LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

2016/2017

JAHRESBERICHT

Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten (IPEK)

Vorwort

Die vergangenen zwei Jahre haben dem Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten (IPEK) eine Fülle von erfreulichen Entwicklungen und Erfolgen beschert. „Tempus fugit“ möchte man meinen, umso mehr ein Grund inne zu halten und einige dieser Ereignisse zu rekapitulieren. Nach den ersten Akzenten der Neuausrichtung im Zuge der Wiederbesetzung des Lehrstuhls für Vaskuläre Medizin zeichnen sich nun eine deutliche Profilierung und Konsolidierung sowie eine weitere Schärfung des wissenschaftlichen Fokus ab. Die neu entstandenen Strukturen, Drittmitteleinwerbungen und exzellente publikatorischen Leistungen sowie vor allem neu rekrutierte zusätzliche Leistungsträger und hoffnungsvolle Nachwuchswissenschaftler sollen Ihnen in der nun vorliegenden Ausgabe 2016/2017 unseres biannualen Jahresberichtes vorgestellt werden. Dies soll Ihnen spannende, überraschende und vielleicht zum Teil erhoffte Einblicke in die Arbeit des IPEK vermitteln und vielleicht auch Ausblicke ermöglichen und weiteres Interesse wecken. Besonders hervorzuheben ist hierbei, dass diese Arbeiten die Grundlage für eine erfolgreiche Verlängerung des SFB1123 für eine zweite Förderperiode 2018-2022 gelegt haben.

In bewährter Tradition finden Sie so auch alle wichtigen Kontaktinformationen und Ansprechpartner für eine Zusammenarbeit mit dem IPEK hilfreich und relevant sein könnten. Damit hoffen wir, Ihnen auch in diesem Jahr eine kurzweilige, aufschluss- und erkenntnisreiche Übersicht über die Aktivitäten in Forschung und Lehre sowie der mögliche Translation neuester Befunde in die vaskuläre Diagnostik und Therapie zur Lektüre empfehlen zu dürfen.

Im Namen des IPEK-Teams

Univ.-Prof. Dr. Christian Weber
Ordinarius und Institutsdirektor

Editorial

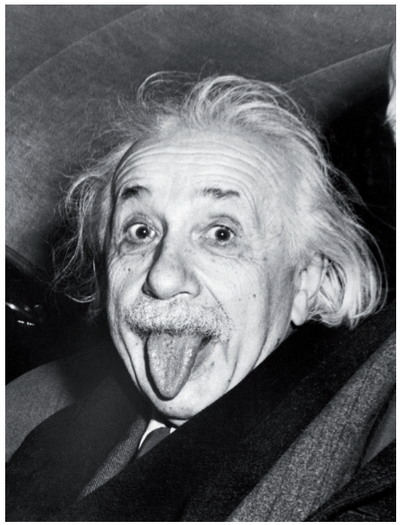
God does not play dice - Der Alte würfelt nicht. (Albert Einstein)

Mit dem diesjährigen Editorial möchte ich ein wenig die Grenzen unserer in den Lebenswissenschaften gewonnen Erkenntnisse erweitern bzw. sogar überschreiten. Heinrich von Kleist hat einen großartigen Text geschrieben, bei dem schon im Titel „Über die allmähliche Verfertigung der Gedanken beim Reden“ die Prämisse aufscheint. Ein vergleichbar dynamisches Prinzip gilt für die allmähliche Entwicklung der Gedanken beim Schreiben. Bei der Suche nach Themen, die mich in den letzten beiden Jahren am meisten bewegt haben, bin ich über den kosmologischen Nachweis von Gravitationswellen, die nicht zuletzt einen wesentlichen Beitrag dazu geleistet haben, dass sich Einsteins theoretische Vorhersagen bewahrheitet haben, zu einem jüngeren physikalischen Befund gelangt, der im Widerspruch zu Einsteins Theorien steht. Ein internationales Experiment, der Big Bell Test (benannt nach dem Physiker John Stewart Bell), hat die Verletzung der Bellschen Ungleichung bestätigt (Nature 2018), anhand derer sich die Gültigkeit von Annahmen der klassischen Physik gegenüber jenen der Quantenphysik überprüfen lässt.

Weltweit mehr als 100,000 Menschen haben Ende November 2016 zu diesem einzigartigen Versuch der Quantentheorie beigetragen, indem sie durch die Erzeugung von Zufallsdaten auf vernetzten Smartphones oder vergleichbaren Geräten unvorhersehbare Zufallsdaten erzeugten, auf deren Basis bestimmt wurde, wie miteinander verschränkte aber an verschiedene Orte verbrachte Partikelpaare wie Atome, Photonen oder Supraleiter Messungen (z.B. Farbe oder Ankunftszeit) unterzogen wurden, um so ein Schlupfloch in der Testung von Einsteins Prinzip der lokalen physikalischen Realität zu schließen. Sollten die Messungen übereinstimmende Ergebnisse aufweisen, unabhängig von den gewählten Messparametern, impliziert dies ein verblüffendes Enigma: entweder die Messung des einen Partikels beeinflusst ohne jede zeitliche Verzögerung das weit entfernte Partikel, oder die Eigenschaft war nie real existent, sondern wurde durch die Messung selbst erschaffen. Beide Möglichkeiten stehen in klarem Widerspruch zu Einsteins Weltsicht, dass eine lokale Realität vulgo das Universum unabhängig von unserer Beobachtung existiert bzw. keine Information darin schneller als Licht übertragen werden kann.

Zum einen wird durch den menschlichen Zufallsgenerator des Big Bell Tests das Schlupfloch der Wahlfreiheit geschlossen, also dass die verschränkten Partikel selbst die Art der Messung beeinflussen, etwa indem Sie mit den physikalischen Systemen zusammenwirken. Zum anderen wird so das Element des freien Willens eingeführt, das von den Partikeln völlig unabhängig ist. Sowohl Vorgehensweise wie auch die Befunde bergen auch eine philosophische Dimension, die sich fast nahtlos mit Arthur Schopenhauers Erkenntnistheorie in *Die Welt als Wille und Vorstellung* verknüpfen lassen. Auf Basis der Apriorität von Raum, Zeit und Kausalität sei die Vorstellung ein Produkt von vier mentalen Funktionen, des Verstandes, der Vernunft, der Sinne und des Selbstbewusstseins. Diese ergeben gemeinsam die Wurzel des Satzes vom zureichenden Grund von Leibniz, der besagt, dass alles, was ist, einen Grund hat *(Nihil sine ratione).* Alles, was wir mit unseren Sinnen auffassen, würde stets in Strukturen zur Wahrnehmung für das erkennende Subjekt gebracht. Wir sind physisch und durch die Vorstellung vom An-sich der Dinge getrennt. Die Welt als Vorstellung für das Subjekt ist eine Auffassung von Objekten, die in dieser Weise an sich nicht existent sind. Schopenhauer meint weiter, dass die Vorstellung wie die Individualität dem Willen unterworfen, mithin dessen Produkte seien. Jedes Individuum besitzt demnach eine eigene Vorstellung von Realität, an der die Außenwelt als Teil einer Subjekt-Objekt-Beziehung gemessen wird, ganz wie die Messung der Partikel. Inwieweit metaphysische Interpretationen für das miteinander verschränkte Verhalten weit entfernter Teilchen Rückschlüsse auf Erklärungsansätze für Transzendenz erlauben oder gar Grundlage für deren Nachweis bilden könnten, bleibt der Vorstellungskraft jedes Einzelnen überlassen. Auch wir bauen bei der Aufklärung komplexer Mechanismen, therapeutischer Zielstrukturen und genetischer Determinanten der Atherosklerose auf die Phantasie und Kreativität unserer Wissenschaftler. Oder, um mit Einstein, gewohnt pointiert, zu schließen: *Imagination is more important than knowledge.*

Christian Weber



Inhaltsverzeichnis

Institutsdirektor

Univ.-Prof. Dr. med. Christian Weber
Ordinarius und Institutsdirektor

Prof. Dr. Christian Weber, LMU München, hat als herausragender Wissenschaftler und Internist wegweisende Beiträge zu einem besseren Verständnis der Pathogenese der Atherosklerose als Grundlage für neue Therapieformen erbracht. Seine konzeptionellen und technischen Innovationen haben international Maßstäbe für die Innere und Vaskuläre Medizin gesetzt. Auf Basis seiner Arbeit als Sprecher wurde von der Deutschen Forschungsgemeinschaft 2014 erstmals ein Sonderforschungsbereich (SFB 1123) zum Thema *Atherosklerose und therapeutische Zielstrukturen* eingerichtet. Über viele Jahre hat Dr. Weber die Rolle von Entzündung und Immunmediatoren in der Atherosklerose maßgeblich definiert. Dabei hat er Pionierarbeit zur mechanistischen Aufklärung der Funktion von Chemokinen und microRNAs in der Atherosklerose geleistet und eine Reihe bahnbrechender Entdeckungen gemacht, die über die Innere Medizin hinaus fundamentale Relevanz und hohes translationales Potential haben.

Plättchen sind eine wichtige Quelle für Chemokine, deponieren diese auf aktiviertem Endothel und befördern so die entzündliche Rekrutierung von Monozyten und die Entstehung atherosklerotischer Plaques *(Circulation 2001; Nat Med 2003).* Die Chemokinrezeptoren CXCR2 und CXCR4 wurden als Signalrezeptoren für das Zytokin MIF *(macrophage migration inhibitory factor)* identifiziert und vermitteln die entzündliche und atherogene Leukozytenrekrutierung *(Nat Med 2007).* Die weitere Strukturanalyse und systematische Kartierung dieser sowie heteromerer Chemokininteraktionen, z.B. von CCL5 mit CXCL4 oder CCL17, die funktionelle Synergie oder Inhibition bedingen, erlaubte die Entwicklung zyklischer Peptide, welche diese Effekte spezifisch unterbinden und so weitgehend ohne Neben-wirkungen Atherosklerose und Entzündung hemmen können *(Nat Med 2009; Sci Transl Med 2017).*

Dagegen sind atheroprotektive Funktionen des Chemokinrezeptors CXCR4 und des Liganden CXCL12 durch die Kontrolle der Homöostase neutrophiler Leukozyten und Förderung der endothelialen Integrität erklärbar und via des erstmals gezeigten interzellulären Transfers einer microRNA (miR-126-3p) durch apoptotische Mikropartikel regulierbar *(Circ Res 2008; Sci Signal 2009; Circulation 2017).* Auch der Komplementärstrang miR-126-5p bzw. Mimetika vermitteln Atheroprotektion, indem über DLK1 Suppression die proliferative Reserve des Endothels an arteriellen Prädilektionsstellen mit gestörtem Fluss regeneriert wird *(Nat Med 2014).* Eine alternative Form der Hämatopoese mit hyperaktiven Neutrophilen wurde in Duffy-negativen Individuen afrikanischer Herkunft mit DARC/ACKR1 Genpolymorphismus und fehlender Expression auf erythroiden Zellen im Knochenmark entdeckt, was erstmals ethnische Unterschiede bei Entzündung und Atherosklerose *(Nat Immunol 2017)* erklären kann.

Bisher haben diese Befunde zu 550 Publikationen (350 Originalia, davon 113 als Erst-/Letztautor) mit einem kumulativen Impact-Faktor > 4.800 geführt, die bisher > 32.000/45.000-mal zitiert wurden und einen h-Index von 95/112 (Scopus bzw. GoogleScholar) erzielt haben. Diese im Fach herausragenden Leistungen wurden von Stiftungen und Gesellschaften durch eine Vielzahl nationaler und internationaler Preise gewürdigt. So wurden Dr. Weber der GlaxoSmithKline Wissenschaftspreis, Paul-Martini-Preis, Arthur-Weber-Preis, Alexander-Schmidt-Preis, Outstanding Achievement Award der ESC, ATVB Special Recognition Award der AHA und Galenus von Pergamon-Preis zugesprochen. Weiter fungiert er als VICI-Preisträger und Professor der Universität Maastricht, Editor-in-Chief von *Thrombosis & Haemostasis* und Senior Editor von *Arteriosclerosis, Thrombosis & Vascular Biology*. Als seltene Auszeichnung auf europäischer Ebene hat Dr. Weber zwei ERC Advanced Grants erhalten und wird von dem Informationsportal ExpertScape als weltweit führender Experte für Atherosklerose gelistet.

Als akademischer Lehrer hat sich Dr. Weber der aktiven Förderung und dem Mentoring der nächsten Forschergeneration verschrieben und hat > 20 Doktoranden und > 17 Postdoktoranden betreut. Mit seiner Unterstützung haben sich viele Nachwuchswissenschaftler zu wichtigen Persönlichkeiten der internationalen Atherosklerose-forschung entwickelt, und Professuren oder Ordinariate erhalten, z.B. Profs. Lutgens, Zernecke, Schober, Soehnlein und Gerdes. Der globalen Gefäßmedizin hat er als Führungspersönlichkeit vieler Organisationen, z.B. ESC, IVBM und DZHK, wichtige Dienste erwiesen.

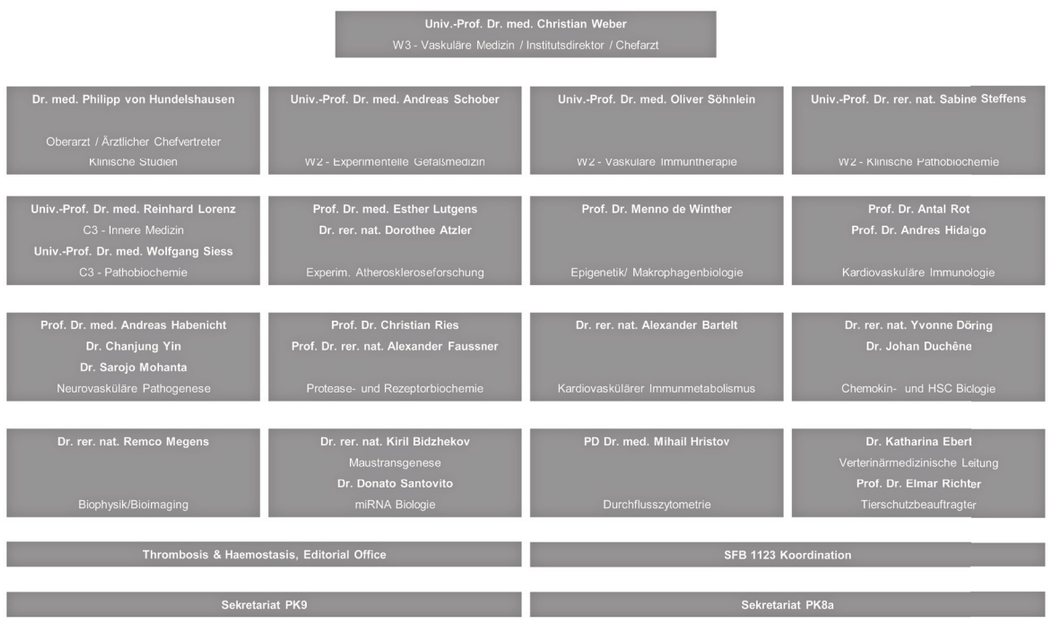
English

Christian Weber is the 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. His group has a strong interest in the molecular interactions and pathophysiological functions of chemokines and immune cell subsets, as well as the role of microRNAs and their targets in vascular disease, namely atherosclerosis, while his clinical interests are focused on developing novel biomarkers and peptide-based biopharmaceuticals. He is the Spokesman of the DFG Collaborative Research Centre SFB1123 and coordinates the partner site Munich Heart Alliance in the German Centre for Cardiovascular Research (DZHK). Among many other awards, he is a double ERC Advanced Investigator Grant recipient with more than 550 publications and an h-index of 95. He serves as the Editor-in-Chief of *Thrombosis & Haemostasis*, Senior Associate Editor of *Arteriosclerosis, Thrombosis & Vascular Biology* and is the co-founder of *Carolus Therapeutics Inc.*

Übersicht

Das Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten (IPEK) wird in zwei eigenständige Bereiche unterteilt, wobei ein Zusammenspiel zwischen Patientenversorgung und Forschung als gegenseitige Bereicherung angestrebt wird.

Organigramm des Lehrstuhls



Neben dem Institutsdirektor betreuen neunzehn Arbeitsgruppenleiter daunter zwei C3-Professoren, drei W2-Professoren sowie sieben außerplanmäßige Professoren, thematisch eigenständige Arbeitsgruppen. Zudem umfasst das Institut den DFG „Atherosklerose“ Sonderforschungsbereich 1123, das Editorial Office des Fachjournals *Thrombosis & Haemostasis* und ist eine der Einrichtungen der Munich Heart Alliance (MHA) als Standort im Deutsches Zentrum für Herz-Kreislaufforschung (DZHK).

Adressen

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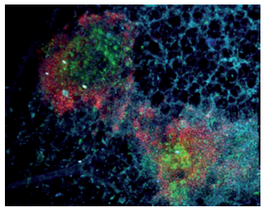
November 2017

The immune response to heart attacks

The damage caused by a heart attack triggers an inflammatory reaction which degrades the affected tissue.



Researchers led by Sabine Steffens, showed that this response is orchestrated by immune cells that reside in the nearby pericardial adipose tissue. Activation of the response occurs in clusters of immune cells (lymphocytes) within the fatty tissues of the so-called pericardium, which surrounds the heart. The findings appeared in the journal *Circulation*.

Horckmans S…., Steffens S. Pericardial adipose tissue regulates granulopoiesis, fibrosis and cardiac function after myocardial infarction. Circulation. 2018

October 2017

Oliver Söhnlein appointed Guest Professor at Karolinska Institute

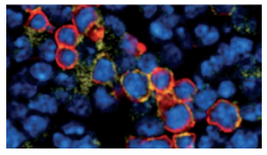
Prof. Söhnlein, was appointed Guest Professor of Inflammation Research at the Karolinska Institute, in Stockholm, a leading medical university in Europe and Scandinavia's largest centre for academic education and medical research. Ole Petter Ottersen, Vice-Chancellor at Karolinska Institute, reminded the new Professors of the profound responsibility medical research holds for the improvement of human lives and health and wished the new professors all the best for their new assignments.

May 2017

How ancestry shapes our immune cells

Virtually the entire population of sub-Saharan Africa, carry a gene variant which results in a trait referred to as Duffy-negative. Carriers of this version of the gene are relatively protected from some strains of malaria and the allele has recently been linked to benign neutropenia – a mild reduction in the numbers of neutrophils.
Dr. Duchêne and Prof. Weber together with Prof. Rot (University of York) and colleagues now revealed how the Duffy-negative variant affects the differentiation of white blood cells and why it leads to a relative paucity of circulating neutrophils. The findings appeared the journal *Nature Immunology.*

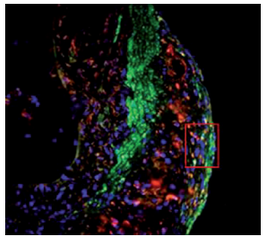
Duchene J… Rot. A Atypical chemokine receptor 1 on nucleated erythroid cells regulates hematopoiesis. Nat Immunol. 2017

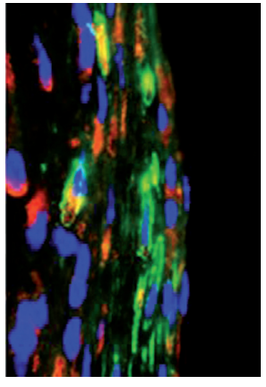


April 2017

Novel Inhibitory signal pathways for atherosclerosis

Atherosclerosis is characterized by the build-up of fat-rich deposits on the inner surfaces of the endothelial cells that form the walls of the blood vessels, leading to a chronic inflammation reaction, which can ultimately result in constriction of the vessel and the obstruction of blood flow in major arteries.





In two studies, which appeared in the journal Circulation, two IPEK research groups described two previously unknown mechanisms that help retard the formation of atherosclerotic plaques. Dr. Döring together with Prof. Weber and colleagues revealed the importance of the CXCL12/CXCR4 pathway in maintenance the integrity of the endothelial cell layer. The team of Prof. Steffens together with Dr. Petteri Rinne (Turku University Finland) identified a novel function of the receptor MC1-R which extrudes excess cholesterol from the macrophages in atherosclerotic lesions, and actively prevents its re-uptake.

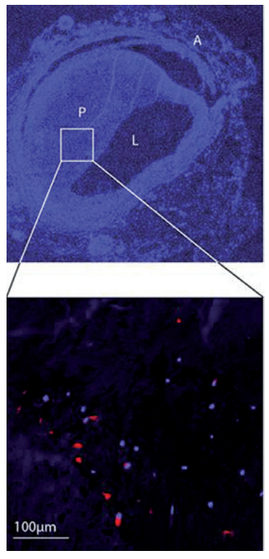
Rinne P… Steffens S. Melanocortin 1 Receptor Signaling Regulates Cholesterol Transport in Macrophages. Circulation. 2017

Döring Y… Weber C. Vascular CXCR4 Limits Atherosclerosis by Maintaining Arterial Integrity: Evidence from Mouse and Human Studies. Circulation. 2017

It takes two to tango

Signal molecules called chemokines often work in tandem to recruit specific sets of immune cells to sites of tissue damage.
In a paper published in the journal Science *Translational Medicine,* researchers led by Prof. Weber and Dr. von Hundelshausen reported the results of the first ever systematic survey of pairwise interactions between individual chemokines and characterized their biological effects, pinpointing potential targets for new therapies

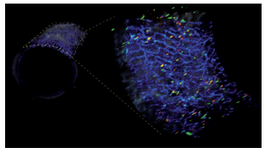
von Hundelshausen P…Weber C. Chemokine interactome mapping enables tailored intervention in acute and chronic inflammation. Sci Transl Med. 2017



September 2016

A molecular specialist for arteries

While the influx of leukocytes in response to messenger substances is an essential healing factor in the context of acute infections, this recruitment exacerbates the course of atherosclerosis.



In a study published in the journal *Circulation*, the team of Prof Söhnlein have identified the protein cathepsin G as a molecule which attracts leucocytes only in the vessel walls of arteries. The discovered mechanism presents the opportunity to selectively inhibit inflammatory processes in arterial vessels for the first time, limiting side effects associated with the treatment of atherosclerosis.

Ortega-Gomez A…Soehnlein O. Cathepsin G controls arterial but not venular myeloid cell recruitment. Circulation. 2016

August 2016

Omega-3 fatty acids against vascular calcification

Treatment strategies for atherosclerosis have focused until now primarily on inhibiting the inflammation reaction.
The team of Prof.Söhnlein have developed a truly novel treatment strategy which focuses on stimulating the body's own healing processes. Active substances contained in fish oil and other sources play a key role in this, improving atherosclerosis in the mice tested. The scientists reported their results in the journal *Circulation Research.*

Viola JR…Soehnlein O. Resolving lipid mediators maresin 1 and resolvin D2 prevent atheroprogression in mice. Circ Res. 2016

May 2016

Rush-hour for neutrophils

The extent of the inflammatory reaction triggered by an acute heart attack, and of the resulting damage to the heart muscle, varies depending on the time of day at which the infarct occurs.
Researchers led by Sabine Steffens, showed that the number of neutrophils present in the circulation naturally fluctuates with the time of day, and that circadian variations in the expression of chemokine receptor CXCR2 play a crucial role in regulating the migration of granulocytes into the damaged tissue. The new findings appear in the journal EMBO *Molecular Medicine.*

Schloss MJ…Steffens S. The time-of-day of myocardial infarction onset affects healing through oscillations in cardiac neutrophil recruitment. EMBO Mol Med. 2016

New Recruits

October 2017

Dr. Alexander Bartelt

Dr. Bartelt came from Harvard University, to set up a new Junior Research Group at the IPEK in October 2017, with the aid of a 5-year grant amounting to 1.25 million euros from the German Center for Cardiovascular Research (DZHK). His Research focuses on metabolic adaption of heart muscle cells to find new therapies for combating heart disease

April 2017

Dr. Dorothee Atzler

Dr. Atzler came from the University of Oxford to join the IPEK and Walther-Straub-Institute for Pharmacology and Toxicology as a group leader.
She is interested in the role of amino acids and cell metabolism in cardiovascular disease, particularly atherosclerosis, and aims to combine experimental and clinical approaches to translate her findings. Dr. Atzler has initiated the early investigator network of the German Centre for Cardiovascular Research (DZHK), the 'Young-DZHK', which she has since chaired. She is also member of the ATVB Early Career Committee to foster international collaborations between early career networks across the cardiovascular research community.

Forschung

Die folgenden Forschungsberichte umfassen Fördermittel und Ausgaben des jeweiligen Jahres, sowie die Anzahl und Gewichtung der veröffentlichten Publikationen.

Forschungsbericht 2016

Anzahl der Planstellen für wissenschaftliche Mitarbeiter: 23
Anzahl der Planstellen für Nicht-wissenschaftliche Mitarbeiter: 22
Anzahl aller drittmittelfinanzierten Mitarbeiter: 78

Drittmittelausgaben (in €)

	Anzahl Projekte	Ausgaben 2016 laut Verwaltung
DFG	28	2.739.556
BMBF, StMWFK, EU	26	1.184.973
Stiftungen (Humboldt, Fondation Leducq, etc.)	13	507.341
LMU excellent	5	168.339
Summe begutachtete externe Drittmittel		**4.600.209**

	Anzahl Projekte	Ausgaben 2016 laut Verwaltung
FöFoLe	1	42.337
Lebmit (Invest.)	15	11.173
Promotionsstipendien	3	24.471
Summe interne Drittmittel		**77.981**
Gesamtsumme verausgabte Drittmittel		**4.678.190**

Publikationen

	Anzahl	ungewichteter IF
Im WoS gelistete Originalarbeiten	48	354,7
Im WoS gelistete Reviews und Editorials	15	118,7
Beiträge in Lehr-/Handbüchern, Monographien		
Gesamtsumme	**63**	**473,4**

Forschungsbericht 2017

Anzahl der Planstellen für wissenschaftliche Mitarbeiter: 23
Anzahl der Planstellen für Nicht-wissenschaftliche Mitarbeiter: 22
Anzahl aller drittmittelfinanzierten Mitarbeiter: 78

Drittmittelausgaben (in €)

	Anzahl Projekte	Ausgaben 2017 laut Verwaltung
DFG	31	2.635.365
BMBF, StMWFK, EU	42	1.702.085
Stiftungen (Humboldt, Fondation Leducq, etc.)	18	394.160
LMU excellent		
Summe begutachtete externe Drittmittel		**4.731.610**

	Anzahl Projekte	Ausgaben 2017 laut Verwaltung
FöFoLe	1	27.889
Lebmit (Invest.)	15	34.882
Promotionsstipendien	2	16.000
Summe interne Drittmittel	**2**	**78.771**
Gesamtsumme verausgabte Drittmittel		**4.810.381**

Publikationen

	Anzahl	ungewichteter IF
Im WoS gelistete Originalarbeiten	49	477,1
Im WoS gelistete Reviews, Editorials	22	209,3
Beiträge in Lehr-/Handbüchern, Monographien		
Gesamtsumme	**71**	**686,4**

Research Groups

Neuroimmunology of atherosclerosis

Prof. Dr. Andreas J.R. Habenicht, MD

Group members
Yuanfang Li, MSc
Chuankai Zhang, MS
Xi Zhang; MSc
Sarajo Kumar Mohanta, PhD
Changjun Yin,PhD
Zhe Ma,MSc
Lu Shu, MS
Ting Sun, MSc
Zhihua Wang,MSc

Our group recently initiated an area of medical research that we tentatively term *neuroimmunology of atherosclerosis.* Neuroimmunology emerged two decades ago when hardwired connections between the nervous system and immune cells were discovered as it was observed that the nervous system directly attenuates the production of inflammatory mediators by macrophages. However, as atherosclerotic plaques are not innervated, there was no incentive to study communications between atherosclerosis and axons of the nervous system leaving atherosclerosis entirely unexplored in the area of neuroimmunology. Yet, our discovery of artery tertiary lymphoid organs (ATLOs) in the outer connective tissue coat of arteries - also referred to as adventitia - led us to challenge this widely accepted view. We learned that the adventitia is used by the nervous system as its principal conduit to reach peripheral tissues. Our observation that immune cells selectively accumulate in adventitia segments that are burdenend by atherosclerotic plaques raised the possibility that adventitial immune cells and their inflammatory mediators might act as proxy atherosclerosis nervous system sensors. Moreover, would the nervous system be capable of responding to the inflammatory cells in any meaningful way? Indeed, following years of explorative studies, we observed that the cardiovascular, the immune and the nervous systems interact at multiple levels in atherosclerosis. Our research has been separated into two broad though interacting areas: One is directed by Dr. Changjun Yin who focuses on the relation between atherosclerosis and the CNS. Dr. Yin discovered that atherosclerosis in hyperlipidemic mice is closely associated with choroid plexus inflammation (the choroid plexus produces the cerebrospinal fluid and acts as the major gateway of immune cells to the brain). His team found that in atherosclerosis and Alzheimer´s disease, the choroid plexus is severely altered resulting in major disruptions of brain homeostasis. The second group is directed by Dr. Sarajo Mohanta who investigates the relation between atherosclerosis and the PNS. Dr. Mohanta and colleagues discovered atherosclerosis brain neuroimmune circuits affecting both ATLO neogenesis and atherosclerosis. When taken together, biologically active neuroimmune platforms connect the diseased arterial wall via its proxy adventitia immune cell aggregates with the nervous system. The challenge for future studies is to delineate the molecular mechanisms of atherosclerosis neuroimmunology, identify the major immune cells involved, and to make attempts to interfere with the nervous system to treat atherosclerosis. For this purpose, Dr. Yin supervises graduate students Chuankai Zhang and Zhihua Wang to identify autoimmune B lymphocytes and autoimmune T lymphocytes, respectively, Zhe Ma to test novel treatment regimens of atherosclerosis using siRNA molecules and Xi Zhang to search for autoimmune antibodies by next generation sequencing of autoimmune immunoglobulins. Dr. Mohanta directs graduate students Yuanfang Li to examine the effects of the sympathetic NS on atherosclerosis, Ting Sun to study the role of the sensory nervous system in atherosclerosis, and Shu Lu to use single cell transcriptome sequencing of PNS and spinal cord neurons and immune cells in atherosclerosis.

Co-stimulatory immune checkpoints in atherosclerosis

Prof. Dr. Esther Lutgens, Dr. Dorothee Atzler

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Dr. Elena Ferrari

Atherosclerosis, the underlying cause of most cardiovascular diseases, including myocardial infarction and stroke, is a lipid driven immunological disease of the large arteries. Within our laboratory, we investigate how the immune system drives atherosclerosis. We particularly focus on immune checkpoint proteins, which are crucial in the communication among different immune cells. Immune checkpoint proteins, including co-stimulatory and coinhibitory molecules can activate or dampen immunoreactivity and are therefore promising therapeutic targets to combat atherosclerosis.
In 2016, the laboratory was led by Prof. Esther Lutgens and Dr. Norbert Gerdes. In 2017, Norbert Gerdes became a University Professor at the University of Düsseldorf, and Dr. Dorothee Atzler was appointed as a group leader.

Scientific highlights

Our research in 2016/2017 focused on the role of different co-stimulatory immune checkpoint proteins in atherosclerosis. The first protein we studied is *Glucocorticoid Inducible TNF Receptor (GITR) ligand*. GITR-GITRL interactions are known to drive T-cells towards effector cells, but also towards regulatory cells, depending on environmental conditions and the pathology involved. We observed that B-cell dependent GITR-ligand activation was able to reduce atherosclerosis by inducing a regulatory T-cell response, thereby reducing inflammation (Meiler et al., Atheroscler Thromb Vasc Biol 2016).
Another co-stimulatory dyad, CD27-CD70, has similar properties than the GITR-GITRL dyad and is also crucial in driving T-effector as well as regulatory T cell responses. Here we found that CD27 plays a crucial role in the development of regulatory T cells, by preventing apoptosis of regulatory T cells in the thymus. Genetic depletion of CD27 in an atherosclerotic mouse model revealed that absence of CD27 increases the initial stages of atherosclerosis, by inducing inflammation (Winkels et al., Eur Heart J 2017). Absence of CD70 resulted in a similar phenotype (Winkels et al., Thromb Haemost 2017).
In 1999, we found that CD40L was an important driver of atherosclerosis and atherosclerotic plaque vulnerability (Lutgens et al., Nat Med 1999). Blocking CD40L reduced atherosclerosis and induced a stable atherosclerotic plaque phenotype. In 2010, we found that the receptor for CD40L, CD40, exerted similar effects on atherosclerosis (Lutgens et al., J Exp Med 2010). In search for cell-types responsible for the protective effects of CD40-

Esther Lutgens

deficiency in atherosclerosis, we found that deficiency of endothelial CD40 is protective against atherosclerosis (Gerdes et al., Atheroscler Thromb Vasc Biol 2016). However, constitutive overexpression of CD40 in dendritic cells unexpectedly induced colitis, resulting in a decrease in cholesterol levels and a decrease in atherosclerosis (Kusters et al., Am J Pathol 2017).
CD40-TRAF6 signaling in macrophages turned out to be responsible for the pro-atherogenic effects of CD40 (Lutgens et al., J Exp Med 2010). We designed a small molecule inhibitor that specifically blocks CD40-TRAF6 interactions and could show that it improved insulin resistance (Chatzigeorgiou et al., PNAS 2014). In 2016/2017, we tested our SMI in another disease model, experimental allergic encephalitis, and we showed that our SMI successfully reduced neuroinflammation (Aarts et al., J Neuroinflammation 2017). We are currently optimizing our CD40-TRAF6 SMIs for use in atherosclerosis.

RECK in human mesenchymal stem cells

Prof. Dr. Christian Ries

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Human mesenchymal stem cells (hMSCs) originate from bone marrow and can migrate into almost all tissues and organs. By asymmetric cell division, hMSCs replicate to maintain an adequate cell population and may also differentiate into various cell types such as osteocytes and adipocytes depending on the presence of environmental stimuli. Another remarkable feature of hMSCs is their property of secreting a broad range of chemokines, cytokines and growth factors, enabling these cells to exhibit important biological effects including immunomodulation, chemoattraction, anti-fibrosis, anti-apoptosis and support of the growth and differentiation of local progenitor cells. Thus, hMSCs have become promising tools in multiple clinical applications including the regeneration of injured tissues.
The membrane-anchored glycoprotein RECK *(reversion-inducing cysteine-rich protein with Kazal motifs)* is well described for its ability to inhibit biosynthesis and activity of various matrix metalloproteinases (MMPs) implicating RECK as a suppressor of tumor cell metastasis. Whereas, research on RECK so far was mainly focused on its importance in cancer, its role in physiological cell function is still unknown. In this study, we investigated RECK´s involvement in essential stem/progenitor cell functions such as migration, proliferation and differentiation of hMSCs. First, we analyzed the effect of decreasing RECK biosynthesis by knockdown of endogenous RECK expression in hMSCs using RNA interference technology. The results of these studies revealed that endogenous RECK suppresses the transcription and biosynthesis of tissue inhibitor of metalloproteinases (TIMP)-2 but does not influence the expression of MMP-2, MMP-9, membrane type (MT)1-MMP and TIMP-1 in these cells. Nevertheless, the lack of RECK in hMSCs promoted monolayer regeneration and chemotactic migration of hMSCs, as demonstrated by scratch wound and chemotaxis assay analyses. These findings indicate that RECK is an attenuator of directed migration in hMSCs by mechanisms different to those in tumor cells. Interestingly, basal levels of endogenous RECK were upregulated upon osteogenic differentiation and diminished after adipogenic differentiation of hMSCs. Consistently, RECK depletion in hMSCs reduced their capacity to differentiate into the osteogenic lineage whereas adipogenesis was increased, demonstrating that RECK differentially modulates osteogenic and adipogenic differentiation by functioning as a master switch between both pathways. Furthermore, the knockdown of RECK in hMSCs inhibited the Wnt/β-catenin signaling pathway as indicated by reduced stability and impaired transcriptional activity of β-catenin as determined by analysis of the target genes DKK1, AXIN2, RUNX2 and use of a luciferase-based β-catenin-activated reporter assay. Thus, endogenous RECK expression stimulates Wnt/β-catenin activity and as a consequence adipogenic differentiation in hMSCs. Taken together, our findings demonstrate for the first time that RECK is a potent regulator of important stem cell functions in hMSCs including directed migration and osteogenic/adipogenic

differentiation. This suggests that modulation of RECK may improve the development of hMSC-based therapeutical approaches in regenerative medicine (Mahl et al., Cell Mol Life Sci 2016).

Novel antiplatelet drugs

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Our previous results showed the crucial function of platelet GPVI in human in vitro models of atherothrombosis (Penz et al., FASEB J. 2005, Reininger et al., J Am Coll Cardiol., 2010, Schulz et al., Basic Res Cardiol. 2008) and the pronounced inhibition of plaque-induced platelet aggregation by recombinant GPVI-Fc at high shear flow (Jamasbi et al., J Am Coll Cardiol 2015). To improve the efficacy of GPVI-Fc, oligomeric GPVI-complexes were created to increase the plaque collagen binding of GPVI-Fc. GPVI-Fc was incubated with anti-human-Fc antibodies to cross-link the Fc tails of GPVI-Fc. Cross-linking GPVI-Fc largely increased the inhibition of human plaque- and collagen-induced platelet aggregation by GPVI-Fc under static and flow conditions. Cross-linking with anti-human-Fc Fab2 was superior to anti-human-Fc IgG whereas monovalent anti-human-Fc Fab control (unable to cross-link Fc-tails) was inactive. Advanced optical imaging revealed a homogenous sheath-like coverage of collagen fibers by cross-linked GPVI-Fc antibody complexes preventing platelet attachment. Of note, cross-linked GPVI-Fc did not increase bleeding time in vitro. We concluded that GPVI cross-linking could be an interesting novel concept to prevent atherothrombosis without increasing systemic bleeding risk (Jamasbi et al., J Am Coll Cardiol Basic Translat Sci 2016)

We further investigated, whether addition of recombinant GPVI-Fc (Revacept) to aspirin, the P2Y12 antagonist ticagrelor and the fibrinogen receptor antagonist abciximab in vitro could further suppress plaque-induced platelet aggregation. It was found that Revacept added on top of ASA or ticagrelor (single antiplatelet therapy), or both antiplatelet drugs (dual antiplatelet therapy: "DAPT") enhanced inhibition of platelet aggregate formation onto human atherosclerotic plaque under arterial flow. Revacept alone or in combination with ASA or ticagrelor did not increase bleeding time in an in vitro assay simulating primary haemostasis. Revacept added on top of abciximab strongly inhibited total and stable platelet adhesion onto human atherosclerotic plaque under arterial flow. It was concluded that Revacept added on top of single or dual antiplatelet therapy with ASA and/or a P2Y12 antagonist may improve anti-atherothrombotic protection without increasing bleeding risk. In contrast, the strong inhibition of platelet adhesion by GPVI-Fc in combination with GPIIb/IIIa inhibitors could be harmful (Mojica Munoz et al., Thromb Haemost 2017).

In a collaborative project, it was investigated whether fusing GPVI-Fc to the ectonucleotidase CD39, which degrades locally accumulating ADP released from platelets attached to atherosclerotic plaques creates a novel lesion-directed antiplatelet therapy that is expected to lack systemic bleeding risks. It was found that in mice models of arterial injury and in the human atherosclerotic plaque model (applying arterial laminar and pulsatile flow conditions) the recombinant GPVI-CD39 fusion

protein potently increased the inhibitory effect of GPVI-Fc in reducing platelet thrombus formation. It was proposed to test the GPVI-CD39 fusion protein in phase I studies to investigate optimal dosing (Degen et al., J Am Heart Assoc 2017).

In a collaborative project with members of CRC1123 (projects A7, B6), it was studied why in patients with atrial fibrillation, oral anticoagulation with oral thrombin inhibitors (OTIs), in contrast to vitamin K antagonists (VKAs), is associated with a modest paradox increase in acute coronary syndromes. It was indeed found that firm platelet adhesion and thrombus formation on immobilised von Willebrand factor, collagen, and human atherosclerotic plaque were increased in the patients obtaining OTIs but not VKA. OTI treatment was also associated with increased thrombus formation in injured carotid arteries of mice. As possible underlying mechanism an interference of OTIs with the thrombin binding site of the platelet receptor GPIbα was found (Petzold et al., Sci Transl Med 2016).

miRNAs and vascular stress response

Prof. Dr. Andreas Schober

In line with our previous research on microRNAs in vascular disease, we studied the cell-specific role of the Dicer, the endonuclease which processes almost all microRNAs into their mature form (Schober et al, Ann Rev Pathol 2016). In endothelial cells, loss of Dicer results in reduced atherosclerosis in mice fed a high fat diet due to the downregulation of microRNA-103, which promotes endothelial inflammation by targeting the transcription factor KLF4 (Hartmann et al., Nat Commun 2016). KLF4 is a critical regulator of a quiescent endothelial phenotype by inhibiting inflammatory gene expression. The production of miR-103 by Dicer in endothelial cells at predilection sites of atherosclerosis results in the upregulation of the chemokine CXCL1 and thereby enhances monocyte recruitment and the formation of atherosclerotic plaques. Accordingly, we showed that treatment with antisense oligonucleotides, which block the binding of miR-103 to KLF4 but not the interaction with other mRNA targets, reduces atherosclerotic lesions in mice. These data indicate that those "Target Site Blockers" could be a promising tool for the treatment of atherosclerosis.

In addition, we investigated the role of Dicer in vascular smooth muscle cells (SMCs) during vascular injury (Zahedi et al., Cell Mol Life Sci 2017). Cell-specific deletion of Dicer in SMCs resulted limited neointima formation after carotid injury in mice by regulating a network of microRNAs, which inhibit the proliferation of SMCs. We found that one of those miRNAs, miR-27a, targeted the Rho guanine nucleotide exchange factor 26 (ARHGEF26), which mediates growth factor signaling, and thereby reduced SMC proliferation. Thus, Dicer protects the vasculature from exaggerated growth response to vascular injury by producing microRNAs, such as miR-27a.

Previously, we have described the proinflammatory effect of the microRNA-155 in macrophages on atherosclerosis. Because inflammatory macrophages also play a role in obesity and insulin resistance, we evaluated the metabolic effects of miR-155 in mice. Surprisingly, we found that hyperlipidemia drives the expression of miR-155 in insulin-producing beta cells in pancreatic islets (Zhu et al., Diabetes, 2017). By targeting the transcription factor MafB, which promotes beta cell function through IL-6-induced GLP-1 production in alpha-cells, miR-155 improves glucose metabolism and the adaptation of beta cells to obesity-induced insulin resistance.

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Myeloid cells in vascular inflammation and therapy

Prof. Dr. Dr. med. Oliver Söhnlein

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Atherosclerosis is a chronic inflammatory disorder of large arteries. Following initial endothelial dysfunction, leukocytes start to infiltrate the arterial vessel wall contributing to lumen narrowing and ultimately to plaque rupture clinically evident as myocardial infarction or stroke. Bone marrow-derived cells have been greatly appreciated for their contribution to atherogenesis, atheroprogression, and atherothrombosis. The group led by Oliver Söhnlein is to a large degree financed by the DZHK and DFG to establish novel concepts for treatment of advanced stages of atherosclerosis to prevent the onset of complications such as myocardial infarction and stroke.

Atheroprogression is a consequence of nonresolved inflammation, and currently a comprehensive overview of the mechanisms preventing resolution is missing. However, in acute inflammation, resolution is known to be orchestrated by a switch from inflammatory to resolving lipid mediators. Therefore, we hypothesized that lesional lipid mediator imbalance favors atheroprogression. Aortic lipid mediator profiling of aortas from hypercholesterolemic mice fed a high-fat diet for 4 weeks, 8 weeks, or 4 months revealed an expansion of inflammatory lipid mediators, Leukotriene B4 and Prostaglandin E2, and a concomitant decrease of resolving lipid mediators, Resolvin D2 (RvD2) and Maresin 1 (MaR1), during advanced atherosclerosis. Functionally, aortic Leukotriene B4 and Prostaglandin E2 levels correlated with traits of plaque instability, whereas RvD2 and MaR1 levels correlated with the signs of plaque stability. In a therapeutic context, repetitive RvD2 and MaR1 delivery prevented atheroprogression as characterized by halted expansion of the necrotic core and accumulation of macrophages along with increased fibrous cap thickness and smooth muscle cell numbers. Mechanistically, RvD2 and MaR1 induced a shift in macrophage profile toward a reparative phenotype, which secondarily stimulated collagen synthesis in smooth muscle cells. Thus, our work reveals evidence for the imbalance between inflammatory and resolving lipid mediators during atheroprogression. Delivery of RvD2 and MaR1 successfully prevented atheroprogression, suggesting that resolving lipid mediators potentially represent an innovative strategy to resolve arterial inflammation (Viola et al., Circ Res 2016).

Therapeutic targeting of arterial leukocyte recruitment in the context of atherosclerosis has been disappointing in clinical studies. Reasons for such failures include the lack of knowledge of arterial-specific recruitment patterns. In a recent study, we employed intravital microscopy of the carotid artery, the jugular vein, and cremasteric arterioles and venules in Apoe-/-and Cathepsin G-deficient mice (Apoe-/-Ctsg-/-) to study site-specific myeloid cell behavior after high-fat diet feeding or tumor necrosis factor stimulation. Atherosclerosis development was assessed in aortic root sections after 4 weeks of high-fat diet, whereas lung inflammation was assessed after inhalation of lipopolysaccharide. Endothelial deposition of CatG and CCL5 was quantified in whole-mount preparations using 2-photon and confocal microscopy. Our observations elucidated a crucial role for CatG during arterial leukocyte adhesion, an effect not found during venular adhesion. Consequently, CatG deficiency attenuates atherosclerosis but not acute lung inflammation. Mechanistically, CatG is immobilized on arterial endothelium where it activates leukocytes to firmly adhere engaging integrin clustering, a process of crucial importance to achieve effective adherence under high-shear flow. Therapeutic neutralization of CatG specifically abrogated arterial leukocyte adhesion without affecting myeloid cell adhesion in the microcirculation. Repetitive application of CatG-neutralizing antibodies permitted inhibition of atherogenesis in mice. In conclusion, our findings present evidence of an arterial-specific recruitment pattern centered on CatG-instructed adhesion strengthening. The inhibition of this process could provide a novel strategy for treatment of arterial inflammation with limited side effects (Ortega-Gomez et al., Circulation 2016).

Increases in plasma LDL-cholesterol have unequivocally been established as a causal risk factor for atherosclerosis. Hence, strategies for lowering of LDL-cholesterol may have immediate therapeutic relevance. Here we study the role of human neutrophil peptide 1 (HNP1) in a mouse model of atherosclerosis and identify its potent atheroprotective effect both upon transgenic overexpression and therapeutic delivery. The effect was found to be due to a reduction of plasma LDL-cholesterol. Mechanistically, HNP1 binds to apolipoproteins enriched in LDL. This interaction facilitates clearance of LDL particles in the liver via LDL receptor. Thus, we here identify a non-redundant mechanism by which HNP1 allows for reduction of LDL-cholesterol, a process that may be therapeutically instructed to lower cardiovascular risk (Paulin et al., EBiomedicine 2017).

Lipid signaling in cardiovascular disease

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Atherosclerosis is responsible for several major adverse cardiovascular events including myocardial infarction and stroke. Myocardial infarction and stroke represent the leading cause of morbidity and mortality in the Western world today. Moreover, patients suffering from a myocardial infarction are at elevated risk to undergo a second infarction and to develop heart failure. It is therefore crucially relevant not only to develop new strategies for prediction, prevention, and treatment of cardiovascular disease, but also to improve the outcome after an acute myocardial infarction.
Myocardial infarction is in most cases due to occlusion of a coronary artery after acute atherosclerotic plaque rupture. If blood flow is not rapidly restored, the lack of oxygen and nutrients (ischemia) will lead to irreversible damage of the cardiac muscle. This induces an inflammatory response which is required for the induction of cardiac repair processes. Various cell types, including neutrophils and macrophages, are involved at different stages of infarct healing, ultimately leading to scar formation and adaptive remodeling to preserve cardiac function. Attracted by cell debris and inflammatory signals released by activated neighboring cells, neutrophils massively infiltrate the infarct area in the first few hours following onset of ischemia. They generate high levels of reactive oxygen species and secrete proteases, which exacerbates local vascular and tissue injury. Subsequently, blood monocyte-derived macrophages are recruited to the heart to remove debris and apoptotic neutrophils, which leads to activation of reparative pathways necessary for scar formation.

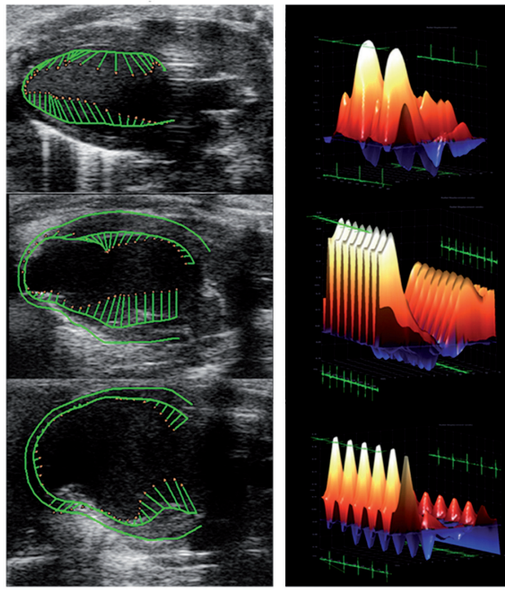
Highlights in 2016/2017

Neutrophils promote cardiac repair

We have recently identified a new role for neutrophils in post-myocardial infarction healing which has been largely neglected so far. In humans, high neutrophil counts are considered as predictor of adverse clinical outcomes and mortality in patients with acute coronary syndromes, and their contribution in the acute inflammatory phase after myocardial infarction is generally considered detrimental. However, in acute inflammation, neutrophils are not only vital for the clearance of pathogens or debris, but also for the resolution of inflammation and return to tissue homeostasis.
In a preclinical model of myocardial infarction, we found that neutrophils are required for resolving post-myocardial infarction inflammation and cardiac healing (Horckmans et al. Eur Heart J 2017). Neutrophil-depleted mice subjected to myocardial infarction had worsened cardiac function, increased fibrosis, and a progressive increase in biomarkers associated with heart failure. This was accompanied by reduced cardiac expression of a phagocytosis receptor that macrophages require for clearance of apoptotic cardiomyocytes. Our findings may therefore have important clinical implications. Beyond their established proinflammatory role in acute post-myocardial infarction injury, we identified neutrophils as pivotal modulators of the healing response after myocardial infarction and consequently cardiac repair and function. This novel role for neutrophils should be taken into account when designing and applying "aggressive" anti-inflammatory treatments in the setting of myocardial infarction. It may also explain why attempts to translate anti-inflammatory strategies from experimental studies into the clinical practice have been unsuccessful so far. In the future, more targeted strategies, potentially based on single molecule resolving mediators rather than broad anti-inflammatory therapies might be more beneficial.

How the circadian rhythm affects myocardial infarction repair

Circadian rhythms are biological processes displaying endogenous oscillations of about 24-h and are known to play a crucial role in physiology. Recently, they further emerged as important regulators of the immune system. The incidence of cardiovascular events, such as myocardial infarction, ischemic stroke, and arrhythmias, exhibits time-of-day dependency in humans, peaking around the sleep-to-wake transition period. The underlying mechanisms for this time-of-day dependency involve circadian fluctuations of glucocorticoids and catecholamines, blood pressure, heart rate, blood viscosity and platelet reactivity, thereby predisposing for plaque rupture and thrombus formation. In addition to the increased prevalence of myocardial infarction in the morning, experimental and clinical evidence suggests that the severity of myocardial infarction exhibits a similar time-of-day dependency. We aimed to clarify how of the circadian rhythm affects myocardial infarction outcome and underlying inflammatory responses.
Circulating leukocytes oscillate between blood and peripheral tissue. These fluctuations in immune cell trafficking into tissues coincide with sensitivity to acute inflammatory stimuli, being highest at the beginning of the active phase. We studied whether these oscillations in immune cell activity occur in the heart after an infarction and which consequences this would have on myocardial healing. We found that the heart represents an immunologically dynamic organ with circadian fluctuations of adhesion molecule and chemokine expression and recruited leukocytes. Neutrophil production and retention in the bone marrow is time-of-day dependent, and circulating neutrophils at the beginning of the active phase have higher capacity to migrate into the myocardium. Myocardial infarction at this time point resulted in significantly higher cardiac neutrophil infiltration. We identified that circadian oscillations of the chemokine receptor CXCR2 on neutrophils were mediating



Mouse Echoradiography

the time-of-day-dependent extend of neutrophil recruitment into the myocardium. Consequently, an ischemic event occurring during the active phase resulted in an exaggerated inflammation and worsened cardiac repair. Limiting neutrophil counts at this time point reduced the infarct size and improved cardiac function (Schloss et al., EMBO Mol Med 2016). In a subsequent study we reported that circadian rhythms also affect inflammatory monocyte recruitment into the myocardium. We found that CCR2 surface expression on classical monocytes in mice and humans changes in a time-of-day dependent manner, which crucially affects cardiac monocyte recruitment after experimental myocardial infarction (Schloss et al., ATVB 2017). In conclusion, the time-of-day of myocardial infarction onset determines neutrophil- and monocyte-mediated inflammation, which might be relevant in view of developing more personalized therapies for myocardial infarction patients that consider the time-of-day of symptom onset.

Other publications

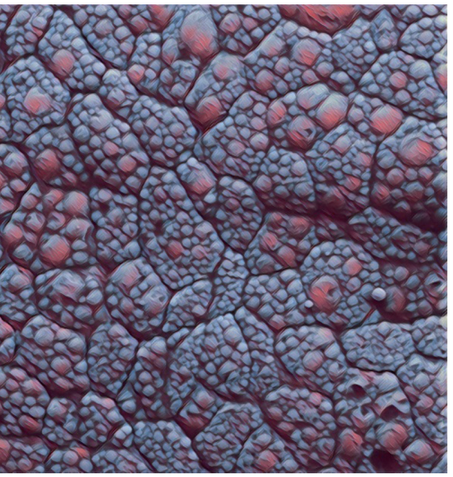
The receptor melanocortin receptor 1 (MC1-R) is best known for its role in activating synthesis of the pigment melanin in the skin, which acts as an endogenous sunscreen and protects against the mutagenic effects of UV radiation. However, the receptor has a variety of other functions. For example, it is thought to be involved in the regulation of inflammatory responses, although its implication in atherosclerosis has not been studied previously. MC1-R is expressed on the surface of macrophages, which are cellular key players in atherosclerosis by ingesting cholesterol and dying cells within the plaque. We found that it regulates the so-called reverse cholesterol transport in these cells (Rinne et al., Circulation 2017). Specifically, our study demonstrates that activation of MC1-R promotes the extrusion of excess cholesterol from the macrophages found within atherosclerotic lesions, and actively prevents its re-uptake. Conversely, inhibition of the MC1-R signal pathway stimulates the transport of cholesterol into macrophages. These findings imply that MC1-R also inhibits the development of atherosclerosis. Excessive uptake of cholesterol converts macrophages into so-called foam cells, which are known to contribute to the chronic inflammation within atherosclerotic lesions. This in turn increases the risk that plaques may rupture and obstruct blood-flow, which can lead to a heart attack or a stroke.

Outlook

A better knowledge of the inflammatory processes involved in myocardial infarction healing may help developing more targeted therapies in order to improve the clinical outcome. In particular, stimulating the post-inflammatory resolution phase towards a well-balanced reparative response with selective mediators may hold great promise. Using proteomic and lipidomic screening approaches, we hope to identify such mediators within the inflammatory cell secretome or cardiac tissue. As to the underlying chronic inflammatory disease leading to myocardial infarction, we also study the contribution of lipid mediators and their signalling receptors in this process. In particular, our preliminary work suggests that the endocannabinoid signalling system is an important endogenous lipid signalling system that links metabolic disorders with atherosclerosis. These ongoing studies may provide the basis for novel therapeutic strategies to limit the progression of atherosclerosis and occurrence of acute cardiovascular events.
Moreover, we are investigating the molecular pathways of G protein-coupled receptor (GPCR) signaling involved in atherosclerosis and myocardial infarction. GPCRs constitute the largest and pharmacologically most important super family of membrane receptors, targeted by 30-50% of all drugs. To better understand GPCR-regulated immune cell responses at a cellular level, we are currently generating receptor-overexpressing cells based on human monocytic and T cell lymphoma cell lines. These cell culture models will be used to study differences in the activation, signalling and regulation mechanisms of certain GPCRs (cannabinoid, bradykinin and chemokine receptors) and their specific ligands.

Cardiovascular immunometabolism

Dr. Alexander Bartelt



Artistic electron microscopy picture of brown fat (copy right: Alexander Bartelt)

In October 2017, Dr. Alexander Bartelt started at IPEK as a principal investigator and group leader. Dr. Bartelt was recruited to IPEK from Harvard T.H. Chan School of Public Health, Boston, USA, where he worked on the molecular principles of immunometabolism in the context of obesity, diabetes and atherosclerosis. Dr. Bartelt's research has focused on the metabolism of brown fat cells, which are specialized fat cells that are activated by cold and burn calories to produce heat. This ability makes brown fat cells an attractive therapeutic target for the treatment of metabolic diseases. The very interesting and unique features of brown fat cells provide insight into the general molecular principles of metabolic adaptation. In his lab, he is now investigating the function and therapeutic potential of the transcription factor Nfe2l1, a cold-inducible switch of brown fat function, for obesity and related cardiovascular pathologies.

Dr. Bartelt received his Diploma in Biochemistry and Molecular Biology from University of Hamburg, Germany in 2007 and his PhD 2010 with highest honors. Dr. Bartelt's contributions to the general understanding of metabolism have been recognized by national and international awards, fellowships and honors. His work has been funded by the Schering Foundation, the European Atherosclerosis Society and the German Research Foundation DFG.

Selected Publications:

- Bartelt et al., Brown adipose tissue thermogenic adaptation requires Nrf1-mediated proteasomal activity. Nat Med 2018.
- Bartelt et al., Thermogenic adipocytes promote HDL turnover and reverse cholesterol transport. Nat. Commun 2017.
- Berbée et al., Brown fat activation reduces hypercholesterolemia and protects from atherosclerosis development. Nat Commun 2015.
- Bartelt & Heeren J. Adipose tissue browning and metabolic health. Nat Rev Endocrinol 2014
- Bartelt et al., Brown adipose tissue activity controls triglyceride clearance. Nat Med 2011

Antigen presenting cells in chronic inflammation

Dr. rer. nat. Yvonne Döring

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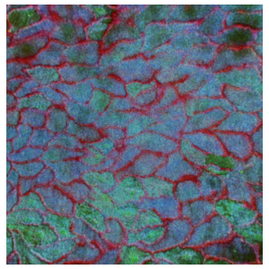
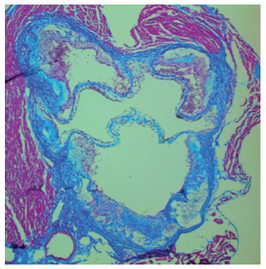
Chemokines and their respective receptors play an important role in the pathophysiology of atherosclerosis orchestrating stage-specific recruitment patterns and immune functions of different leukocyte subsets. However, many ligands and receptors have not been studied in detail yet.
The CXCL12/CXCR4 chemokine ligand/receptor axis controls (progenitor) cell homeostasis and trafficking. So far, an atheroprotective role of CXCL12/CXCR4 has only been implied through pharmacological intervention, in particular, because the somatic deletion of the CXCR4 gene in mice is embryonically lethal (Döring et al., Front Physiol 2014). Moreover, cell-specific effects of CXCR4 in the arterial wall and underlying mechanisms remain elusive, prompting us to investigate the relevance of CXCR4 in vascular cell types for atheroprotection. Thus, we examined the role of vascular CXCR4 in atherosclerosis and found that cell-specific deletion of CXCR4 in arterial endothelial cells or smooth muscle cells markedly increased atherosclerotic lesion formation in hyperlipidemic mice. In summary we could show that vascular CXCR4 limits atherosclerosis by maintaining i) arterial integrity, preserving endothelial barrier function, and ii) a normal contractile smooth muscle cell phenotype. Enhancing these beneficial functions of arterial CXCR4 by selective modulators might open novel therapeutic options in atherosclerosis (Döring et al., Circulation 2017).
In another project we further examine a myeloid subset of dendritic cells (DCs) expressing the chemokine CCL17. The latter promotes chronic inflammation and atherosclerosis by controlling regulatory T cell (Treg) maintenance and survival (Weber et al., J Clin Invest 2011). Tregs encountered in atherosclerotic plaques or lymphoid organs are important in limiting lesion inflammation, however underlying mechanisms by which CCL17+ DCs suppress Treg homeosta-sis remain to be clarified. So far we could show that mice lacking the bona fide CCL17 receptor CCR4 do not phenocopy effects of CCL17 deficiency and treatment of CCR4-bearing T cells or Tregs with CCL17 does not affect Treg differentiation or apoptosis, implicating a DC-intrinsic mediator and an alternative receptor in this effect. In an unbiased approach, we aim at identifying another receptor for CCL17 and a secondary mediator which drives DCs to exacerbate atherosclerosis and chronic inflammation by suppressing Treg homeostasis.

Another subset of dendritic cells plasmacytoid dendritic cells (pDCs) have also been implicated in the pathogenesis of atherosclerosis (Döring et al., Circulation 2012) and express the chemokine-like receptor ChemR23 which has been particularly suggested to mediate trafficking of pDCs to sites of inflammation and polarization of M2 macrophages. Studies in our group now show that Apoe-/- ChemR23e/e mice displayed reduced lesion formation and reduced leukocyte adhesion to the vessel wall and an increased proportion of M2 cells and a more stable plaque phenotype. Additional experiments

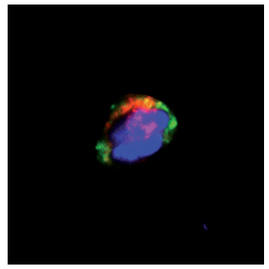
revealed that ChemR23-deficiency induces a systemic reduction in pDC frequencies and reduced accumulation of ChemR23-deficient pDCs in atherosclerotic lesions. We hypothesize that ChemR23-deficiency increases the proportion of alternatively activated M2 macrophages in atherosclerotic lesions and attenuates recruitment to atherosclerotic lesions, which synergistically restricts atherosclerotic plaque formation and progression.



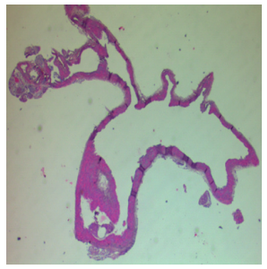
Mouse vessel wall
Red = lining of endothelial cells



Mouse aortic root Trichrome staining



Mouse plasmacytoid dendritic cell
Red – SiglecH
Green – ChemR23



Mouse aortic arch HE staining

Atypical chemokine receptor and the immune response

Dr. Johan Duchêne

Group members
Maria Alsani, MSc
Markus Haberbosch, MTA

Natural selection has shaped patterns of genetic variation in the human genome which has enabled our adaptation to specific geographical environments. Indisputably, infectious diseases have played a crucial role in the evolution of human genetics. In particular, malaria has exerted a strong selective pressure in recent human history. A polymorphism, which is highly prevalent in Africa, abolishes the expression of a molecule called Duffy antigen in erythrocytes. This protects the individuals of African ancestry against the malaria parasite, Plasmodium vivax, which otherwise highjacks the Duffy antigen to invade red blood cells. We have now revealed that the Duffy polymorphism may confer an even more profound selective advantage.

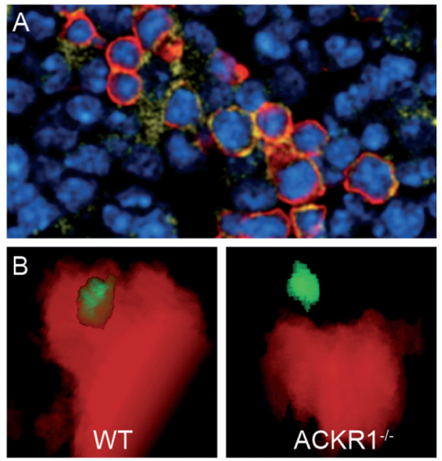
Throughout life, bone marrow hematopoiesis continuously produces all mature blood cells. Hematopoietic stem and progenitor cells (HSPCs) reside at the top of the hematopoietic hierarchy, harboring the potential to generate all cell types found in the bloodstream. Neutrophils, which take part in the first line of defense against infections, are constantly derived from HSPCs. We found that the lack of Duffy antigen had a major influence on hematopoiesis and neutrophil phenotype.

Duffy antigen, which was recently renamed atypical chemokine receptor 1 (ACKR1), is structurally similar to classical chemokine receptors, involved in leucocyte trafficking, but fails to induce the full spectrum of downstream intracellular signaling characteristic of chemokine receptors. Instead ACKR1 may transport, present or scavenge chemokines to effectively regulate chemokine availability in tissue microenvironments such as the bone marrow. All sub-Saharan Africans carry the variant rs2814778(G) for ACKR1. Individuals who are homozygous for the allele do not express ACKR1 on circulating erythrocytes, causing a Duffy-negative phenotype. In addition, it has been long known that individuals of African ancestry have low blood neutrophil counts without however showing increased infectious susceptibility. Such benign ethnic neutropenia has been recently linked with the allelic variant rs2814778(G) of ACKR1, but the mechanism underlying this association remained unexplored.

We found that ACKR1 is in fact highly expressed by nucleated erythroid cells (NECs) in the bone marrow (Figure 1A) where it regulates the homeostasis of HSPCs and modulates downstream hematopoiesis (Duchene et al, Nat Immunol 2017). We discovered that NECs directly interact with HSPCs in an ACKR1-dependent manner. In the absence of ACKR1, bone marrow HSPCs localize remotely from NECs (Figure 1B). As a result, an alternative pattern of hematopoiesis occurs and gives rise to phenotypically distinct neutrophils, which carry key molecules involved in antimicrobial defenses. Finally, we found that these alternatively armed neutrophils, readily leave the blood stream and migrate to the tissues, which explains the apparent neutropenia observed in Duffy-negative individuals of African ancestry.

Overall, our findings highlight that ACKR1 expression in the erythroid lineage regulates

patterns of hematopoiesis and the ultimate phenotype of neutrophils. The specific properties of the neutrophils produced in Duffy-negative individuals may have a positive impact on innate immune responses against pathogens. It is likely that the ACKR1 genetic variant not only provides a selective advantage against malaria but also to a much broader spectrum of infectious diseases. An alternative immune system may thus be an advantage to fight infections. On the other hand, a stronger immune response may be detrimental in the context of chronic inflammation and autoimmune disease. Indeed, individuals of African ancestry are more susceptible to cardiovascular disease, stroke and several autoimmune and inflammatory diseases. Therefore, not only do our findings provide an explanation for the long puzzling benign ethnic neutropenia of people from African ancestry and for the positive selection of the Duffy polymorphism in Africa until now solely attributed to malaria, but may also pave the way towards elucidating pathogenic mechanisms and developing therapies specifically tailored to tackle diseases in individuals of African ancestry.



ACKR1 on NECs promotes interaction with HSPCs. A) ACKR1 is expressed by NECs. Bone marrow section was stained using antibodies to ACKR1 (yellow) and erythroid marker (Ter119, red) and DAPI (blue). **B)** Localization of HSPCs (green) and NECs (red) in representative 3D reconstructed images from whole-mounted femurs of WT and ACKR1-deficient mice.

Chemokine interactome mapping in acute and chronic inflammation

Dr. Philipp von Hundelshausen

Signal molecules called chemokines often work in tandem to recruit specific sets of immune cells to sites of tissue damage. A systematic analysis of their interactions pinpoints potential targets for new therapies.

Group members
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Julian Leberzammer, cand. med.
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Chemokines are small signal proteins that are secreted by their producer cells, and act as attractants for specific cell types, summoning them to sites in the body where they are needed. Most of these proteins act on cells of the immune system, and recruit them to sites of injury or infection. The cells reach their targets by following the rise in the concentration of the chemokine back to its cellular source in the tissues, a process known as chemotaxis. Hence, chemokines are involved in initiating and regulating inflammation reactions, which are triggered by acute tissue damage or metabolic imbalances. For example, chemokines are intimately involved in the pathogenesis of atherosclerosis, i.e., the localized deposition of fat-rich deposits which can obstruct the flow of blood through major arteries. For these ‘plaques’ are themselves the product auf chronic inflammation reactions.

Distinct chemokines are capable of binding to each other to form so-called heterodimers, i.e. functional units consisting of two distinct subunits, and such interactions may either potentiate or attenuate their function. This makes heterodimers interesting as drug targets for novel therapies for the treatment of acute and chronic inflammation.

All pairwise combinations of the about 50 known chemokines were systematically screened for their ability to form heterodimers, and we identified those interactions that are functionally relevant and potentially targetable for therapeutic purposes.

Using an array of analytical methods to probe structure-function relationships and a set of transgenic mouse strains as experimental models, we found that chemokines that are secreted in the course of inflammatory reactions are particularly prone to heterodimerize with each other (Figure 1). Furthermore, we were able to show that these binding interactions can be classified into two structural types, which are referred to as CC and CXC dimers. These two subtypes differ functionally: Heterodimers of the CC class (Figure 2) have a more potent chemoattractant effect, and in mouse models they promote acute inflammation of the lung and atherosclerosis. Dimers of the CXC type, on the other hand, repress chemotaxis. Thus, the formation of chemokine heterodimers enables the organism to fine-tune the overall level of chemokine activity. Specially designed synthetic peptides specifically inhibit the ability of CC heterodimers to stimulate the development of atherosclerosis and acute inflammation of the lung, as well as the capacity of CC heterodimers to promote platelet aggregation and thus

increase the risk of thrombosis. Appropriately designed peptides could therefore serve as the basis for the creation of new.

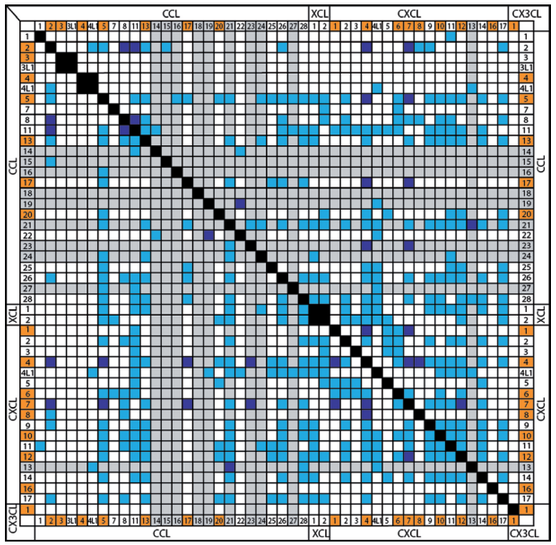


Figure 1. Map of the chemokine interactome
Chemokine-chemokine interactions were detected by bidirectional immuno-ligand blotting. Known atherogenic chemokines are highlighted in orange and non-mucosal homeostatic chemokines are shaded in grey. Grey and white squares both indicate no interaction for non-mucosal homeostatic chemokines (grey) or all other chemokines (white). Black squares indicate that antibody binding indistinguishably detects both immobilized and soluble (complexed) chemokine. Chemokine interactions were considered positive (cyan) if the densitometric signal exceeded that of the negative control by 5% (on average) on either side of the blot (n=2-4 independent experiments). Chemokine interactions previously identified and experimentally confirmed by other techniques are indicated in dark blue.

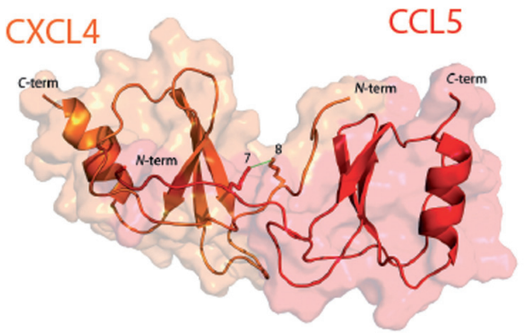


Figure 2. Structure model of a CC-type heterodimer
Energy-minimized structure model depicting the CC-type interaction of CCL5 (grey) and CXCL4 (blue) trapped via a covalent oxime linkage (magenta), resulting in an obligate platelet factor 4-RANTES heterodimer (OPRAH).

Cardiovascular imaging technologies

Dr. Remco Megens

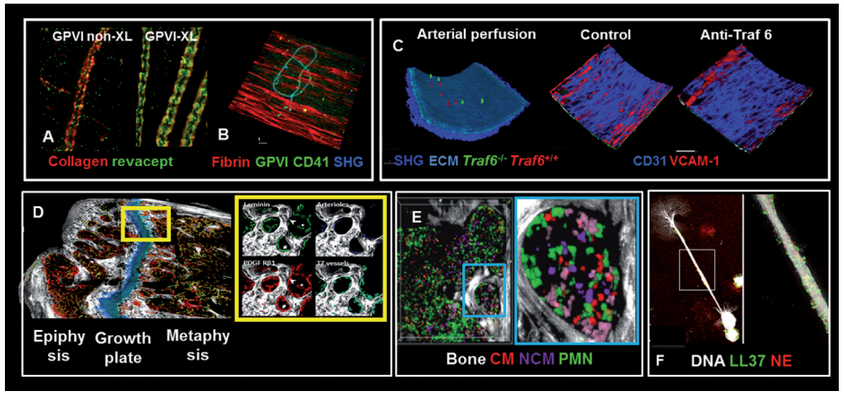
In order to further elucidate the processes involved in initiation and progression of atherosclerosis, insight in cardiovascular structure and function is essential. Histology has provided a detailed insight in various aspects of human and experimental atherosclerosis. However, the utilized preparation 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 (intracellular) resolution level in a physiological setting.

The IPEK working group on biophysics of microscopy focusses on the application of advanced optical fluorescence microscopic and nanoscopic techniques such as confocal (CLSM) and two-photon laser scanning microscopy (TPLSM), and Stimulated Emission Depletion (STED) for (molecular) imaging of atherosclerotic structures and processes in cardiovascular samples. Furthermore, the Megens laboratory functions as an optical imaging core facility for internal and external collaborators and offers technology, expertise, and training. The core facility comprises a Leica SP5IIMP Two photon microscope and an SP8 3X confocal/STED microscope (both funded by DFG/LMU).

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

Besides Facilitating and advancing optical methodologies, our group aims to unravel the role of monocyte subsets and monocyte conversion in steady state and cardiovascular disease (figure D-E; in collaboration with the Duchene Group). To achieve the latter, quantitative multicolor (whole mount) bone marrow imaging and a novel marker for non-classical monocytes have been developed (Mariaelvy Bianchini, CRC1123). Finally, we focus on the functionality and (nanoscopic) morphology of neutrophil extracellular traps (NETs) and will study their role in atherosclerosis (figure F).

Group members
Mariaelvy Bianchini, MSc
Yvonne Janssen, Bsc., MTA



Binding of (non)cross-linked GPVI fusion protein (Revacept®) to collagen fibers (Jamasbi et al., JACC Basic Transl Sci 2016). B) Kinetics of GPVI-Fc binding to collagen (blue) but not to fibrin (Ebrahim et al., Thromb Haemost 2018). C) Arterial perfusion assay (left panel: van der Vorst et al., Bio Protoc 2017) and VCAM-1 expression in TRAF-6 (un)treated carotid artery (right panel: Seijkens et al., J Am Coll Cardiol 2018). D) Multicolor whole mount bone marrow imaging utilizing TPLSM, and E) Detail of leukocyte distribution in bone marrow niches. F) Confocal (left) and nanoscopic STED (right) imaging of granule proteins LL37 and elastase on a neutrophil extracellular trap.

Third-party funding

Project	Sponsor *Reference*	Principal investigator Collaboration partner	Time frame
Cxcl12 und Cxcr4/7 in atherosclerosis	**DFG** *SFB1123, TP A1*	**Y. Döring, C. Weber** *S. Hofmann, L. Holdt*	07/2014-08/2018
Molecular mechanisms linking the CXCL12 pathway to atherosclerosis	**NIH**	**Y. Döring, C. Weber**	2017-2020
Study of the role of endothelial CXCR4 in vascular permeability	**BMBF/DZHK**	**Y. Döring, C. Weber** *H. Noels*	2016
Role of NETs in atherogenesis	**DFG** *SFB1123, TP B5*	**O. Söhnlein, Y. Döring** *S. Massberg*	07/2014-06/2018
Apoptotic neutrophils in atherosclerosis	**NWO**	**O. Söhnlein** *M. Daemen, E. Lutgens*	2012-2017
Infection resolution in Atherosclerosis	**LMUexcellent**	**O. Söhnlein** *N. Cenac, M. Perretti*	2013-2017
Apoptotic neutrophils in atherogenesis	**DFG** *SO876/6-1*	**O. Söhnlein** *C. Kupatt, N. Cenac, M. Perretti*	2014-2017
European Vascular Interventions and Therapeutic Innovation Network	**EU**	**O. Söhnlein** *M. Perretti*	2015-2019
Investigating the role of FPR2/ALX in myocardial repair	**EU** **WHRI Academy**	**O. Söhnlein, G. Leoni** *M. Perretti*	2014-2017
Neutrophils in advanced atherosclerosis	**LMU** *FöFoLe*	**C. Silvestre-Roig**	2015-2016
Ultra-sound for small animals	**BMBF/DZHK**	**O. Söhnlein**	seit 2015
Neutrophils in plaque destabilization	**DFG** *SO876/11-1*	**O. Söhnlein** *M. Daemen, E. Lutgens*	2015-2018
Role of PMN in fibrous cap rupture	**B. Braun Stiftung**	**O. Söhnlein**	2015-2016
Alarmins mediating homeostatic leukocyte alterations in atherosclerosis	**DFG** *SFB1123, TP A6*	**O. Söhnlein, M. Drechsler** *A. Hidalgo*	07/2014-06/2018

Project	Sponsor *Reference*	Principal investigator Collaboration partner	Time frame
Neutrophils and platelets cooperate during monocyte recruitment	**DFG** *SFB914, TP B8*	**O. Söhnlein, C. Weber** *G. Nicolaes, T. Hackeng*	2011-2019
Proteomic analysis of the resolving macrophage in cardiovascular inflammation	**BMBF/DZHK** *81X2600226*	**O. Söhnlein** *G. Dittmar*	2015-2016
Vascular Immunotherapy	**DZHK** *MHA1.2KD*	**O. Söhnlein**	2014-2018
Annexin A1 in Myokardinfarkt	**Förderverein Thyssen Foundation** *19.16.2.023MN*	**O. Söhnlein, G. Leoni**	2016-2019
NTFs in plaque destabilisation	**Else-Kröner-Fresenius Stiftung**	**C. Silvestre-Roig**	2017-2020
Co-stimulatory molecules in atherosclerosis	**DFG** *SFB1123, TP A5*	**E. Lutgens**	07/2014-08/2018
The role of hypercolesterolemy on co-stimulatory molecules	**DFG** *SFB1054, TP B8*	**E. Lutgens**	01/2013-12/2016
Co-stimulatory molecules in adiposis	**DFG** *SFB1054, TP B8*	**E. Lutgens** *diverse*	01/2013-12/2016
TRAF-STOP	**BMBF/DZHK** *DZHK 81X2600247*	**C. Weber, E. Lutgens**	07/2017-03/2019
REPROGRAM	**EU** *EU 667837*	**E. Lutgens**	01/2016-12/2019
Role of the periperal endocannabinoid system in Atherosclerosis	**DFG**	**S. Steffens**	08/2014-06/2018
Role of Endocannabinoid and the cyrcadian rythm on wound healing after heart attack	**DFG**	**S. Steffens**	12/2015-12/2018
Role of the peripheral Serotonin system in Atherosclerosis	**Else-Kröner-Fresenius Stiftung**	S. Steffens	10/2013-02/2017
Role of the new Cannainoid receptor GPR55 in wound healing after heart attack	LMU *FöFoLe*	S. Steffens	04/2016-09/2017

Project	Sponsor *Reference*	Principal investigator Collaboration partner	Time frame
Specific contribution of vascular and macrophage cannabinoid receptor CB1 signaling to the cardiometabolic effects of endocannabinoids	BMBF/DZHK	S. Steffens	01/2015-12/2016
Proteomic screening for neutrophil-derived mediators promoting myocardial infarction repair	BMBF/DZHK	S. Steffens	09/2016-12/2017
Role of CB1 cannabinoid receptors in atherosclerosis	LMU *FöFoLe*	S. Steffens	04/2017-09/2018
Functional characterisation of T and B cells autoimmune reactions of atherosclerosis in hyperlipidemic mice.	DFG	A. Habenicht	01/2013-03/2017
Atherosklerosis B Cell Autoimmunity in Aged Hyperlipidemic Mice	DFG	A. Habenicht	01/2016-12/2019
Immune Injury of the Central Nervous System in Aged Humanized Transgenic apolipoprotein E Isoform-specific Knockin Mice	DFG	C. Yin	01/2016-02/2019
Atherosclerosis Peripheral Nervous System Crosstalk in Apolipoprotein E-deficient and Human Apolipoprotein E Isoform-specific Knock-in Mice	DFG	S. Mohanta	01/2016-04/2019
Optical imaging platform	DFG *SFB1123, TP Z1*	R. Megens	07/2014-06/2018
Chemokine-Heteromers in atherosclerosis	DFG *SFB1123, TP A2*	P. von Hundelshausen	07/2014-06/2018
Homoarginine for Heart and Health (H4H2)	**LMUexcellent**	**D. Atzler**	06/2016-12/2017
Role of microRNAs in metabolic reprogramming during macrophage polarization“	**Else-Kröner-Fresenius Stiftung**	**A. Schober**	02/2015-01/2018
Mechanisms and targeting of proatherogenic and atheroprotective microRNAs	**DFG** *SFB1123, TP B4*	**A. Schober, C. Weber**	07/2014-06/2018

Project	Sponsor *Reference*	Principal investigator Collaboration partner	Time frame
Lysophosphatidic acid and autotaxin in atherosclerosis	**DFG** *SFB1123, TP B8*	**A. Schober, W. Siess**	07/2014-06/2018
Role of miRNA-regulated lncRNAs in endothelial cells during atherosclerosis	**DZHK**	**A. Schober**	2015-2016
Glycoprotein VI new therapeutic strategies	**Bayerische Forschungsstiftung** *AZ 1145-14*	**W. Siess** **M. Ungerer (AdvanceCor)**	04/2015-09/2017
Anti-atherothrombotic effects of Ylanthia® anti-GPVI antibodies	**MorphoSys AG München**	**W. Siess, C. Weber** **M. Urban** **S. Runz (Morphosys)**	06/2016-11/2016
Cell-specific vascular protection by CXCL12/CXCR4 PROVASC	**European Research Council**	**C. Weber**	10/2016-09/2021
DC and T cell function in atherosclerosis	**DFG** *SFB1054, B4*	**C. Weber**	01/2013-12/2016

Prizes and Awards

D. Atzler - Rudolf-Buchheim Prize 2017

Dr. Dorothee Atzler has been awarded the Rudolf-Buchheim-Preis 2017 of the German Society of Pharmacology and Toxicology (DGPT) for her translational research approach, which she published in the two manuscripts "Dietary supplementation with homoarginine preserves cardiac function in a murine model of post-myocardial infarction heart failure" (Circulation 2017) and "Oral supplementation with L-homoarginine in young volunteers" (Br J Clin Pharmacol. 2016).

O. Söhnlein - Preis der GSK Stiftung „Medizinische Grundlagenforschung" 2017

Prof. Söhnlein was awarded the prize of the Glaxo Smith Kline (GSK) Foundation for his work „Cathepsin G Controls Arterial But Not Venular Myeloid Cell Recruitment." (Circulation, 2016).

O. Söhnlein - ESCI Young Investigator Award 2017

Professor Oliver Soehnlein received the Young Scientist Award at the annual meeting of the European Society of Clinical Investigation (ESCI) in Genoa, for his translational research achievements, which have led to high ranking publications and patent applications.

C. Weber - ExpertScape world's leading expert on Atherosclerosis 2016

Professor Christian Weber has been named by the health information website, ExpertScape, as the world's leading expert on Atherosclerosis in a ranking of experts for the treatment and understanding of this disease. ExpertScape produces its rankings through analysing data gathered via PubMed. Professor Weber's position is based on 104 articles published between 2006 and 2015.

S. Steffens - ESC Outstanding Achievement Award 2016

The Outstanding Achievement Award 2016 was given to Prof. Sabine Steffens by the ESC Council for Basic Cardiovascular Science (CBCS). The Award recompenses outstanding basic researchers in the early stage of their career. Prof. Steffens was honored for her scientific contributions on the role of the endocannabinoid signaling in cardiovascular disease, and more recently on the relevance of neutrophils in post-myocardial infarction repair

P. Hartmann - Förderpreis für Diplom-Trophologin 2016

The € 5,000 prize awarded by the Institut Danone Nutrition for Health e.V. to the graduate in Trophology Petra Hartmann. The junior researcher was rewarded for her molecular-biological PhD research project on the importance of a special enzyme in the development of atherosclerosis.

E. Lutgens - Jeffrey Hoeg Award 2016

During the annual Scientific Sessions of the ATVB council of the American Heart Association, May 4-6, Nashville, TN, USA, Prof. Esther Lutgens received the prestigious Jeffrey Hoeg award, and gave the award lecture. She received the award for her groundbreaking work on the role of immune checkpoint regulators (ie co-stimulatory molecules such as CD40L and CD40) in vascular disease.

Thrombosis & Haemostasis

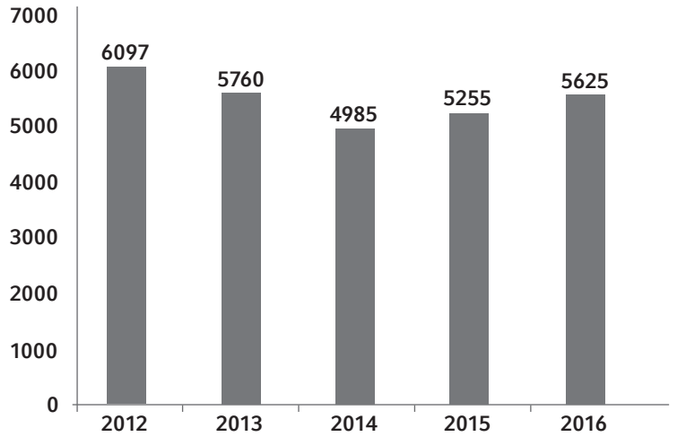
Thrombosis & Haemostasis is a leading journal of the now Thieme (previously Schattauer) Publishing Group, which brings out novel and high quality reports on basic and clinical research in the areas of thrombosis and haemostasis, vascular biology and medicine, inflammation and infection, platelet and leukocyte biology, from genetic, molecular & cellular studies, diagnostic, therapeutic & preventative studies to high-level translational and clinical research.
Target group: Haematologists, clinical pharmatologists, cardiologists, surgeons, gynaecologists, internal specialists and laboratory physicians. The journal acts as a platform for the exchange of ideas and concepts fostering cross-disciplinary insights in basic and clinical research. Thrombosis and Haemostasis publishes position, guideline and state-of-the-art papers, as well as expert analysis, commentaries, and dedicated Theme issues covering recent developments and key topics in the field. Prof. Weber serves as the Editor-in-Chief (Basic Sciences) since 2010.

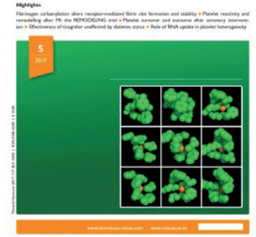
General Information

The journal is published monthly in print (ISSN 0340–6245) and online (www.thrombosis-online.com). The journal is referenced in the main abstracting and indexing services worldwide. The journal continues serving as a link journal for the European Society of Cardiology Working Groups on Thrombosis and on Atherosclerosis and Vascular Biology, as well as being the official journal of the Spanish Society on Thrombosis and Haemostasis (SETH), the Gesellschaft für Thrombose- und Hämostaseforschung (GTH) and the Australian Vascular Biology Society (AVBS). Thrombosis and Haemostasis supports disseminating of important position documents, epitomizing the journal's cutting-edge information and consensus recommendations.

Highlights 2016-2017

The number of submissions for the first time significantly exceeded the millennium mark in 2013 and remains around this level since then. Nevertheless the average time to first editorial decision could be reduced to 20 days over the last two years.
In 2015 the Impact Factor for Thrombosis and Haemostats has again risen to 5.255 terms representing one of the leading journals in its field.





The Journal articles are split in two categories: Basic and Clinical Research. The eight subcategories are as follows: Coagulation and Fibrinolysis, Cellular Haemostasis and Platelets, Blood Cells, Inflammation and Infection, Endothelium and Angiogenesis, Cellular Signalling and Proteolysis, New Technologies, Diagnostic Tools and Drugs, Stroke, Systemic or Venous Thromboembolism, Atherosclerosis and Ischaemic Disease.

In 2017, the cover design of *Thrombosis and Haemostasis* was modernized. The coulour changes each month, to match the selected front page figure. One volume with 12 issues comes out each year, making the numbering more straightforward to our readers. The 2017 volume is called 117 (issues 1–12).

Thrombosis and Haemostasis is active in the digital sphere. The latest papers are online immediately after acceptance (www.thrombosis-online.com). Selected news are also highlighted on social media (Facebook, Twitter as well as Linkedin)

In 2017 an open access offspring journal 'TH Open' was launched. This new journal is off to a great start, especially with its "pay what you want" Open Access model.

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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 Verhütung 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 Vermögensverwaltung 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 Kultusministerium vertreten. 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.

Bauliche Entwicklungen

Neue Labor- und Büroräume am Max-Lebsche-Platz

In Großhadern am Max-Lebsche-Platz 30 entstanden auf über 350 m² ein neues Labor und Büroräume für insgesamt 30 Mitarbeiter des IPEK. In unmittelbarer Nähe zum Klinikum Großhadern und dem Biomedizinischen Centrum wurde durch zahlreiche Neuanschaffungen und Umbaumaßnahmen den Arbeitsgruppen von Prof. Dr. Andreas Habenicht, Prof. Dr. Christian Ries und Dr. Alexander Bartelt neuer moderner Arbeitsraum bereitgestellt. Neben komplett neuer Labor- und Büromöbelausstattung wurden ein spezieller Laborraum für besondere Einzelzelleanalysen eingerichtet, der sterile Arbeitsbereich komplett erneuert und die für gentechnisches Arbeiten notwendige Infrastruktur geschaffen. Darüber hinaus wurde eine neue biochemische und molekularbiologische Grundausstattung angeschafft, die moderne Zentrifugen, Spectrometer, Elektrophorese-Anlagen und ein spezielles Fluoreszenz-Mikroskop enthält. Somit wurde für ein erfolgreiches Arbeiten an den molekularen Grundlagen der Kreislaufkrankheiten der Grundstein gelegt.

Interdisciplinary Research Networks and Project Funding

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 (MHA)

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

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

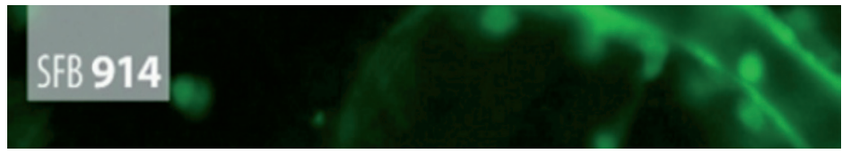
The **Munich research area** is the ideal site to address these goals, as it combines excellent basic and clinical research on the disease mechanisms and interventions to prevent and treat CHD. In particular, Munich provides the nation's leading cardiovascular framework to conduct large clinical phase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

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

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

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

DFG Sonderforschungsbereich 914



Trafficking of Immune Cells in Inflammation, Development and Disease

Trafficking 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.

DFG Sonderforschungsbereich 1054

T lymphocytes are at the center of the immune defense, but also cause immune-mediated disease. Although autoimmunity, allergy, tumors and chronic infections affect a significant percentage of the world population, the reasons for the divergent roles of T cells are largely unknown. The interplay between antigen presenting cells and T cells determines the outcome and quality of adaptive immunity. The emergence of functionally divergent T and dendritic cell subsets is a hallmark of adaptive immunity, but we are only beginning to understand the developmental pathways and signals controlling these cell-fate decisions. These cells preserve a high degree of plasticity to adjust their functional programs to novel contexts, but the driving forces and signals for their differentiation are largely unknown.

The CRC 1054 will explore control and plasticity of cell-fate decisions in the immune system, identify input signals that determine stability and flexibility of differentiation, and characterize the molecular basis for how these signals are decoded.

The long-term research goal of the CRC 1054 is to identify targets that allow the control of immune cell differentiation for specific therapeutic manipulation. Thus the findings from this CRC will ultimately be used to exploit plasticity of immune cell-fate decisions for optimizing vaccination strategies, resuscitating exhausted T cells in chronic infections and the reverting cell-fate decisions for the treatment of allergy, autoimmunity and cancer.

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 Sonderforschungsbereich 1123

Atherosclerosis - Mechanisms and Networks of Novel Therapeutic Targets

Academic profile of the Collaborative Research Centre

Vascular disease including coronary artery disease (CAD) and stroke remains the leading cause of death and morbidity worldwide despite significant advances in interventional and medical treatment. As impressively illustrated by the global burden of disease study, cardiovascular disease, which is overwhelmingly caused by atherosclerosis as the underlying pathology, is the **global killer number one,** claiming 15.6 million lives in 2010. Compared with other entities, this prevalence will continue to dominate, owing to an increasing life expectancy in Western but also emerging societies. In the EU, CAD represents the most frequent cause of death, accounting for 40% or 2 million per year. The enormous socio-economic costs imposed by CAD on European healthcare systems are estimated at 110 billion Euro per year and continue to rise. This dilemma could be limited by improving vascular prevention and therapy based on a more **refined mechanistic pervasion of atherosclerosis,** prompting a more efficient and reliable identification and validation of new targets for potential translation to drug development. The latter is mandated by declining success rates for transition beyond clinical phase II and numerous recent failures in clinical phase III, which illustrate inherent pitfalls of cardiovascular drug development. Hence, it is the mission of the planned collaborative research center (CRC) to improve the in-depth mechanistic understanding of **molecular networks in atherogenesis, atheroprogression and atherothrombosis** as the pathological sequence of CAD, leading to the identification and verification of worthwhile targets for treating atherosclerosis.

Atherosclerosis is characterized by a delicate continuum of early atherogenesis amenable to prevention and a progression to vulnerable plaques. This can either lead to stabilization and remodeling or to destabilization with plaque rupture, atherothrombosis and occlusion, giving rise to stroke or myocardial infarction. We will limit our **focus to the spectrum of arterial pathology,** which is accessible to specific targeting, but we will not cover myocardial damage by infarction or ischemia/reperfusion. The latter area has benefited from recent advances in interventional therapy and is a central topic of various other research initiatives. In contrast, atherosclerosis requires chronic treatment, which carries a considerable risk of side effects. The stagnation in therapeutic development and multiple failures in clinical validation e.g. due to off-target effects, are less surprising when considering the **complex levels of pathophysiological regulation and interactions of potential targets.** This predicament also explains the tendency of the pharmaceutical industry to resort to known therapeutics and why no specific cardiovascular therapeutic has been introduced recently. We thus plan to adequately map the pathogenic complexity and to discover novel mechanisms, their interactions and targets with a better predictable efficacy and safety.

Atherogenesis is driven by a disturbed equilibrium of lipid accumulation, maladaptive immune responses and their clearance, entailing chronic inflammation of the artery wall, crosstalk with pro-coagulant pathways and culminating in plaque rupture and thrombosis. New **atherogenic and/or protective pathways mutually linking lipid, inflammation and coagulation biology** have been discovered, and profiling studies, namely genome-wide association studies (GWAS), unveiled risk **genetic variants and epigenetic factors** for CAD. This multitude of variables gives rise to complex network effects creating specific signatures for this disease. Bioinformatics analysis, next generation sequencing (NGS) and omics tools will be instrumental for the discovery of **biologicals** for vascular disease, which will gain importance over classical drug candidate or high-throughput approaches, since their **structure-function relationship** can be more readily probed, while off-target effects and toxicity can be better anticipated. An identification of worthwhile targets within such networks requires unbiased screening of different targets, a thorough pathogenic basis and analysis of their interactions in relevant model systems in vivo. We aim to systematically elaborate such intricately linked molecular mechanisms for different target families (cytokines, signal proteins, nucleic acids and lipid mediators), some of which have been verified in relevance by GWAS, allowing for a suffi-ciently broad yet coherent spectrum. We will propagate their validation by **molecular imaging technologies** in human tissue or animal models, e.g. using an array of **transgenic and knockout mouse models** of cell-specifically inducible gene deletion, knockin insertion of mutants and/or fluorescent labeling. We will further aim to extend the boundaries of subcellular visualization by implementing newly developed methods of optoacoustic imaging and super-resolution nanoscopy.

Primary goal of the planned CRC 1123 will be to improve and accelerate the identification and validation of novel targets to treat the pathogenetic sequence of atherosclerosis culminating in plaque rupture and/or atherothrombosis. The disturbed equilibrium between lipid metabolism and immune reactivity entailing chronic inflammation of the arterial wall is shaped by leukocyte trafficking and homeostasis governed by guidance cues, e.g. chemokines or lipid mediators. The c**hronic inflammatory reaction and maladaptive immune response** features effector cells of both innate and adaptive immunity, for instance neutrophils, dendritic cells and

their interactions identified by our group members. The growing appreciation of the inflammatory processes and mediators involved has uncovered an intriguing diversity of targetable mechanisms that could be exploited to complement lipid-lowering therapies. In the planned CRC, we aim to implement **harmonized model systems and standardized protocols** and to employ **bioinformatic network analyses**, which reflect the multifactorial and complex nature of this disease, to identify the cross-talk and interaction of the molecular mechanisms and individual targets. In particular, we see an important **triad** emerging that links chronic inflammation to **lipid mediators and metabolism,** to **procoagulative/ thrombogenic pathways** and to **genetic/epi-genetic risk factors.** These pathways are represented in two target areas with **signal proteins and cytokines (area A)** and **nucleic acids and lipid mediators (area B),** wherein multiple projects exemplify the cross-talk of inflammation with lipid biology or with coagulation and thrombogenicity **(Fig. 1).**

We envision that the planned CRC, by assembling an internationally leading group of scientists, will contribute to a significant conceptual advance in the field of atherosclerosis research by introducing harmonized protocols, bioinformatic network analysis and interactive modeling of a complex disease, and implementing state-of-the-art transgenic and novel molecular imaging technology. This may help to redefine the standards of target discovery and validation and to open desired therapeutic options.

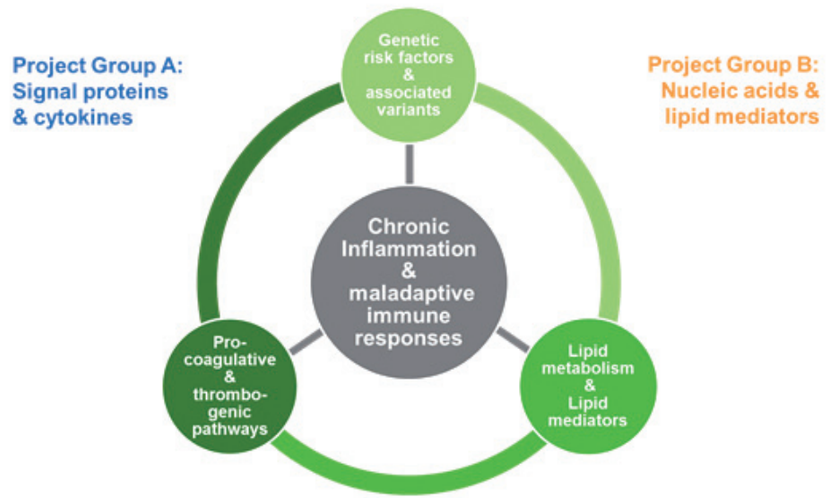


Figure 1: Pathogenesis of atherosclerosis: creating mechanistic links between target families/pathways

Summary

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

Kennzahlen

Die Kennzahlen werden unterteilt in den wissenschaftlichen Bereich und die internistische Ambulanz mit ihren Mitarbeitern.

Mitarbeiter

Zahlen im Bereich des wissenschaftlich tätigen Personals

Berufsbezeichnung	Gesamtzahl	Haushaltsfinanzierung 2016-2017	Drittmittelfinanzierung 2016-2017
Institutsdirektor	1	1	
Professoren	12	11	1
Arbeitsgruppenleiter	6	6	
Post-Doktoranden	24	5	19
Doktoranden	37		37
nichtwissenschaft-liche Mitarbeiter	43	22	21
Gesamt	**123**	**45**	**78**

Aufgrund von überlappenden Aufgabenverteilungen in hauptsächlich grundlagen-wissenschaftlich tätigem oder teilweise klinisch wissenschaftlich arbeitendem Personal, beläuft sich die Gesamtzahl der Mitarbeiter auf **123** Personen. In dieser Zahl enthalten sind ebenfalls Mitarbeiter, die über Stipendien finanziert werden und/oder eine 50-75%-Teilzeitanstellung am IPEK ausüben.

Mitarbeiter

Ahmadsei, Maiwand
Aslani, Maria
Atzler, Dorothee, Dr. rer. nat.
Auer, Sandra

Badmann, Tobias
Bayer, Julia
Bianchini, Mariaelvy
Bidzhekov, Kiril, Dr. rer. hum. biol.
Blanchet, Xavier, PhD
Braster, Quine
Bretzke, Eva
Bürger, Christina
Busygina, Kristina

Clados, Adelheid, Dr. med.
Chèvre, Raphael
Cimen, Ismail
Corbalán Campos, Judit

Deininger, Matthias
de Jong, Renske
De Winter, Menno
Döring, Yvonne, Dr. rer. nat.
Drechsler, Maik, Dr. rer. nat.
Duchene, Johan, PhD

Ebrahim, Mariam
Eckhardt, Veit, cand. med.
Egea Alonso,Virginia, Dr. rer. nat.

Faußner, Alexander, PD Dr. rer. nat.
Farima, Zahedi
Ferrari, Elena
Ferraro, Bartolo

Geißler, Claudia
Gerdes, Norbert, Dr. rer. nat.
Gimpfl, Christiane
Gippner-Steppert, Cornelia, Dr.rer.nat.
Guillamat-Prats, Raquel

Habenicht, Andreas, Prof. Dr.
Haberbosch, Markus
Hartmann, Petra, Dipl. Troph.
Hering, Daniel
Herrle, Corinna
Heyll, Kathrin
Hidalgo, Andres, Prof. Dr.
Hilby, Michael
Homann, Karina
Horckmans, Michael, Dr. biol.
Hristov, Michael, PD Dr. med.

Jamasbi, Janina, Apothekerin
Jansen, Yvonne, BSc.

Karshovska, Ela, Dr. rer. biol. hum.

Lacy, Michael
Lemnitzer, Patricia
Leoni, Giovanna, PhD
Li, Yuanfang
Lorenz, Reinhard, Univ.-Prof. Dr. med.
Lutgens, Esther, Prof. Dr. med., PhD
Lu, Shu

Ma, Zhe
Maas, Sanne
Mahl, Christian
Mandl, Manuela
Megens, Remco T.A., PhD

Mohanta, Sarajo, PhD
Mohibullah, Rokia
Moshkova, Irina, Dipl.-Ing.
Mückter, Harald, PD Dr.
Mühlberger, Sonja
Müller, Phillip

Natarelli, Lucia, MSc
Nazari-Jahantigh, Maliheh, MSc
Neideck, Carlos

Ortega Gomez, Almudena, Dr.

Paulin, Nicole
Pawig, Lukas
Pérez Olivares, Laura
Pilz, Veronika
Pitsch, Thomas
Puhl, Sarah-Lena
Putz, Emanuel
Preischl, Carina

Rami, Martina
Reichenberger, Monika
Reim, Sigrid
Richter, Elmar, Prof. Dr. med. vet.
Riedasch, Annalena, Dr. med. vet.
Ries, Christian, PD Dr. rer. nat.
Rodrigues Viola, Joana, Dr. rer. nat.
Rot, Antal
Rügamer-Biese, Karola
Ruiz-Heinrich, Lourdes

Santovito, Donato, Dr. med.
Saroyan, Lusine
Schengel, Olga
Schiener, Maximilian, Dipl. Chem.
Schmitt, Martin, Dipl. Biol.
Schober, Andreas, Univ.-Prof. Dr. med.
Schumski, Ariane
Seidl, Cornelia
Seijkens, Tom
Sharifi, Mohammad
Siess, Wolfgang, Univ.-Prof. Dr. med.
Silvestre-Roig, Carlos, PhD
Simon, Stefan
Söhnlein, Oliver, Univ.-Prof. Dr. Dr. med.
Steffens, Sabine, Univ.-Prof. Dr. rer. nat.
Stöger, Brigitte
Streicher, Sabine

v. Hundelshausen, Philipp, Dr. med.
v. Oheimb, Kathrin
van der Vorst, Emiel

Wagner, Diana
Weber, Christian, Univ.-Prof. Dr. med.
Wei, Yuanyuan, PhD
Winkels, Holger
Winter, Carla
Winter, Janine

Yin, Changjun, Dr. rer. nat.

Zahedi, Farima, MSc
Zhang, Chuaraki
Zhang, Panimei
Zhang, Xi
Zhao, Zhen
Zhu, Mengyu, MSc
Zimmermann, Christof

Publications

2016

	n	IF Sum	IF Average
Total	63	473.4	8.0
First/Last Auhtorship IPEK	38	264.5	7.6

	n	IF Sum	IF Average
Original articles	48	354.7	8.0
First/Last Authorship IPEK	21	145.8	7.3

	n	IF Sum	IF Average
Reviews and Commentaries	15	118.7	7.9
First/Last Authorship IPEK	15	118.7	7.9

Original Articles

Alam A, Leoni G, Quiros M, Wu H, Desai C, Nishio H, Jones RM, Nusrat A, Neish AS. The microenvironment of injured murine gut elicits a local pro-restitutive microbiota. Nat Microbiol. 2016; 1:15021. (IF 0.500)

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2017

	n	IF Sum	IF Average
Total	71	686.4	9.7
First/Last Auhtorship IPEK	38	416	10.7

	n	IF Sum	IF Average
Original articles	49	477.1	9.7
First/Last Authorship IPEK	19	212	11.2

	n	IF Sum	IF Average
Reviews and Commentaries	22	209.3	9.5
First/Last Authorship IPEK	19	204	10.2

Original articles

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