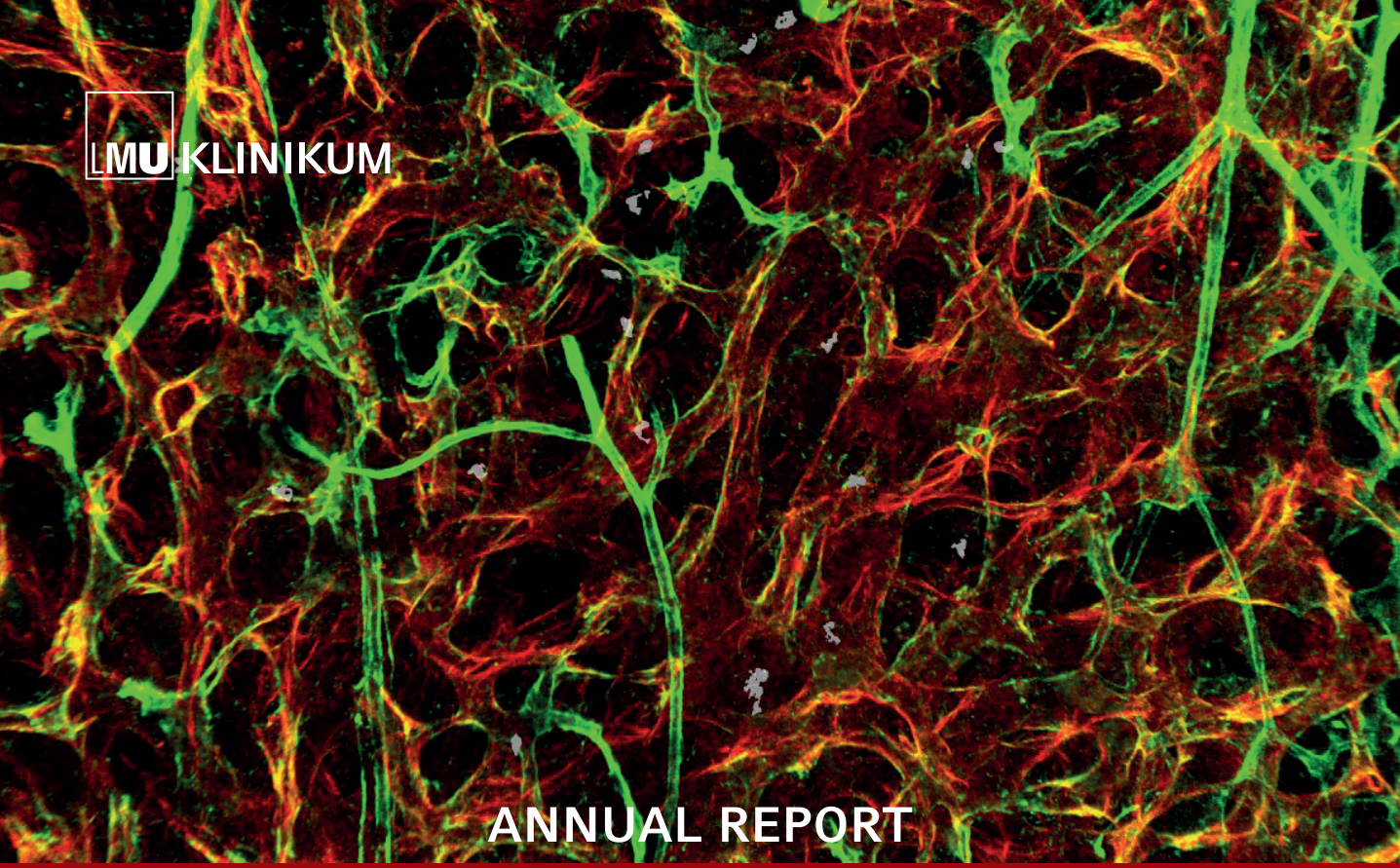

LMU KLINIKUM

ANNUAL REPORT

2020-2021

Institute for Cardiovascular Prevention

IPEK

Editorial

Eines Tags geschah es Kant,
dass er keine Worte fand.

Stundenlang hielt der den Mund,
und er schwieg nicht ohne Grund:

Ihm fiel absolut nichts ein,
drum liess er das Sprechen sein.

Erst als man zum Essen rief,
wurd' er wieder kreativ,

und sprach die schönen Worte:
«Gibt es hinterher noch Torte?»

Kant (Robert Gernhardt)

Another memorable two years have passed with a differentially perceived velocity and with many of us encountering and overcoming some severe health and social issues imposed during and extending beyond the pandemic. Despite all these obstacles, we are proud and delighted to follow our tradition and convey the many achievements at IPEK, which are summarized and to be reflected upon in this biennial report. Most notably, our DFG-funded collaborative research centre CRC 1123 on atherosclerosis has been extended for a third funding period of 4 years against all odds.

As most of this has already been stated and better accomplished by others, discussing the implications and consequences of the pandemic should not be the focus here. Instead, I would like to introduce the observations and conclusions deduced from the formative work of the philosopher Hannah Arendt, which can be stunningly applied as a caveat to many facets of our modern live. Hannah Arendt notes that total control, which proceeds from organizing all individuals in their infinite plurality and diversity, as if they all constituted only one human being, is possible only if it succeeds in reducing each human being to an identity of reactions that is always constant and uniform, so that each of these bundles of reactions is interchangeable with one another to produce one single species of man. This should be avoided at all costs. Much rather, multitude and variety should not only be preserved in nature, culture and art but also in man, in individual opinions, thoughts, ideas and of course in science. We are all different and unique, and this is a major blessing for mankind, much reminiscent of the philosopher Peter Sloterdijk once describing his concept for the society of the future in his “Sphärologie” as a foam: Individuals are like bubbles, which are co-isolated. Each bubble lives for itself, and yet they are interconnected at their borders, thereby sharing and exchanging what makes them different. This way all of you can make a difference!

Best wishes
Christian Weber

Markus Muntean & Adi Rosenblum
"Ohne Titel – we would like to.. 2022"
© The Albertina Museum, Vienna

Contents

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

Sofar, his pivotal findings have led to 415 original publications (123: first/senior author, 292: co-author) and been cited more than 48,000/72,000-times to yield an hindex of 119/141 (Scopus/GoogleScholar). He has received the distinction of Highly Cited Researcher 2018, 2020-22 by Clarivate Analytics. In sciencewide citation metrics of all authors, his ranking of #3163 (Cardiovascular #148; Biochemistry #232) indicates his influence and impact.

Institute Director

The innovations of Dr. Weber are also 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 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 Consulting Editor of Cardiovascular Research.

Dr. Weber initiated the first DFG collaborative research centre committed to atherosclerosis in 2014 (CRC 1123). Following an exceptional evaluation of his contributions, funding was renewed in 2018. He has been instrumental for introducing new technologies, e.g. two-photon, optoacoustic and super-resolution imaging, an array of conditional mouse models and structural and bioinformatics analysis to map the pathogenic complexity and identify individual mechanisms and targets. At the international level, Dr. Weber has received 2 consecutive European Research Council (ERC) Advanced Grants (Atheroprotect in 2010 and PROVASC in 2016). From 2011 to 2016, he served as the European Coordinator of the Leducq Transatlantic Network of Excellence, CVGeneF(x). All of this clearly 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 highly 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 dedicated 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.

Organisation

The Institute for Cardiovascular Prevention (IPEK) is organised into 2 independent divisions, with an interplay between clinical care and research. In addition to its director, the institute is led by 28 group leaders with distinct research fields, including 2 C3 professors, 4 W2 professors and 9 associate professors, who supervise individual research groups. The Institute also comprises the DFG "Atherosclerosis" Collaborative Research Center 1123, the Editorial Office of the journal Thrombosis & Haemostasis and is one of the Institute of the Munich Heart Alliance (MHA) the German Center for Cardiovascular Research (DZHK).

August-Lenz-Stiftung

Hintergrund

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

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

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

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

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

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

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

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09/2020
ESC YOUNG INVESTIGATOR AWARD & PAUL DUDLEY WHITE INTERNATIONAL SCHOLAR AWARD

IPEK scientist Michael Lacy has been awarded the European Society of Cardiology Young investigator Award for his presentation at the ESC Congress in the category Basic Science.

The prestigious Young Investigators Awards are sponsored by the ESC to support original research and scientific excellence. These sessions, held during ESC Congress, offer a unique opportunity for young investigators to expose their most innovative and novel research to the scrutiny of panels of renowned experts in the specific fields.

In May 2020, Michael Lacy had been selected as Paul Dudley White International Scholar for an abstract submitted to the Vascular Discovery: From Genes to Medicine Scientific Sessions 2020 Conference.

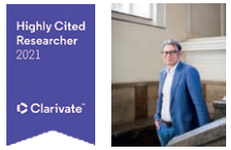
The esteemed Paul Dudley White Award is named in honor of one of Boston's most revered cardiologists, Dr. Paul Dudley White, who was a founding father of the American Heart Association and widely regarded as the founder of preventive cardiology. This award epitomizes the organization's most prestigious tribute. The stellar work from Michael Lacy and his co-authors was chosen by his peers to reflect Dr. White's vision for global excellence in cardiovascular science and medicine. Michael Lacy is the first author of the highest ranked accepted abstract from Germany.

2020
ATVB SPECIAL RECOGNITION AWARD

Esther Lutgens has received the ATVB Special Recognition Award for her pioneer work on discovering the role of co-stimulatory molecules in atherosclerosis.

The Council on Arteriosclerosis, Thrombosis and Vascular Biology (ATVB) established the Special Recognition Award in 1981 to recognize council members who have made significant contributions to the council as well as the fields of Arteriosclerosis, Thrombosis and Vascular Biology. The award is presented annually during the ATVB Business Meeting and Awards Reception at the American Heart Association's Scientific Sessions

11/2021
HIGHLY CITED RESEARCHER 2021



Prof. Weber has received the honour of being named Highly Cited Researcher for 2021 by Clarivate Analytics. He is among an elite group recognized for exceptional research performance demonstrated by production of multiple highly cited papers that rank in the top 1% by citations for field and year in *Web of Science.* This distinction earned derives not from *Clarivate Analytics* but from peers, who have time and again acknowledged the influence of his research contributions in their publications and citations.

11/2021
GERMAN OBESITY SOCIETY RESEARCH AWARD

Alexander Bartelt has received the German Obesity Society Research Award. Every year the German Obesity Society (DAG) honors young scientists under the age of 40 for outstanding work in the field of obesity research.

Alexander Bartelt investigates how fat cells grow, shrink, and remain healthy in the process. During his time in USA, he made an interesting discovery: a previously unknown mechanism ensuring that fat cells continuously regenerate from within, which prevents inflammation and dysfunction. Metabolism expert Bartelt expects that this protective mechanism will provide new lines of therapeutic research for the so-called metabolic syndrome: obesity, insulin resistance, high blood lipids, hypertension in conjunction increase the risk for cardiovascular disease and other major illnesses.

"Metabolic research is a very timely and very relevant topic, as our society is becoming bigger with half the population being overweight today. During the sedentary months of the pandemic, the Germans put on even more weight, "says Bartelt. In his lab he focuses on the gene switch Nfe2l1: "Nfe2l1 controls the breakdown of protein waste. Apparently, it is a key factor that helps recycling waste products of metabolism and thus prevents cells from being stressed - be it in muscle cells, fat cells, or in the heart, "explains the scientist.

News

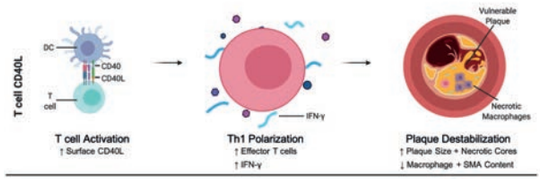
T-cell regulation in atherosclerosis

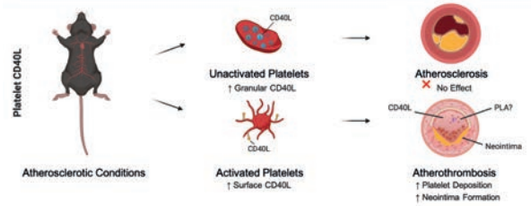
Dorothee Atzler & Esther Lutgens

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

Dr. rer. nat. Dorothee Atzler
Esther Lutgens, MD/PhD
Dr. rer. nat. Katrin Nitz
Cecilia Assunta Bonfiglio, MD
Irem Avcilar Kukukgoze, PhD
Venetia Bazioti, PhD cand
Sigrid Unterlugauer, RA
Roberta Migheli, RA
Yonara Freire, PhD, RA
Michael Lacy, PhD
Yuting Wu, PhD cand
Mahadia Kumkum, HiWi

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 unraveled 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, termed TRAF-STOPs. TRAF-STOP treat-ment successfully blocked (established) atherosclerosis and is currently being tested and optimized for human administration. Using conditional knock-out mice for CD40 and CD40L, we found that CD40 on dendritic cells and macrophages as well as CD40L on T cells are crucial for atherogenesis. Moreover, we discovered that the co-stimulatory molecule CD27 is a critical mediator for regulatory T cell (Treg) survival, which led to attenuated inflammation and retards atherosclerosis. Activation of GITR also induced a Treg response and inhibited





atherosclerosis progression. Currently we aim to extend our studies on how aberrant T-cell regulation emanating from changes in co-stimulatory molecules or alterations in T-cell metabolism may be pro- or anti-atherogenic. We are following a more global and a candidate-based approach. In search of novel master-switches of T-cell reactivity in atherosclerosis, we identified two novel and promising candidates: the immune checkpoint regulator and E3 ubiquitin ligase casitas Blineage Lymphoma-b (cbl-b) and the amino acid homoarginine (HA). Preliminary data show that global deficiency of cbl-b increases atherosclerosis and T-cell activation by modulating costimulation. Moreover, we found that HA, an amino acid that we previously established as being protective in cardiovascular disease, suppresses T-cell reactivity in atherosclerotic mice.

Research Groups

Key Publications

Lacy M, Bürger C, Shami A, Ahmadsei M, Winkels H, Nitz K, van Tiel CM, Seijkens TTP, Kusters PJH, Karshovka E, Prange KHM, Wu Y, Brouns SLN, Unterlugauer S, Kuijpers MJE, Reiche ME, Steffens S, Edsfeldt A, Megens RTA, Heemskerk JWM, Goncalves I, Weber C, Gerdes N, Atzler D*, Lutgens E*. *Cell-specific and divergent roles of the CD40L-CD40 axis in atherosclerotic vascular disease.* **Nat Commun.** 2021;12(1):3754.

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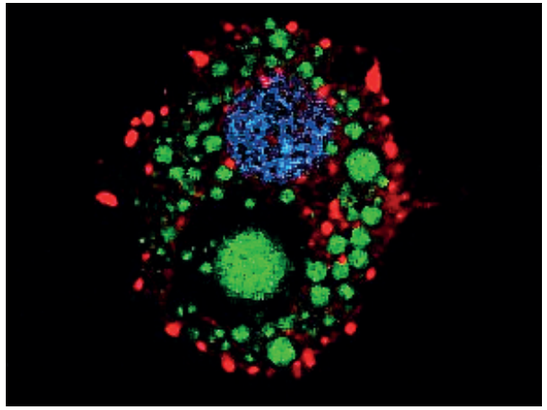
Cardiovascular Immunometabolism

Alexander Bartelt

The Bartelt Lab studies metabolic adaptation as a fundamental process by which cells and organisms respond to environmental challenges. We are particularly interested in the regulation of energy balance, adipocyte health, and obesity-associated comorbidities such as type 2 diabetes and cardiovascular disease. Our goal is to understand the molecular basis of metabolic biology and find new approaches to tackle metabolic disease clusters.

Univ.-Prof. Dr. Alexander Bartelt - Team Leader, Prof. Dr. Christian Ries - Group Leader, Dr. vet. Henrika Jodeleit - Manager of Animal Operations, Henver Brunetta, PhD - PostDoc, Dr. rer. nat. Virginia Egea - PostDoc, Dr. rer. nat. Joel Guerra - PostDoc, Dr. vet. Karina Lutterberg - PostDoc, Leonardo Matta, PhD - PostDoc, Alba Mena Gomez, M.Sc. - PhD student, Anna Jung, M.Sc. - PhD student, Imke Lemmer, M.Sc. - PhD student, Carolin Muley, M.Sc. - PhD student, Anahita Ofoghi, M.Sc. - PhD student, Nienke Willemsen, M.Sc. - PhD student, Jan Caca, cand. med. - MD student, Yurii Kechur, cand. med. - MD student, Stefan Kotschi, cand. med. - MD student, Batou Bayer, B.Sc. - Master student, Lukas Blaas, B.Sc. - Master student, Hala Zahran, B.Sc. - Master student, Ana Bici - Research assistant, Ejona Gijka - Research assistant, Thomas Pitsch - Research technician, Silvia Weidner - Research technician

Brown fat thermogenesis and metabolic health: Thermogenic adipocytes are a remarkable type of metabolic cell. These UCP1-expressing cells are activated by cold and use energy-dense nutrient such as fatty acids, carbohydrates, and derived carbohydrates for producing heat to maintain body temperature homeostasis. 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. 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. Shivering, exercise and skeletal muscle function: Next to age and genetic predisposition, physical activity and exercise are the most



A microscopy picture of a stressed adipocyte

important factors for maintaining a healthy metabolism throughout life. Also, even as a therapeutic life style intervention, exercise or mild physical activity have beneficial effects on cardiometabolic health. Somewhat paradoxically, in other severe myopathies, such as muscle wasting in immobilized subjects or cancer cachexia, similar metabolic alterations take place as in beneficial exercise but the underlying mechanisms remain elusive. Our goal is to identify novel regulators of skeletal myocyte adaptation, and explore how these relate to physical activity and metabolic disease.

Key Publications

Muley C, Kotschi S, Bartelt A. *Role of Ubiquilins for Brown Adipocyte Proteostasis and Thermogenesis.* **Front Endocrinol (Lausanne).** 2021 Sep 28;12:739021. doi: 10.3389/fendo.2021.739021. eCollection 2021.

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Cell specific immune responses in chronic vascular inflammation

Yvonne Döring

We focus on chemokine(-receptor) biology on leukocytes and vascular cells in cardiovascular diseases. We examine cell-specific roles of CXCL12 and its receptors CXCR4 and ACKR3 in chronic arterial vascular inflammation. Furthermore, we elucidate how CCR8 impacts on anti-inflammatory immune responses and how the chemokine-like receptor ChemR23 mediates macrophage polarization and vascular immune responses in atherosclerosis.





Yvonne Döring, PhD - Group leader
Emiel van der Vorst, PhD - Senior Postdoc
Yi Yan, PhD - Postdoc
Selin Gencer, MSc - PhD student
Yvonne Jansen - Senior Technician
Soyolmaa Bayasgalan - Technician

During the last two years we newly 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. **(PMID 31837653)**

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. **(PMID 32078474)**

Dysfunctional adipose tissue (AT) may contribute to the pathology of several metabolic diseases. Hence, we explored the role of ACKR3 in adipocyte-specific knockouts of *Ackr3* in ApoE-deficient mice in order to determine its impact on lipid levels under hyperlipidemic conditions. Adipocytespecific deletion of *Ackr3* results in reduced AT triglyceride and cholesterol content in ApoE-deficient mice, which coincides with increased PPAR-γ and *Angptl4* expression. The role of adipocyte ACKR3 in lipid handling seems to be tissue-specific as hepatocyte ACKR3 deficiency did not demonstrate comparable effects. **(PMID 33917642)**

We also investigated the role of the calcium sensing receptor (CaSR) in adipose tissue inflammation and atherosclerosis development *in-vivo*. Applying a conditional mature adipocyte specific CaSR deficient mouse on a hyperlipidemic and atherosclerosis prone *Apoe*$^{-/-}$ background it could be shown that CaSR deficiency in adipocytes does neither contribute to initiation nor to progression of atherosclerotic plaques. Additionally, CaSR deficiency did not influence gonadal visceral adipose tissue (vAT) inflammation *in-vivo*. **(PMID 34001955)**

We further hypothesized that proprotein convertase subtilin/kexin type 9 (PCSK9) affects the expression of chemokine receptors, major mediators of inflammation, to influence cardiovascular health. However, overexpression of PCSK9 in murine models *in-vivo* and PCSK9 stimulation of myeloid and vascular cells *in-vitro* did not reveal influences of PCSK9 on the expression of certain chemokine receptors that are known to be involved in the development and progression of atherosclerosis and vascular inflammation. Hence, additional research is required to elucidate which mechanisms are mediated by PCSK9, independent of LDLR. **(PMID 34884827)**

Key Publications

van der Vorst EPC, Daissormont I, Aslani M, Seijkens T, Wijnands E, Lutgens E, Duchene J, Santovito D, Döring Y, Halvorsen B, Aukrust P, Weber C, Höpken UE, Biessen EAL. *Interruption of the CXCL13/CXCR5 Chemokine Axis Enhances Plasma IgM Levels and Attenuates Atherosclerosis Development.* **Thromb Haemost.** 2020 Feb;120(2):344-347. doi: 10.1055/s-0039-3400746. Epub 2019 Dec 14. PMID: 31837653

Döring Y, Jansen Y, Cimen I, Aslani M, Gencer S, Peters LJF, Duchene J, Weber C, van der Vorst EPC. *B-Cell-Specific CXCR4 Protects Against Atherosclerosis Development and Increases Plasma IgM Levels.* **Circ Res.** 2020 Mar 13;126(6):787-788. doi: 10.1161/CIRCRESAHA.119.316142. Epub 2020 Feb 5. PMID: 32078474

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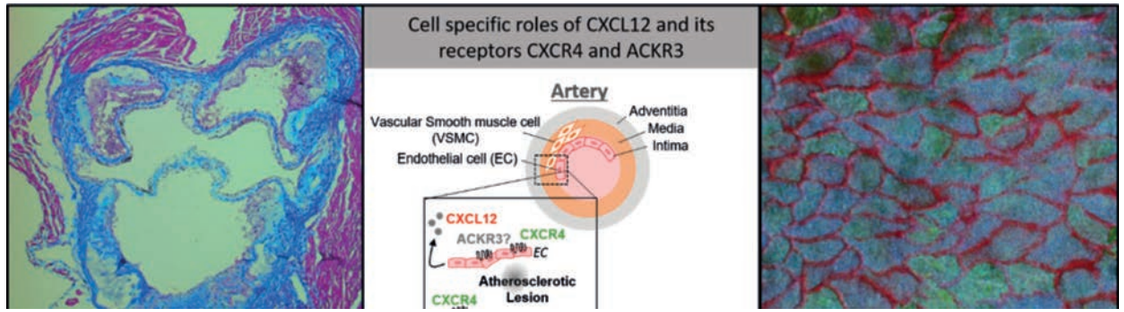

(Left) Haematoxylin staining of a mouse aortic root with atherosclerotic lesions; (Middle) Schematic overview of published and ongoing research on the role of CXCL12 and its receptors CXCR4 and ACKR3 in experimental atherosclerosis; (Right) Close up of mouse arterial endothelium, VE-cadherin lining the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

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Inflammation in CVD

Johan Duchêne and Remco Megens

The main objective of our research is to investigate the molecular and cellular mechanisms of immune responses in cardiovascular disease (CVD).

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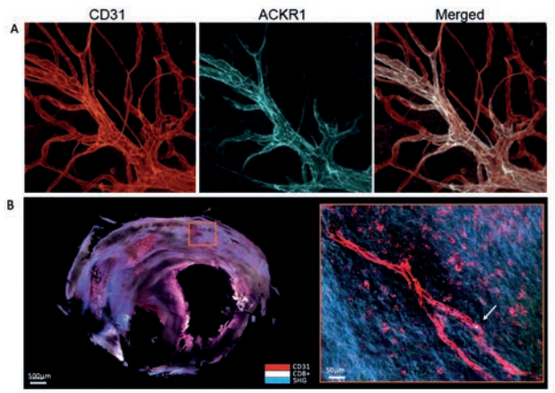
At the core of all noncommunicable diseases such as CVD, is inflammation, a highly complexed process tightly orchestrating the action of multiple inflammatory molecules. Among the receptors expressed by the hematopoietic and non-hematopoietic cells, chemokine receptors play a key role in inflammation. Chemokines control immune cell migration and other inflammatory functions. In addition to 'classical' chemokine receptors, chemokines also bind to atypical chemokine receptors (ACKRs). ACKRs regulate the bioavailability of chemokines. While 'classical' chemokine receptors have been extensively studied in inflammation, the roles of ACKRs are still poorly understood. More efforts are thus needed to better understand ACKRs functions in steady state and inflammation.

ACKR1 in immune response

ACKR1, also known as Duffy-antigen, binds inflammatory chemokines and was ascribed a unique expression profile in erythrocytes, venular endothelial cells and cerebellar Purkinje neurons. Individuals of African ancestry carry a genetic variant, rs2814778(G), in the gene encoding ACKR1. This variant results in the specific absence of ACKR1 expression on erythroid cells while its expression is maintained in endothelium and cerebellum, causing a Duffy-negative phenotype. Using CRISPR/Cas9 genome editing, we recently generated a new erythroid-deficient mouse model which carries the mouse equivalent of the human rs2814778(G) polymorphism. We are currently investigating the function of erythroid-ACKR1, using this mouse model which phenocopies Duffynegative individuals, in the context of atherosclerosis, an inflammatory cardiovascular disease.



*(**A**) ACKR1 is expressed by CD31+ endothelial cells. Immunostaining showing the expression of ACKR1 in post-capillaries venules. (**B**) CD8+ T-cell invasion (arrow) in human plaque culture. The tissue was optically cleared and visualized using two-photon microscopy.*

ACKR3 in hematopoiesis

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

Monocyte development

Monocytes can be divided into two major subsets, known as classical and non-classical monocytes, which serve different functions in the immune system. We identified PD-L1 as a marker for nonclassical monocytes. Using this marker, we were able to show that non-classical monocytes play a direct regulatory role in the adaptive immune response. Indeed, non-classical monocytes are able to infiltrate a specific type of inflamed tissue – known as tertiary lymphatic organs – for instance in the context of myocardial infarction, where they function as direct regulators of the adaptive immune response by modulating the activities of T cells. We are currently investigating the development of monocytes in the context of inflammation and western diet.

Human atherosclerotic plaques imaging

We apply state-of-the-art imaging technology to study native CD8+ T-cells and their interactions with atherosclerotic structures in human plaques to identify their potential impact on the disease of atherosclerosis. We investigate the functions of chemokine receptors in the migration of CD8+ T-cells inside atherosclerotic plaques. The proposed project may lead to new protective pathways and therapeutic intervention strategies for treatment of atherosclerosis.

Key Publications

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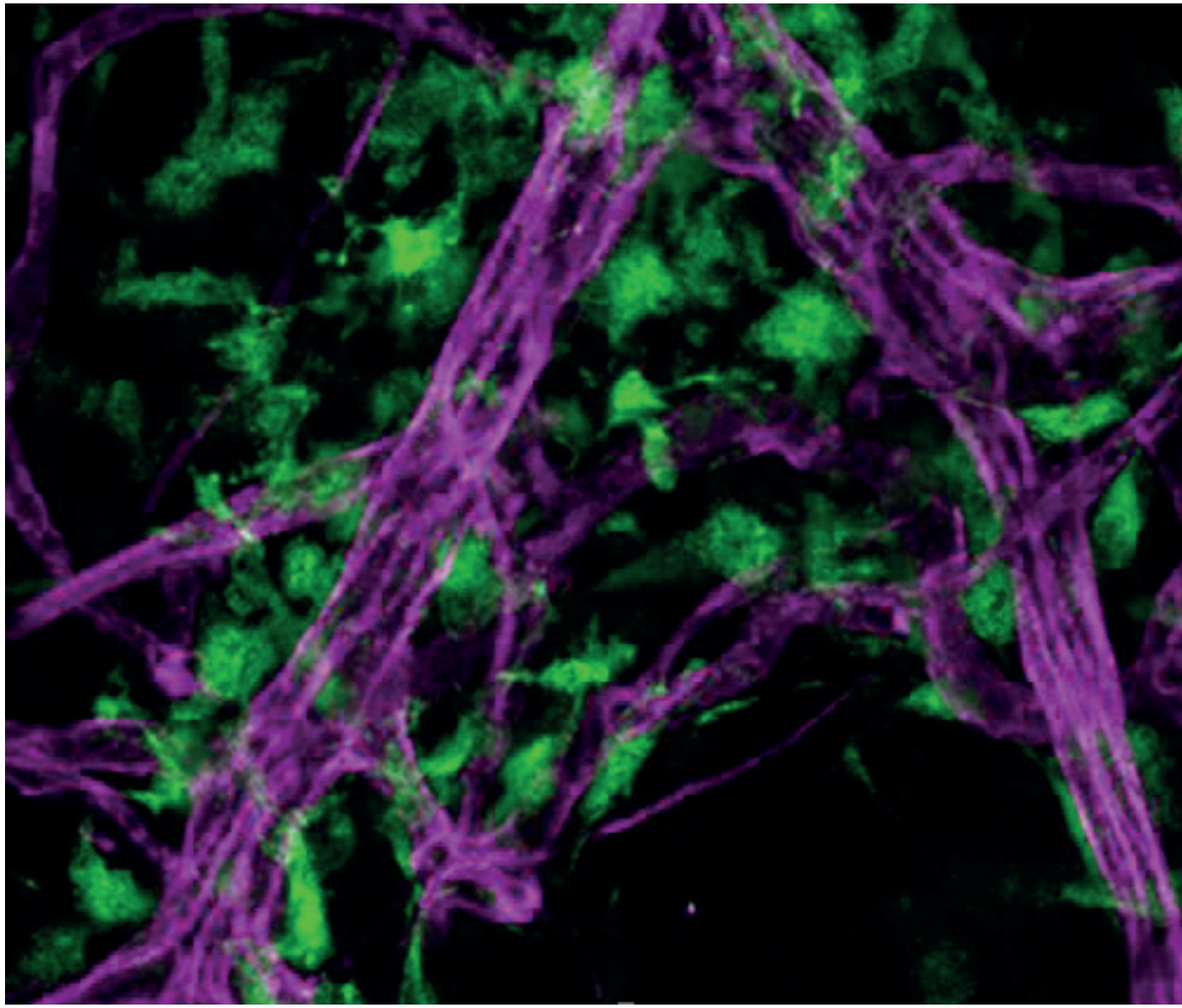
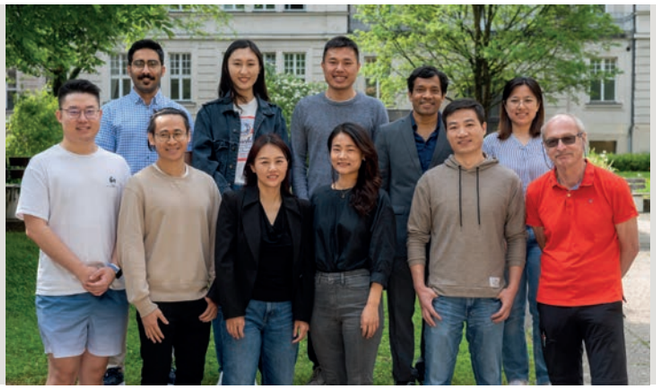


Figure: Confocal microscopic imaging of excised omentum of a Cx3cr1gfp/+ mouse with macrophages in green and vascular endothelial cells in purple(Cd31).

Neuroimmune Cardiovascular Interface

Andreas Habenicht

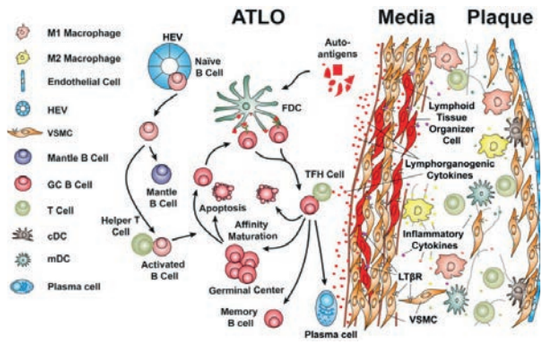
Our group focuses on three areas of the immunology of cardiovascular diseases during aging: i. Define common molecular mechanisms of atherosclerosis and Alzheimer´s disease; ii. Search for atherosclerosis-specific autoimmune lymphocytes; and iii. Identify and delineate neuroimmune cardiovascular interfaces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



Professor Dr. med. A. Habenicht – PI and group leader
Dr. rer. nat. C. Yin – PI and group leader
Dr. S. Mohanta – PI and group leader
Zhe Ma – graduate student
Zhihua Wang – graduate student
Ting Sun – graduate student
Shu Lu – graduate student
Yutao Li – graduate student
Rui Su – graduate student
Mingyang Hong – graduate student
Xinyi Deng – graduate student
Mohammad Rafiee Monjezi – graduate student

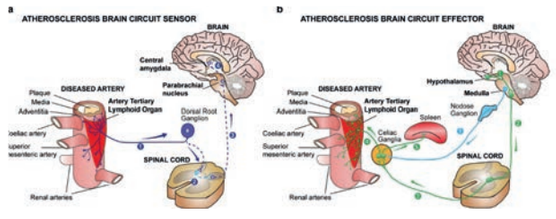
Atherosclerosis and Alzheimer´s disease
ApoE has been implicated in Alzheimer´s disease (AD), atherosclerosis, and other unresolvable inflammatory conditions but a common mechanism of action remains elusive. We found in ApoE-deficient mice that oxidized lipids activated the classical complement cascade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

Atherosclerosis and autoimmunity
A fundamental unresolved issue in the pathogenesis of atherosclerosis is whether the advanced and clinically significant disease is associated with the generation of arterial wall-specific autoantigens recognized by autoimmune T cells or B cells. Our group has proposed a hypothesis how such autoimmune lymphocytes (shown for B2 B cells in Figure 1) may be generated. Accordingly, we have begun to isolate germinal center B2 cells from artery tertiary lymphoid organs (ATLOs) that develop in the adventitia, i.e. the outer connective tissue coat of arteries, using aged ApoE-/- mice as the experimental model.



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

Neuroimmune cardiovascular interfaces (NICIs) and artery brain circuits (ABCs):
Atherosclerotic plaques emerge in the inner intimal layer of arteries causing heart attacks and strokes. As plaques lack innervation, the impact of neuronal control on atherosclerosis remains unknown. However, the immune system responds to plaques by forming leukocyte-infiltrates in the adventitia which forms the outer connective tissue-coat of arteries. Because the peripheral nervous system (PNS) uses the adventitia as their principle conduit to reach distant targets, we postulated that the PNS 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 including growth-cones at axon endings forming junctions with immune cells and media smooth muscle cells. Murine NICIs established atherosclerosis-brain-circuits (ABCs): abdominal-adventitia nociceptive afferents entered the central NS (CNS) through spinal cord



Schematics of ABC sensor and ABC effector.

T6-T13 dorsal-root-ganglia; multiple sensory and sympathetic CNS neurons were traced to brainstem, parabrachial and central amygdala neurons; and sympathetic efferents projected from medullary and hypothalamic neurons to the adventitia through spinal cord intermediolateral neurons and celiac ganglia. Moreover, PNS components of the ABC were activated: splenic sympathetic and celiac vagus nerve activities increased during disease progression while celiac ganglionectomy led to disintegration of adventitial NICIs, reduced disease progression, and enhanced plaque stability. Thus, the PNS employs NICIs to assemble ABCs and its therapeutic interruption attenuates atherosclerosis (Mohanta et al. 2021. Nature, in revision).

Key Publications

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MicroRNAs and autotaxin in necrotic core formation

Andreas Schober

We are studying how microRNAs, such as miR-21, regulate macrophage function and necrotic core formation in atherosclerotic plaques. We are particularly interested in the mechanism by which microRNAs control energy metabolism and circadian apoptosis in plaque progression. Moreover, we are trying to determine the sex-specific role of autotaxin, a lysophospholipase D, in endothelial cells and macrophages in atherogenesis.

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Claudia Geißler – Lab technician
Anja Fusco – Lab technician
Anna Eberlein – Lab technician
Kathrin Heyll – Lab technician
Nan Li, MSc – PhD student
Yi Ru Msc – Ph.D. student
Mati Kakar cand. med.
Brigitta Brumec cand. dent. med.

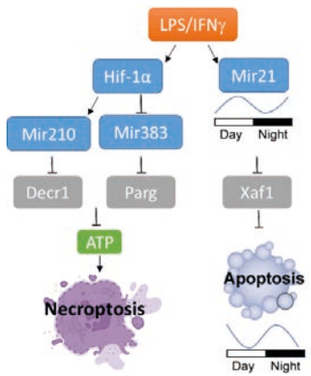
The necrotic core in atherosclerotic plaques comprises cholesterol crystals and cell debris. It develops due to increased cell death and reduced removal of the dead cells by macrophages. The size of the necrotic core determines the risk for plaque rupture and cardiovascular events such as myocardial infarctions. Thus, limiting necrotic core expansion may be a promising therapeutic approach to preventing cardiovascular diseases.

Hypoxia-inducible factor-1 promotes macrophage necroptosis by miRNA regulation.

We analyzed the metabolic mechanisms involved in the death of plaque macrophages. We found that activation of the transcription factor hypoxia-inducible factor 1 after inflammatory stimulation increases necroptotic cell death by upregulating miR-210 and downregulating miR-383. Whereas miR-210 inhibits oxidative phosphorylation by targeting 2,4-dienoyl-CoA reductase, downregulation of miR-383 impairs DNA damage repair due to derepression of poly(ADP-ribose)-glycohydrolase. Together, the opposite regulation of miR-210 and miR-383 by HIF-1 results in ATP depletion and necroptosis.

miR-21 controls circadian apoptosis and necrotic core formation in atherosclerotic plaques

Myocardial infarctions occur more frequently in the early morning. We found that miR-21 is regulated in a circadian manner in atherosclerotic plaques. It reduced levels of miR-21 and increased apoptosis during the transition from the inactive to the active phase by derepressing the proapoptotic factor XAF1 in mice and humans. Therefore, a death clock in macrophages increases necrotic core formation at the beginning of the active phase due to a disbalance between apoptosis and efferocytosis.



Autotaxin promotes atherosclerosis by producing lysophosphatidic acid.

Oxidative modifications of low-density lipoproteins are pro-atherogenic. In addition to the role of oxidatively-modified LDL in foam cell formation, it also provides substrates for the lysophospholipase D activity of autotaxin, generating lysophosphatidic acid (LPA). Our previous results showed that LPAs enhance plaque growth by inflammatory activation of endothelial cells. Now, our focus is on the role of autotaxin in macrophages and endothelial cells generating LPAs and atherosclerosis.

Key publications

Gomez I, Ward B, Souilhol C, Recarti C, Ariaans M, Johnston J, Burnett A, Mahmoud M, Luong LA, West L, Long M, Parry S, Woods R, Hulston C, Benedikter B, Niespolo C, Bazaz R, Francis S, KissToth E, van Zandvoort M, Schober A, Hellewell P, Evans PC and Ridger V. *Neutrophil microvesicles drive atherosclerosis by delivering miR-155 to atheroprone endothelium.* **Nat Commun**. 2020;11:214.

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Molecular mechanisms of impaired wound healing

Christian Ries

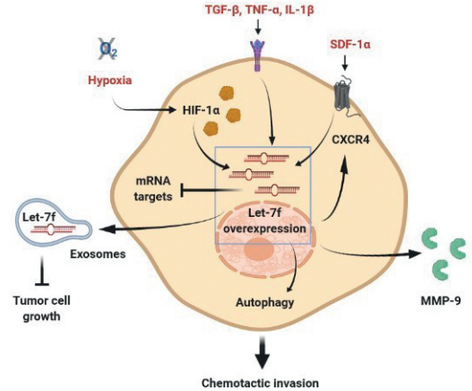


Prof. Dr. rer. nat. Christian Ries – Group leader
Dr. rer. nat. Virginia Egea – Postdoc
Dr. med. vet. Karina Lutterberg – Postdoc
Lan Zang – Cand. med.
Thomas Pitsch – TA

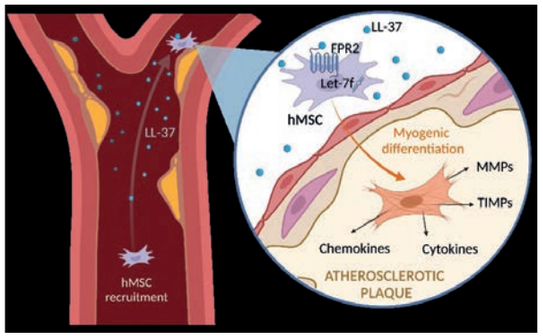
The main objective of our research is to investigate the molecular mechanisms of cell migration in the context of inflammatory diseases such as wound healing, cancer, and atherosclerosis. We are interested in human mesenchymal stem cells (hMSCs) and microRNAs which represent a group of small non-coding RNAs involved in gene silencing thereby regulating various biological processes. Our goal is to identify key microRNAs with anti-tumor and athero-protective properties in hMSC-based therapy.

hMSCs originate from bone marrow and are recruited to tissue sites of damage and disease where they contribute to repair. This multi-step process involves chemokine-directed migration of hMSCs and on-site release of factors that influence target cells and tissues.

Let-7f in tumor growth. Attracted by the inflammatory milieu, hMSCs are known to infiltrate neoplastic tissues and affect tumor growth and progression. Our findings indicate that hMSC tropism toward tumor tissue is driven by paracrine SDF-1α and inflammatory cytokines as well as hypoxia. These conditions cause augmentation of endogenous let-7f in hMSCs promoting their invasion by increased secretion of ECM degrading proteases and elevated autophagy in these cells. Furthermore, we showed that elevated levels of let-7f in hMSCs facilitate its release in exosomes and uptake by mammary tumor cells thereby suppressing tumor growth. Our results support the idea of hMSCs or hMSC-derived exosomes in cell-based and cell-free clinical applications of anti-tumor therapy.



hMSC exposure to inflammatory cytokines, SDF-1α, and hypoxia upregulates let-7f in the cells promoting chemotactic invasion via engagement of autophagy and release of ECM-degrading proteases. In a paracrine manner, exosomal let-7f affects tumor growth. Picture taken from Egea V. et al., Cell Death and Disease, 12:516, 2021.



Elevated expression of let-7f facilitates LL-37-mediated recruitment of hMSCs to atherosclerotic plaques involving upregulation 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 (manuscript accepted).

Let-7f in atherosclerosis. 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.

In summary, let-7f is a key promotor of hMSC tropism to neoplasias and atheromas enhancing the anti-tumor and athero-protective potential of these cells. In the future, increasing let-7f levels in hMSCs may represent a strategy to advance the clinical application of these cells in the treatment of inflammatory diseases.

Key publications

Egea V. et al. *Let-7f miRNA regulates SDF-1α- and hypoxia-promoted migration of mesenchymal stem cells and attenuates mammary tumor growth upon exosomal release*. **Cell Death and Disease**, 12:516, 2021

Egea V. et al. *Properties and fate of human mesenchymal stem cells upon miRNA let-7fpromoted recruitment to atherosclerotic plaques.* **Cardiovascular Research** (manuscript accepted for publication).

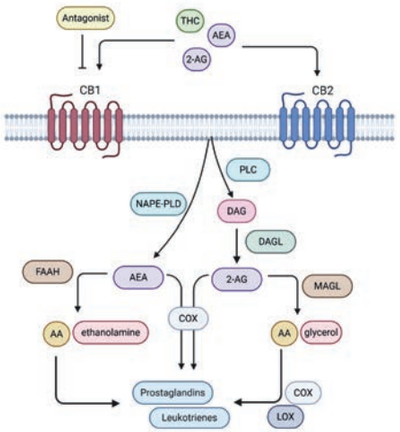
Lipid signaling in cardiovascular disease

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.

Prof. Dr. rer. nat. Sabine Steffens - Group Leader
Prof. Dr.rer.nat. Alexander Faussner - Group Leader
Dr. rer. nat. Sarah-Lena Puhl - PostDoc
Dr. Raquel Guillamat-Prats (PhD, until March 2021) PhD - PostDoc
Yong Wang PhD - student
Bingni Chen PhD - student
George Shakir PhD - student
Guo Li PhD - student
Anna Kaltenbach PhD - student
Shia Yi Xuan PhD - student
Aishvaryaa Prabhu - MSc candidate
Silviya Wolkerstorfer - technical assistant (until December 2021)
Theodora Astalaki - technical assistant
Martina Geiger - technical assistant

Cardiovascular diseases are among the most frequent causes of death. In most cases, they are caused by atherosclerosis, which is a chronic disease of the arterial vessels. Treatment of this chronic inflammation may represent a new therapeutic approach to reduce the risk of myocardial infarction, supported by promising recent clinical trial results. In this context, we are studying the role of the endocannabinoid system, which is an endogenous lipid signaling system. In the long term, our studies will not only lead to a better understanding of the pathophysiology of atherosclerosis, but also provide new therapeutic approaches for the treatment of chronic vascular inflammation. In this context, clarification of the anti-inflammatory effects of selectively peripherally acting CB1 cannabinoid receptor antagonists is of particular interest, as these might also be efficient for treating metabolic diseases such as diabetes and obesity, which are risk factors for atherosclerosis. Another focus of our research group are inflammatory processes involved in repair and remodeling processes of the myocardium after myocardial infarction or in response to chronic pressure load such as hypertension. Acute myocardial infarction is the leading cause of death in Europe and is associated with high morbidity. Death of ischemic myocardium results in fibrotic scarring and structural remodeling of the ventricle, which can lead to decreased cardiac function and ultimately heart failure. To date, research has focused primarily on the processes occurring in the ischemic heart. A possible cross-talk with the adipose tissue surrounding the pericardium and coronary vessels, however, has been largely ignored so far. We pursue the question whether there is a mutual influence between cardiac adipose tissue and myocardium and how this "communication" is controlled. We hope to contribute to a better understanding of inflammatory processes after acute myocardial infarction and during adverse cardiac remodelling leading to heart failure. Thus, we hope to identify new therapeutic approaches that could lead to a better clinical outcome of myocardial infarction and heart failure patients.



Endocannabinoid synthesis and degradation_with_COX_LOX

Key Publications

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Puhl SL, Steffens S (2019). *Neutrophils in post-myocardial infarction inflammation: damage versus resolution?* **Frontiers in Cardiovascular Medicine** 18;6:25

Lutgens E, Atzler D, Döring Y, Duchene J, Steffens S, Weber C (2019). *Immunotherapy for cardiovascular disease.* **European Heart Journal** 40(48):3937-3946.

Tahir S, Steffens S (2021). *Non-classical monocytes in cardiovascular physiology and disease.* **American Journal of Physiology-Cell Physiology** 1;320(5): C761-C770. Steffens S, Nahrendorf M, Madonna R (2021). *Immune cells in cardiac homeostasis and disease: emerging insights from novel technologies.* **European Heart Journal** (Online ahead of print) PMID: 34897403

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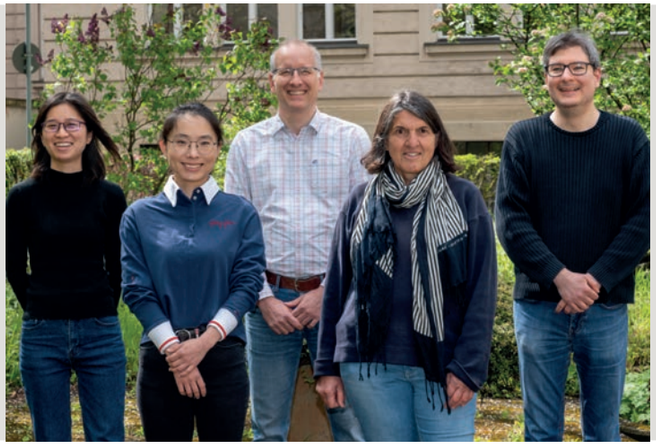
Guillamat-Prats R, Hering D, Rami M, Härdtner C, Santovito D, Rinne P, Bindila L, Hristov M, Pagano S, Vuilleumier N, Schmid S, Janjic A, Enard W, Weber C, Maegdefessel L, Faussner A, Hilgendorf I, Steffens S (2021). *GPR55 in B cells limits atherosclerosis development and regulates plasma cell maturation.* **bioRxiv** 2021.12.20.473518; doi: https://doi.org/10.1101/2021.12.20.473518

Targeting chemokine-heteromers in atherosclerosis/thrombosis

Philipp von Hundelshausen

We are studying effects of chemokines on platelet activity which is related to atherosclerosis and thrombosis. We are particularly interested in the fact that chemokines associate with themselves or other soluble mediators to form oligomeric complexes thereby altering the functional behaviour of chemokines. Our goal is to elucidate the role of chemokines in atherosclerosis and thrombosis resulting in new targets and novel therapeutics.



PD Dr. med. Philipp von Hundelshausen - group leader
Prof. Dr. med. Wolfgang Siess,- group leader
Dr. Xavier Blanchet - Post Doc
Dr. med. Veit Eckardt - MD
Dr. med. Rundan Duan - MD, Gerok
Ya Li, Master's Degree in Clinical Medicine - PhD student
Tomasz Lakomiec, Msc biotechnology/bioengineering - PhD student
Julian Leberzammer, Medicine - MD student

Atherosclerotic vascular disease (ASCVD) is a chronic inflammatory disease of the arterial wall and the prerequisite for plaque erosion and rupture, the pathophysiological substrate of acute coronary syndromes and ischemic stroke which account for the major cause of mortality and disability worldwide. The results of several clinical trials targeting inflammatory mediators including IL-1β prove that targeting inflammation is worthwhile, but needs to be more specific to avoid immunerelated side effects and preserve efficacy so that further research toward immunomodulatory pathways for atherosclerosis/ thrombosis is warranted. Chemokines and galectins form heterodimers to modulate inflammation

Chemokines and galectins are simultaneously upregulated and mediate leukocyte recruitment during inflammation.
Until now, these effector molecules have been considered to function independently. We tested the hypothesis that they form molecular hybrids. By systematically screening chemokines for their ability to bind galectins-1 and -3, we identified several interacting pairs, such as CXCL12 and galectin-3. Based on NMR and MD studies of the CXCL12/ galectin-3 heterodimer, we identified contact sites between CXCL12. Gal-3 attenuated CXCL12-stimulated signaling via its receptor CXCR4 in a ternary complex with the chemokine and receptor, consistent with our structural model. This first report of heterodimerization between chemokines and galectins reveals a new type of interaction between inflammatory mediators that can underlie a novel immunoregulatory mechanism in inflammation.

Btk is a central signalling molecule in platelets and a potential target in atherothrombosis
Bruton tyrosine kinase inhibitors (BTKi) are used in B-cell malignancies and in development against various autoimmune diseases. Since Btk is also involved in specific pathways of platelet activation, BTKi might be considered to target platelet GPVI/GPIb-mediated atherothrombosis and platelet FcgRIIA-dependent immune disorders. However, BTKi treatment of patients with B-cell malignancies is frequently associated withmild bleeding events caused possibly by off-target inhibition of Tec. We compared the platelet effects of two novel BTKi that exhibit a high (remibrutinib) or low (rilzabrutinib) selectivity for Btk over Tec. We found that Remibrutinib and rilzabrutinib inhibit Btkdependent pathways of platelet aggregation upon GPVI, VWF/GPIb, and FcgRIIA activation. Remibrutinib being more potent and showing a better profile of inhibition of Btk-dependent platelet activation vs. hemostatic impairment than rilzabrutinib may be considered for further development as an antiplatelet drug.

Key Publications

Eckardt V, Miller MC, Blanchet X, Duan R, Leberzammer J, Duchene J, Soehnlein O, Megens RT, Ludwig AK, Dregni A, et al. *Chemokines and galectins form heterodimers to modulate inflammation.* **EMBO Rep.** 2020;21:e47852. doi: 10.15252/embr.201947852

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Duan R, Goldmann L, Li Y, Weber C, Siess W, von Hundelshausen P. *Spontaneous Platelet Aggregation in Blood Is Mediated by FcgammaRIIA Stimulation of Bruton's Tyrosine Kinase.* **Int J Mol Sci.** 2021;23. doi: 10.3390/ijms23010076

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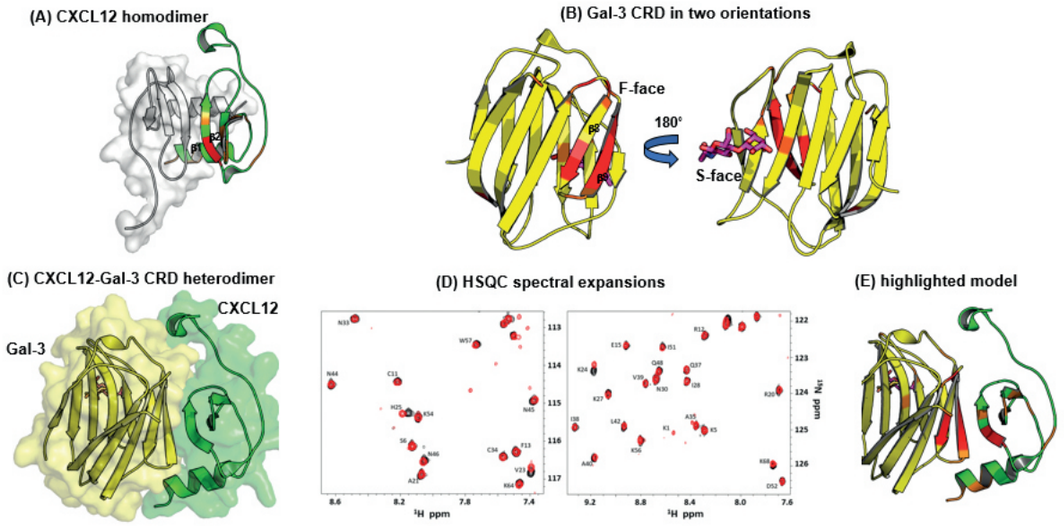

Figure Heterodimer by CXCL12-Gal-3 CRD association. (A) The crystal structure of the CXCL12 homodimer (PDB code 4UAI) is shown with one monomer subunit highlighted in green and red. (B) The structure of the Gal-3 CRD (in yellow and red) bound with lactose (in magenta) (PDB code 1A3K) is shown. (C) A model of the heterodimer formed between CXCL12 (green) and Gal-3 (yellow) derived from NMR-directed protein-protein docking, MD simulations and BFE calculations is shown. (D) Spectral expansions of HSQC data of 15N-labelled CXCL12 in the absence (black contours) and presence (red contours) of unlabelled Gal-3 CRD are shown. (E) The NMR-based heterodimer model is shown with residues that are most perturbed by interactions between Gal-3 and CXCL12 highlighted in red and orange

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Non-coding RNA biology in cardiovascular disease

Christian Weber

We investigate the contribution of non-coding RNAs (ncRNAs) in cardiovascular physiology and pathology. We are particularly interested in mechanisms of regulation, trafficking, and function of ncRNAs in the maintenance of vascular homeostasis and their involvement in the development of vascular diseases, such as atherosclerosis. Our goal is to shed light on the relevance of ncRNAs in the development of vascular disease and to unveil their possible application as therapeutic or diagnostic/prognostic tools in patients with cardiovascular diseases.

Prof. Dr. med. Christian Weber – Group Leader
Dr. Donato Santovito – Group Leader
Dr. Lucia Natarelli, PhD – PostDoc
Dr. Ismail Çimen, PhD – PostDoc
Dr. James M. Henderson, PhD – PostDoc
Dr. Floriana M. Farina, PhD – PostDoc
Zahra Abedi Kichi – PhD Student
Elizabeth Mann-Fallenbuchel – Lab Technician

Non-canonical functions of microRNAs. MicroRNAs (miRNAs) are short (20-25 nucleotide long) ncRNAs mediating post-transcriptional repression of gene expression by pairing with target transcripts in RNA-induced silencing complexes (RISCs), where effector proteins promote decay or transcriptional repression. Our research provides evidence that miRNAs exert their functions also outside of this dogmatic mechanism. We provided the first evidence that miRNAs can directly affect protein functions by biophysical interactions. In particular, we reported how miR-126-5p in endothelial cells can engage in interactions with caspase-3 upon induction of autophagy (e.g., by protective high-shear stress). The binding to miR-126-5p inhibits the proteolytic activity of caspase-3 and limits apoptosis. This ultimately preserves endothelial integrity and protects against the development of atherosclerosis.

Long non-coding RNAs and genomic stability. Long non-coding RNAs (lncRNAs) are RNA transcripts longer than 200 nucleotides that do not translate into protein but contribute to cell biology by epigenetic regulation, miRNA sponging, and direct protein interactions. We have previously identified a novel lncRNA, named lncWDR59, able to regulate endothelial proliferation through the Notch and Wnt/β-catenin pathways. More recently, we studied the role of this and other lncRNAs in the maintenance of genomic stability and in limiting the accumulation of DNA damage upon atherogenic stimuli. Ongoing research focuses on the contribution of lncRNAs in the formation of extranuclear chromatin structures named micronuclei, with the aim of exploiting their use to preserve genomic stability and prevent endothelial dysfunction and atherosclerosis.

COVID19 and vaccine-induced thrombotic thrombocytopenia (VITT). The COVID19 strongly challenged the health system and researchers worldwide focused on molecular mechanisms for treatment and prevention. Analyzing the SARS-CoV-2 genome, we identified motifs in the 5'UTR leader sequence interacting with 57 miRNAs mainly via noncanonical binding modes and the interaction of the transcript of the viral Spike (crucial for the infection) with the lncRNA H19. Beside the disease, the occurrence of thrombocytopenia and thrombosis (VITT) after adenoviral vector– based vaccination has alarmed the public and we proposed a therapeutic approach finding that low concentrations of the Bruton's ty

Key Publications

Santovito D, Egea V, Bidzhekov K, Natarelli L, Mourão A, Blanchet X, Wichapong K, Aslani M, Brunßen C, Horckmans M, Hristov M, Geerlof A, Lutgens E, Daemen MJAP, Hackeng T, Ries C, Chavakis T, Morawietz H, Naumann R, von Hundelshausen P, Steffens S, Duchêne J, Megens RT, Sattler M, Weber C. *Noncanonical inhibition of caspase-3 by a nuclear microRNA confers endothelial protection by autophagy in atherosclerosis.* **Sci Transl Med** 2020;12(546): eaaz2294. doi: 10.1126/scitranslmed.aaz2294. PMID: 32493793.

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Microscopic imaging core facility

Remco Megens, PhD

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

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

The IPEK microscope facility focusses on the application of 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.

The microscope facility of IPEK supports internal and external collaborators and offers several microscope systems: three Leica Thunder microscopes (upright, inverted, organism imager), a Leica SP5IIMP Two photon microscope, and a Leica SP8 3X confocal/STED microscope. IPEK members and collaborators have successfully applied the latter microscopy methodologies in various studies and for various projects (figure). In collaboration with various IPEK groups, the facility will further develop and apply imaging applications for studying various processes and structures of the (diseased) cardiovascular system. Finally, it aims at expanding the optical imaging facility with the latest microscope technology.

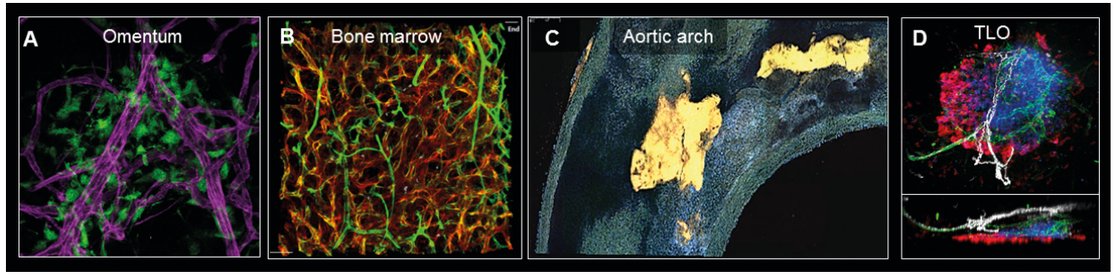


Figure: examples of preliminary image data conducted at the microscope facility: A) Whole mount Omentum imaged in 3D using Thunder microscopy; B) whole mount and optically cleared bone marrow visualized with CLSM; C) whole mount 3D overview of optically cleared aortic arch with label-free plaque visualization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

Shared Ressource Labs

Transgenic and Gene Targeting Technology

Dr. rer. biol. hum. Kiril Bidzhekov

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

Shared Ressource Labs

Cell Sorting and Flow Cytometry

Dr. med. habil. Michael Hristov

BD LSRFortessa

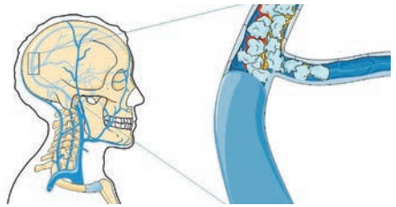
Dr. Johan Duchêne, PhD

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. 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 offers an access to a BD LSRFortessa X-20 cell analyzer that delivers high performance and multicolor analysis. 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

11/2021

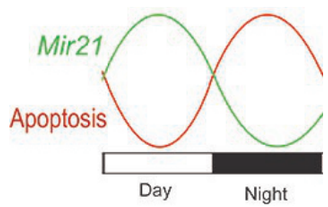
BTK inhibitors against vaccine-related thrombotic complications



IPEK scientists propose treatment for rare, life-threatening complication from Astra-Zeneca vaccine. Certain drugs used in cancer therapy, known as BTK inhibitors, are able to normalize the pathological activation of platelets with associated blood clot formation which occurs in rare cases after vaccination with the Astra-Zeneca COVID-19 vaccine. This is reported by IPEK director Christian Weber and colleagues in the latest issue of the New England Journal of Medicine. Weber calls the development "an urgently needed way of treating this worrying vaccine complication." Germany has seen well over twelve and a half million doses of Astra-Zeneca's Vaxrevia vaccine administered so far, and over 67 million doses have been given EU-wide. The severe side effect known as VITT (vaccineinduced immune thrombotic thrombocytopenia) that has been the subject of much attention occurs in about one to one and a half out of 100,000 vaccinations, "so it is a rare but life-threatening side effect with high mortality," says Weber. Moreover, many more doses of the Astra-Zeneca vaccine have been and are being donated to countries in need around the world, making VITT a global problem.

08/2021

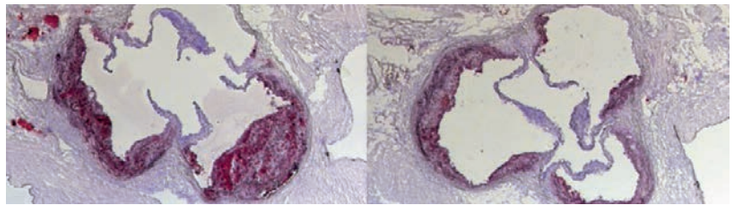
Why the risk of heart attack is higher early in the day



In the journal Circulation, a team led by IPEK scientists Maliheh Nazari-Jahantigh and Andreas Schober provides an answer. The risk that an atherosclerotic plaque will rupture varies with the time of day. That's why heart attacks and strokes are more likely to occur in the morning than at other times.
A normal day/night schedule of activity reduces the risk of heart attack, but circadian processes that take place within plaques can enhance the risk of rupture. The action of microRNA-21 causes more cells in plaques to die at the beginning of the active phase in the morning – at a time when they cannot be disposed of efficiently. The ensuing accumulation of dead cells amplifies the risk of plaque rupture.

07/2021

Atherosclerosis and the immune system



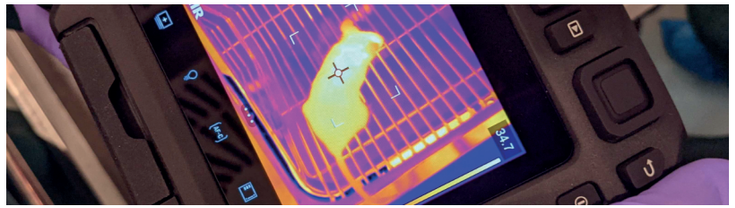
Atherosclerosis is characterized by the build-up of cholesterol and other fatty metabolites in the arterial wall directly below the endothelial cell layer, which is in direct contact with the bloodstream. This process results in constriction of the artery, which obstructs blood flow and can trigger heart attacks and strokes. Atherosclerosis is generally treated with drugs that reduce the concentration of lipids in the circulation, often using compounds called statins. However, statins effectively reduce the risk of cardiovascular disease in only 35 to 40% of the patients treated. The remaining 60% fail to respond to the medication.
This has prompted the search for other drug targets. Since atherosclerosis is linked to chronic inflammatory processes, the immune system might offer new therapeutic options for tackling the disease. A group of researchers led by Professor Esther Lutgens and Dr. Dorothee Atzler from the LMU Medical Center have now elucidated an important component of the immune reaction involved in atherogenesis.
Lacy et al. have now shown that the interaction between proteins called CD40L and CD40 represents a promising drug target for the suppression of atherosclerosis. The protein CD40L is synthesized by, and expressed on the surface of specialized cells of the immune system. It is recognized by the CD40 protein, a membrane-bound receptor that is expressed on antigen-presenting cells. Their group is now extending their studies of the effects of CD40 und CD40L to other cell types, with the aim of developing drugs that can inhibit the functions of these proteins in a cell-specific fashion.

News Research

News Research

01/2021

Brown fat can burn calories : listen to IPEK scientist Alexander Bartelt on radio



Hibernators convert fat into heat to survive the cold season. 'Humans have also retained this ability' says IPEK scientist Alexander Bartelt who researches brown fat - and has written a book about it. You can now listen to the interview he gave on Deutschland Rundfunk with Ute Welty.
Too much body fat promotes disease. It strains the metabolism, circulation and musculoskeletal system. However, the "good" brown fat is considered to be the counterpart of the "bad" white fat. Unlike white fat, it does not store energy in the body, but can convert energy into heat.
Brown fat was discovered as early as the 16th century and initially assigned exclusively to hibernators among animals, says Alexander Bartelt.
Using body scans, brown fat has also been detected in humans, Bartelt explains. Brown fat is located primarily on the collarbone and along the spine, he says.
"Brown fat tissue is activated by cold. That means when you go for a walk or put a foot in an ice-cold bath, the skin signals that to the brain. It sends a cold stimulus, which is relayed to the brown adipose tissue. And what the cells then do: they actively start converting stored calories, but also just calories that they're getting from the rest of the body, into heat."

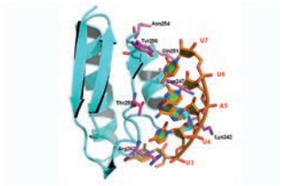
11/2020

Reduce heart attack risk after infections

After an infection, the risk of a heart attack in cardiovascular risk patients increases up to twenty times. IPEK scientists have found that the immune cells are involved in this in a mouse model However, specific molecules and antibodies can slow down the immune cells and protect risk patients after an infection.
In mice, Oliver Söhnlein and his team mimicked an acute bacterial infection to understand the increased risk of heart attack better. The mice also had atherosclerosis and were, therefore, a suitable model for cardiovascular patients at risk of infarction. In atherosclerosis, the blood vessels' inner wall is chronically inflamed, and deposits called plaques form. When these deposits break loose, they can trigger a heart attack or stroke.
The researchers observed that the infection increased the size of the mice's plaques and boosted inflammation.

06/2020

How a miRNA binds and inhibits Caspase-3 to confer vascular integrity



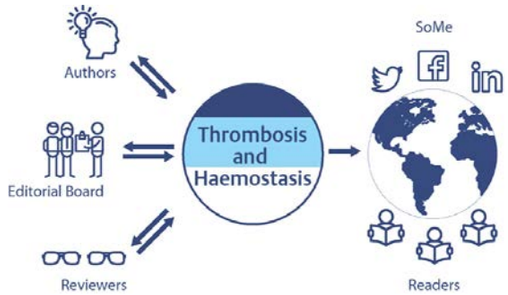
Short RNA molecules known as microRNAs (miRNAs) play a vital role in the regulation of gene expression. Anomalies in miRNAs expression and function have been implicated in pathological processes, such as the development of chronic diseases like atherosclerosis. The regulatory functions of miRNAs usually take place in the cytoplasm, where they interact with target RNA transcripts to inhibit their translation into protein or promote their decay.
IPEK Reseracher Donato Santovito and colleagues have now described an exceptionally different mode of action. By investigating a miRNA named miR-126-5p, Christian Weber's team demonstrates that this molecule can unexpectedly be transferred into the cell nucleus and, by simply interacting with it, suppresses the activity of an enzyme, named caspase-3, which is responsible for killing the cell by programmed cell death. In this way, the molecule protects vascular integrity and reduces the extent of atherosclerotic lesions.
Atherosclerosis is often referred to as "hardening of the arteries" and underlies the development of cardio- and cerebrovascular diseases which represent the main cause of death worldwide. The condition occurs almost exclusively at bifurcations of the arterial tree, where turbulence of blood flow promotes damage to the endothelial cells that line the vessels, favoring the recruitment of inflammatory cells and the eventual development of atherosclerotic plaques. Endothelial cells express particularly high concentrations of miR-126-5p to protect them from damage. The new study set out to uncover the molecular mechanisms that mediate this function. The results demonstrate that the protective effect is initiated by the high shear stress imposed on the endothelial cells by the laminal flow of blood over their surfaces.

Journal Aims and Scope

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

2020-2021

The Impact factor (2020 / 2021 5.25) and CiteScore have maintained a stable trend in comparison to others in the field, specifically reflected by the CiteScore Percentile in the category hematology, which matched near 90th, over the past 5 years.
The full retro-digitalization now lets readers browse through issues dating back to he first published issue in 1957 (then under the name Thrombosis et Diasthesis Haemorrhagica) TH Open, the open access companion



journal of Thrombosis and Haemostasis launched in 2017, is now listed on PubMed Central and the Directory of Open Access Journals. Its unique "pay-what-you-want" policy gives everyone a chance to submit open access. As such, all articles in TH Open are freely available at www.thieme.com/tho.
With the successful move to the Thieme Publisher group, Thrombosis and Haemostasis got a new cover design visually matching the very distinct look from Thieme, a very strong brand which is known worldwide for high-quality medical publishing.

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Thrombosis and Haemostasis

Teaching (Selection)

Atzler D	Dosierübungen/DANI Seminar
Bartelt A	Cardiovascular, Lung and Metabolism
Bidzhekov K	Classical and modern strategies in mouse transgenesis (7C0482)
Bidzhekov K	BioImaging (19184)
Döring Y	Biochemische Grundlagen der Arteriosklerose
Döring Y	Research School Vascular Biology / Immunology
Döring Y	Immune cell crosstalk in inflammation
Döring Y	The adaptive immune system in inflammatory disease, vascular biology and atherosclerosis
Duchene J	Flow Cytometry & Optical Imaging – Seeing is Believing (7C0741)
Duchene J	Flow Cytometry in Clinical Practice (7C4071)
Megens R	BioImaging (19184)
Megens R	Cardiovascular, lung and metabolism (19476)
Ries C	Anleitung zum experimentellen wissenschaftlichen Arbeiten auf dem Gebiet der Molekularund Zellbiologie im Rahmen von Doktor- und Masterarbeiten 7C0479
Ries C	Kolloquium über die neuesten Forschungsergebnisse zu molekularen Mechanismen der Zellmigration und Differenzierung 7C0478
Ries C	Neue Einblicke in die mikroRNA-Analyse.
Schober A	Cardiovascular, Lung and Metabolism (19287)
Schober A	Practical training in performing independent scientific work in the field of experimental vascular medicine (7C0365)
Schober A	Discussion of scientific literature on experimental vascular medicine (7C0366)
Schober A	Macrophage biology in atherosclerosis (7C0462)
Schober A	MicroRNAs in vascular pathogenesis (7C0461)
Schober A	Molecular Mechanisms of vascular remodeling (7C0363)
Schober A	Experimental vascular medicine (7C0364)
Steffens S	Current Topics (19202)
Steffens S	Bioimaging (19199)
Steffens S	Cardiovascular, Lung Metabolism (19223, 19224, 19287)
Von Hundelhausen P	Echokardiographie (7M3410)
Von Hundelhausen P	Ausgewählte Kapitel aus der Pathophysiologie vaskulärer Erkrankungen (7C0302)
Von Hundelhausen P	Master Lecture Series SFB1123 (7C0438)
Von Hundelhausen P	Struktur-Funktionsanalyse von Protein-Proteininteraktionen. (7C0434)
Von Hundelhausen P	BioImaging - Practical course und Seminar (19199)

Teaching

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

Doctoral researchers enrolled in the IRTG program are offered a three-year structured PhD program, allowing the students to collect the necessary ECTS points to obtain their PhD in Medical Research. MD students are welcome to join the study program for the duration of their medical thesis research project in the lab. IRTG 1123 students are located at LMU, TUM and Helmholz and are encouraged to choose individual seminars, lectures or courses offered by other organizations and graduate schools.

In 2021, about 30 students were enrolled in the IRTG 1123 while an additional 26 students were associated to us, working on related topics in participating CRC research groups. In addition to our biweekly IRTG 1123 seminar series, we also offered methods courses on editing, processing and analysis of scientific images; on ethics in research publications, on figures and illustrations; on effective visual communication for scientists and on advanced image analysis and macro scripting.
The 2021 IRTG 1123 annual retreat coincided with the 9th "Cardiac Regeneration and Vascular Biology" Conference that took place as a hybrid event on the campus of the Venice International University (VIU) on the island of San Servolo in Italy and online. From October 18th until October 20th, 2021, the PhD students could profit from the presence of renowned national and international scientists and researchers from the fields of cardiac regeneration and vascular biology. Alongside the speaker lectures, there were Poster Sessions and a Young Investigator Award Competition. Four PhD students were selected and received the opportunity to present their work in form of a short talk.

Hosted by Prof. Dr. rer. nat. Sabine Steffens, Prof. Dr. rer. nat. Jürgen Bernhagen and Prof. Dr. Christian Kupatt, the event was realised in close cooperation between the LMU Klinikum and the TU Munich and was funded by the Deutsche Forschungsgemeinschaft, the Deutsches Zentrum für HerzKreislauf-Forschung and the Munich Heart Alliance.

Graduate School

Student Name, Lab, Start/complete date

S. Kotschi, Bartelt Lab, Started 2020
I. Arigoni, Bartelt Lab, Started 2021
A. Wallney, Bartelt Lab, Started 2021
J. Caca, Bartelt Lab, Started 2022
Y. Kechur, Bartelt Lab, Started 2022
S. Gencer, Döring Lab, Completed 2022
M. Aslani, Duchene/Megens Lab, Completed 2021
M. Bianchini, Duchene/Megens Lab, Completed 2020
Yuanfang Li, Habenicht Lab, Completed 2021
L. Zang, Ries Lab, Started 2017
Z. Abedi Kichi, Santovito/Weber Lab, Started 2018
B. Avsec, Schober Lab, Completed 2022
R. Mohibullah, Schober Lab, Started 2017
S. Saboor Maleki, Schober Lab, Started 2018
M. Kakar, Schober Lab, Started 2017
N. Li, Schober Lab, Started 2020
I. Baatsch, Schober Lab, Started 2018
A Popal, Schober Lab, Started 2018
D. Hering, Steffens Lab, Completed 2022
M. Hilby, Steffens Lab, Started 2016
M. Volz, Steffens Lab, Started 2017
B. Schopohl, Steffens Lab, Started 2018
L. Keidel, Steffens Lab, Started 2019
Y. Wang, Steffens Lab, Completed 2023
B. Chen, Steffens Lab, Completed 2023
G. Shakir, Steffens Lab, Started 2020
A. Kaltenbach, Steffens Lab, Started 2021
G. Li, Steffens Lab, Started 2021
S. Yi Xuan, Steffens Lab, Started 2021
V. Eckardt, Von Hundelshausen Lab, Completed 2021
R. Duan, Von Hundelshausen Lab, Started 2017
J. Leberzammer, Von Hundelshausen Lab, Started 2016
Ya Li, Von Hundelshausen Lab, Started 2020
T. Lakomiec, Von Hundelshausen Lab, Started 2019

Theses

Project	Sponsor *Reference*	Principal Investigator *Collaboration Partner*	Time frame
Role of the chemokine receptor CCR8 in DC/T-cell crosstalk during atherosclerosis	DFG, CRC 1123, A1	Y. Döring C. Weber	2018-2022
Physical and functional interactions of chemokines with potent inflammatory effectors in atherosclerosis: focus on galectins	DFG, CRC 1123, A2	P.v. Hundelshausen H.-J. Gabius	2018-2022
Master switches of T-cell reactivity in atherosclerosis	DFG, CRC 1123, A5	E. Lutgens D. Atzler	2018-2022
Role of ACKR1/DARC in the myeloid pathogenesis of atherosclerosis	DFG, CRC 1123, A10	J. Duchene C. Weber	2018-2022
miRNA-regulated energy metabolism in macrophage-derived foam cells	DFG, CRC 1123, B04	M. Nazari-Jahantigh, A. Schober	2018-2022
Role of peripheral CB1 receptors in atherosclerosis	DFG, CRC 1123, B09	S. Steffens, S. Herzig	2018-2022
Integrated Research Training Group	DFG, CRC 1123, MGK	S. Steffens, J. Viola	2018-2022
B Cell Autoimmunity in ApoE-deficient ($ApoE^{-/-}$) Mice	DFG, YI 133/3-5	C. Yin A. Habenicht	2019-2022
The role of the arginine/arginase 1 metabolism in atherosclerosis	DFG (451372580) AT 172/3-1	D. Atzler	2021-2023
MicroRNA let7-b and long non-coding RNAs in endothelial regeneration during atherosclerosis	DFG NA 1373/2-1	M. Nazari Jahantigh	2017-2021
Role of microRNA-147 in adipose tissue macrophages during obesity	DFG ZH908/2-1	M. Zhu	2020-2023
IRONBAT	DFG-SPP2306	A. Bartelt	2021-2024
Role of GPR55 in atherosclerosis	DFG STE1053/6-1	S. Steffens	2018-2021
Mechanisms of pericardial fat activation after myocardial infarction	DFG STE1053/8-1	S. Steffens	2021-2023
Structural basis and mechanisms of strand-specific microRNA trafficking and function in cardiac disease	DFG TRR267, A2	C. Weber M. Sattler	2019-2023
Role of ChemR23 on macrophages in perivascular adipose tissue in atherosclerosis	DZHK-Förderlinie 'PostDoc Start up – late career'	Y.Döring	2019-2020
Establishing a new interplay between PCSK9 and chemokine receptors in chronic vascular inflammation	DZHK-Förderlinie 'Promotion of women scientists'	Y.Döring	2019-2020
The aryl hydrocarbon receptor (AhR), a friend that turns out to be a foe?	DZHK-Förderlinie 'PostDoc Start up – late career'	E. van der Vorst	2020-2021
Re-screening for novel CD40-TRAF6 interaction inhibitors (TRAF-STOPs 2.0)	DZHK TRP	D. Atzler E. Lutgens C. Weber	2021-2022

Third Party Funding

Project	Sponsor *Reference*	Principal Investigator *Collaboration Partner*	Time frame
The role of T cell H3K27 trimethylation on T cell polarization and its effects on atherosclerosis	DZHK Shared Expertise (81X2600262)	D. Atzler M. Lacy E. Schwedhelm	2021-2022
Immuno-metabolic phenotyping of the amino acid homoarginine in atherosclerosis	DZHK women scientist (81X3600219)	D. Atzler	2020-2022
Genetic discovery-based targeting of the vascular interface in atherosclerosis	DZHK-BHF	J. Duchene C. Weber	2019-2022
Pericardial immune cell cross talk in cardiac repair and remodeling	Federal Ministry of Research & Education (BMBF), DZHK 81Z0600205	S. Steffens	2019-2025
ERA-CVD NEMO-IMMUNE	Federal Ministry of Research & Education (BMBF)	S.L. Puhl	2019-2022
Immune-Lipid Crosstalk Research group	Aachen Interdisciplinary Center for Clinical Research grant	E. van der Vorst	2019-2021
AtheroInside. Local immunomodulation of atherosclerosis by CD8+ T cell-based nanomedicines	ERA-CVD	R. Megens	2019-2023
CD40 goes innate	ERC Consolidator (681493)	E. Lutgens	2018-2022
PROVASC: Cell-specific vascular protection by CXCL12/CXCR4	ERC AdG°682511	C. Weber	2016-2022

Project	Sponsor *Reference*	Principal Investigator *Collaboration Partner*	Time frame
Fighting Atherosclerotic Plaques in Coronary Artery Disease Via Targeting Neuroimmune Interfaces	ERA-NET on Cardio Vascular Diseases (ERA-CVD), PLAQUEFIGHT	A. Habenicht G. Lembo Z. Mallat T. Guzik	2018-2023
Elucidating the cellular and molecular mechanisms behind the pro-atherogenic role of miRNA-26b	Fritz-Thyssen Stiftung	E. van der Vorst	2021-2023
The role of GITR in atherosclerosis	Novo Nordisk	E. Lutgens	2021-2024
Targeting immune-lipid crosstalk in cardio-metabolic diseases: focus on myeloid cells	NWO-ZonMw Veni	E. van der Vorst	2019-2021
Unravelling consequences of SARS-CoV-2 mediated inflammatory immune responses in heart and vasculature	SNF NRP 78 Project “CoVasc”, main applicant of a consortium with three other applicants	Y.Döring N.Mercader 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
Unravelling the role of vascular ChemR23 expression in atherosclerosis	Swiss Heart foundation	Y.Döring	2021

Research Networks

Leducq Transatlantic Network of Excellence

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

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

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

National Institute of Health

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

Munich Heart Alliance

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

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

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

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

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

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

Research Networks and Project Funding

DFG Sonderforschungsbereich 914

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

VIAgenomics
BHF-DZHK Partnership

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

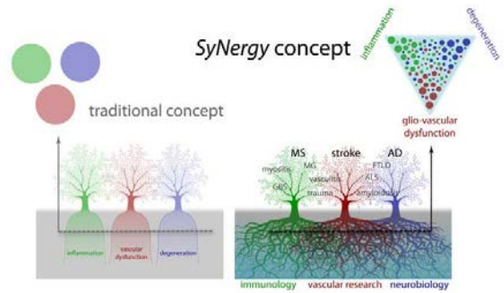
The researchers plan to combine innovative computational and experimental methods to understand the role of these risk genes at the vascular interface and to identify novel drug targets for therapies.

DFG Collaborative Research Centre
Transregio TRR 267

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

Munich Cluster for Systems Neurology

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



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

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

Large-scale Project Funding

ERC Advanced Grant PROVASC

Professor Dr. med. Christian Weber, Director of IPEK and Chair in Vascular Medicine at LMU has been awarded his second ERC Advanced Grant. This ERC Grant entitled PROVASC is an exceptional distinction for Weber, who is one of the few researchers to receive the honor of a second award in the course of his career to date. Atherosclerosis is a major cause of morbidity and premature death in modern societies, and the principal goal of all of Christian Weber's research is to contribute to our understanding of this condition and to identify new drug targets opening up new routes more effective and personalized treatment. Weber analyzes the molecular mechanisms involved in the pathogenesis and progression of the disorder. Commonly known as hardening of the arteries, atherosclerosis is primarily characterized by the development of fatty deposits on the inner surfaces of major blood vessels, which provoke chronic inflammation that leads to obstruction of blood flow. In his first ERC Advanced Grant, entitled "Atheroprotect", he studied the role of pro-inflammatory signal proteins which control the immune response that initiates the inflammation process and hampers its timely resolution. The title of his new ERC project is PROVASC, which will be devoted to elucidating the mechanisms responsible for "cell-specific vascular protection by CXCL12/CXCR4". CXCL12 is a signal protein which binds to the receptor CXCR4, which in turn activates a particular homeostatic signal pathway. Moreover, studies of genetic variation in human populations have indicated that this pathway can protect the vasculature against atherosclerosis. Weber plans to characterize the downstream signal relay and elucidate the basis for its ability to reduce the risk of developing atherosclerosis. To this end, he will investigate the effects of defined genetic risk variants on the activity of the CXCL12/CXCR4 pathway, and explore ways of modulating its action in a targeted fashion. Interestingly, so-called microRNAs – short RNA fragments that are involved in regulating the synthesis of specific proteins – have been implicated in the pathway and offer possible targets for new therapies.

DFG Collaborative Research Centre 1123

Atherosclerosis - Mechanisms and Networks of Novel Therapeutic Targets

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-the-art, 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 high-impact 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 atheroscleorsis with minimal side effects on immune responses or homeostatic activities.

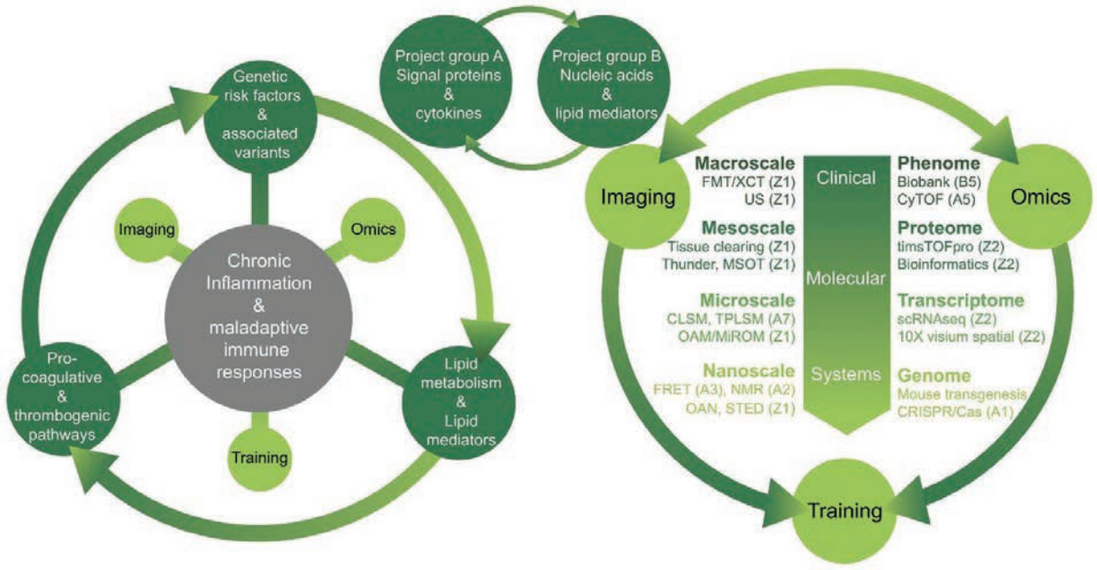


Figure: CRC 1123. Complex pathogenesis of atherosclerosis: mechanistic links of target pathways and central technologies.

Performance Report 2020

Number of budget-funded scientific employees: 23
Number of budget-funded non-scientific employees: 19
Number of all externally funded employees: 75

Third party funds spent (in €):

Source	Number of projects	Funds spent 2020
DFG	35	3.952.012
BMBF, StMWFK	20	1.544.473
EU	6	1.169.598
Foundations (Humboldt, Foundation Leducq, etc...)	9	250.576
Total external third party funding	70	**6.916.659**

Source	Number of projects	Funds spent 2020
FöFoLe	1	54.408
PhD Fellowship	2	4.102
Total internal third party funding		**58.510**
Total third party funding spent		**6.975.169**

Performance Reports

Performance Report 2021

Number of budget-funded scientific employees: 21
Number of budget-funded non-scientific employees: 17
Number of all externally funded employees: 52

Third party funds spent (in €):

Source	Number of projects	Funds spent 2021
DFG	38	3.935.720
BMBF, StMWFK	23	1.758.667
EU	5	722.843
Foundations (Humboldt, Foundation Leducq, etc...)	7	143.563
Total external third party funding	75	**6.560.793**

Source	Number of projects	Funds spent 2021
FöFoLe	1	2.613
PhD Fellowship	2	7.861
Total internal third party funding		**10.474**
Total third party funding spent		**6.571.267**

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

Position	Total	Budget funded 2020-2021	Third-party funded 2020-2021
Institute Director	1	1	
Professors	15	15	
Research Group Leaders	13	7	6
Postdoctoral Researchers	30	9	21
PhD candidates	34		34
Non-scientific Staff	33	19	14
Total	126	51	75

Due to overlapping distribution of tasks mainly in basic science and partly in clinical science staff, the total number of employees amounts to **126 persons**. This number also includes staff members who are funded by grants and/or work 50-75% part-time at IPEK.

Key Figures

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Zhu, Mengyu, MSc

2020

	n	IF Sum	IF Average
Original articles	39	520,6	13,3
Reviews	39	325,2	8,3
Total number of articles	78	845,8	10,8
First/Last authorship by IPEK	42	446,3	10,6

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2021

	n	IF Sum	IF Average
Original articles	60	732,5	12,1
Reviews	41	447,8	10,9
Total number of articles	101	1180,3	11,6
First/Last authorship by IPEK	52	626,6	12,0

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Art at the Garden Pavillion, "The Snowmermaid"

By: Mohammad Rafiee Monjezi; Yutao Li; Xinyi Deng (in picture) and Rui Su; Mingyang Hong.

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