Nat Cardiovasc Res. 2022;1:1056-1071. (IF: 0.5)

20. Habenicht LKL, Wang Z, Zhang X, Li Y, Mogler C, Huspenina JS, Schmid RM, Weber C, Mohanta SK, Ma Z, Yin C. The C1q-ApoE complex: A new hallmark pathology of viral hepatitis and nonalcoholic fatty liver disease. Front Immunol. 2022;13:970938. (IF: 8.8)

21. Haghikia A, Zimmermann F, Schumann P, Jasina A, Roessler J, Schmidt D, Heinze P, Kaisler J, Nageswaran V, Aigner A, Ceglarek U, Cineus R, Hegazy AN, van der Vorst EPC, Doring Y, Strauch CM, Nemet I, Tremaroli V, Dwibedi C, Krankel N, Leistner DM, Heimesaat MM, Bereswill S, Rauch G, Seeland U, Soehnlein O, Muller DN, Gold R, Backhed F, Hazen SL, Haghikia A, Landmesser U. Propionate attenuates atherosclerosis by immune-dependent regulation of intestinal cholesterol metabolism. Eur Heart J. 2022;43:518-533. (IF: 35.9)

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23. Heuschkel MA, Babler A, Heyn J, van der Vorst EPC, Steenman M, Gesper M, Kappel BA, Magne D, Goueffic Y, Kramann R, Jahnen-Dechent W, Marx N, Quillard T, Goettsch C. Distinct role of mitochondrial function and protein kinase C in intimal and medial calcification in vitro. Front Cardiovasc Med. 2022;9:959457. (IF: 5.8)

24. Immler R, Nadolni W, Bertsch A, Morikis V, Rohwedder I, Masgrau-Alsina S, Schroll T, Yevtushenko A, Soehnlein O, Moser M, Gudermann T, Barnea ER, Rehberg M, Simon SI, Zierler S, Pruenster M, Sperandio M. The voltage-gated potassium channel KV1.3 regulates neutrophil recruitment during inflammation. Cardiovasc Res. 2022;118:1289-1302. (IF: 13.1)

25. Kahles F, Rau M, Reugels M, Foldenauer AC, Mertens RW, Arrivas MC, Schroder J, Idel P, Moellmann J, van der Vorst EPC, Marx N, Lehrke M. The gut hormone glucose-dependent insulinotropic polypeptide is downregulated in response to myocardial injury. Cardiovasc Diabetol. 2022;21:18. (IF: 8.9)

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27. Karshovska E, Mohibullah R, Zhu M, Zahedi F, Thomas D, Magkrioti C, Geissler C, Megens RTA, Bianchini M, Nazari-Jahantigh M, Ferreiros N, Aidinis V, Schober A. Endothelial ENPP2 (Ectonucleotide Pyrophosphatase/Phosphodiesterase 2) Increases Atherosclerosis in Female and Male Mice. Arterioscler Thromb Vasc Biol. 2022;42:1023-1036. (IF: 10.5)

28. Kichi ZA, Natarelli L, Sadeghian S, Boroumand MA, Behmanesh M, Weber C. Orphan GPR26 Counteracts Early Phases of Hyperglycemia-Mediated Monocyte Activation and Is Suppressed in Diabetic Patients. Biomedicines 2022; 10:7. (IF: 4.7)

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30. Kichi ZA, Natarelli L, Sadeghian S, Boroumand MA, Behmanesh M, Weber C. Orphan GPR26 Counteracts Early Phases of Hyperglycemia-Mediated Monocyte Activation and Is Suppressed in Diabetic Patients. Biomedicines. 2022;10. (IF: 4.8)

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2023

	n	IF Sum	IF Average
Original Articles	48	550.5	11.5
Reviews, Editorials	33	389	11.8
TOTAL NUMBER OF ARTICLES	**81**	**939.5**	**11.6**

1. Aghdassi A, Schwedhelm E, Atzler D, Nauck M, Kuhn JP, Kromrey ML, Volzke H, Felix SB, Dorr M, Ittermann T, Bahls M. The relationship between homoarginine and liver biomarkers: a combination of epidemiological and clinical studies. Sci Rep 2023; 13(1) (IF: 4.6)

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PUBLICATIONS 2023

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HONORS, AWARDS

D. Atzler, 2023, ESC Outstanding Achievement Award

V. Bazioti, 2023, Among 3 highest scoring abstracts from Germany, ESC Congress

V. Bazioti, 2023, Best session poster and best poster presentation finalist , Annual Meeting of the German Society for Cardiology DGK

M. Bonetti, 2022, Erasmus International Scholarship, University of Brescia, Italy

Y. Döring, 2023, ESC Outstanding Achievement Award

J. Duchêne, 2023, Habilitation as Privat Dozent in Immunology and Cardiovascular Disease

F. Farina, 2022, Travel Grant, European Society of Atherosclerosis

A. Kaltenbach, 2022, Hans-Jürgen-Bretschneider poster award, Basic Science Meeting, German Cardiac Society

I. Lemmer, 2022, Best poster award ELC Tutzing

E. Lutgens, 2023, Alexander W. Clowes Distinguished Lecture, Vascular Research Initiatives/ ATVB Conference

S. Mohanta, 2022, Galenus von Pergamon Prize

S. Mohanta, 2022, August Wilhelm and Lieselotte Becht Research Prize

M. Nazari Jahantigh, 2022, LMU Medical Scientist of the Year

D. Santovito, 2023, National Scientific Habilitation as Associate Professor of Cardiology

N. Sobczak, 2023, Best Presentation, young European Federation of Immunological Societies (yEFIS)

S. Steffens, 2023, Arthur Weber Prize, German Cardiac Society

S. Steffens, 2023, Silver Honorary Needle, German Cardiac Society

N. Willemsen, 2022, Best poster award ELC Tutzing

C. Weber, 2022, Highly Cited Researcher from Clarivate Analytics

C. Weber, 2023, Highly Cited Researcher from Clarivate Analytics

AWARDS

CONFERENCES, EVENTS

Bartelt, **European Lipoprotein Club,** Tutzing, GER, Sep 2022, Organizer

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Duchêne J, **Symposium 40 Years of Atherosclerosis**, Thrombosis and Vascular Biology, Vienna, Austria, 2022 Invited Speaker

Duchêne J, **European Chemokine and Cell Migration Conference (ECMC)**, Leuven, Belgium, 18-21 September 2023, Invited Speaker

Duchêne J, **Munich Heart Alliance (MHA) - Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK)** – Winter Meeting, Munich, Germany, 31 January 2023, Invited Speaker

Duchêne J, **Gordon Research Conference (GRC)**, Chemotactic Cytokines, Les Diablerets, Switzerland, 12-17 June 2022, Invited Speaker

Lutgens E, **ESC Working Group on Atherosclerosis and Vascular Biology**, European Society of Cardiology, 2022-2024, Chair

Lutgens E, **Gordon Research Conference on Atherosclerosis**, Barcelona, Spain, 2023, Vice Chair

Parma L, **Young DZHK retreat**, Potsdam, Germany, September 2023, Co-organizer

Parma L, **Young DGK Science meeting**, Halle, Germany, December 2023, Co-organizer

Santovito D, **52. Jahrestagung der Deutschen Gesellschaft für Angiologie**, Leipzig, Germany, 21-23 September 2023, Invited Speaker

Steffens S, **DGK/DZHK Translational Workshop**, Bonn, Germany, October 2022, Co-organizer

Steffens S, **CRC1123 International Symposium**, Munich, Germany, October 2023, Co-organizer

Steffens S, **IRTG1123 Retreat**, Tutzing, Germany, October 2023, Organizer

Steffens S, **10th Cardiac Regeneration and Vascular Biology Meeting**, San Servolo, June 2023, Co-organizer

Weber C., **EAS Congress, 2023**, Keynote Lecture and Speaker

Weber C., **ESC Congress**, Barcelona, Spain, 2022, Invited Spealer

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EDITORIAL AND CONTENT

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Cover

Bone Marrow Organoid (BMO) - Confocal Microscopy

(Nuclei in Yellow, Mesenchymal Cells in Blue)

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Bone Marrow Organoid (BMO) - Confocal Microscopy

(Endothelial cells in Orange, Mesenchymal Cells in Blue)

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