LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

2014/2015

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 exzellenten publikatorischen Leistungen sowie vor allem neu rekrutierte zusätzliche Leistungsträger und hoffnungsvolle Nachwuchswissenschaftler sollen Ihnen in der nun vorliegenden Ausgabe 2014/2015 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. In bewährter Tradition finden Sie so auch alle wichtigen Kontaktinformationen und Ansprechpartner, die 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 möglichen Translation neuester Befunde in die vaskuläre Diagnostik und Therapie zur Lektüre empfehlen zu dürfen.

Im Namen des gesamten IPEK-Teams

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

Editorial

Atherosklerose ist eine chronisch entzündliche Erkrankung des arteriellen Gefäßsystems, die zu Stenosen, z.B. der Herzkranzgefäße, mit akuten und chronischen Komplikationen führt. William Heberden fasste die klassischen Symptome der koronaren Herzerkrankung 1772 als Angina pectoris zusammen. Erst zu Beginn des 20. Jahrhunderts wurde der Grund für die Symptome mit arteriellen Stenosen erklärt. Den Terminus Atherosklerose (aus dem griechischen athere = Schleim, scleros = hart) prägte der deutsche Pathologe Felix Jacob Marchand, der damit im Jahr 1904 die fettigen Veränderungen verhärteter Arterien beschrieb. Bereits 1856 postulierte Rudolf Virchow in seinen Gesammelten Abhandlungen zur Medizin, dass die Atherosklerose als Endarteritis chronica deformans durch Plasmabestandteile verursacht wird, welche eine entzündliche Reaktion in der Gefäßwand auslösen. Nach wie vor ist die Atherosklerose mit ihren Folgen Myokardinfarkt und Schlaganfall nicht nur führende Todesursache, sondern auch einer der wesentlichen Gründe für die Morbidität in den Industrienationen. Nach über einem Jahrzehnt konsequent und nachhaltig verfolgter Forschung an verschiedenen Ansatzpunkten für eine bessere Vorhersage und Behandlung dieser Volkskrankheit, ist es 2014 einem schlagkräftigen Team von Wissenschaftlern unter Federführung des Instituts für Prophylaxe und Epidemiologie der Kreislaufkrankheiten der LMU gelungen, am Standort München erstmals einen Sonderforschungsbereich der Deutschen Forschungsgemeinschaft zum Thema „Atherosklerose - Mechanismen und Netzwerke neuer therapeutischer Zielstrukturen“ (SFB1123) einzurichten. Hier soll den molekularen Ursachen einer Trias von Entzündung, Genetik und Fettstoffwechsel, ihrer Interaktion und therapeutischen Anwendbarkeit auf den Grund gegangen werden.

Für einen solchen langfristigen Erfolg in der Wissenschaft sind nicht nur enorme Resilienz und Frustrationstoleranz wichtige Voraussetzung, sondern auch Geduld und die Fähigkeit, den vorherrschenden und schnelllebigen, vulgo “gehypten“, Strömungen der Wissenschaft zu widerstehen, dem „citius, altius, fortius“ neue Akzente entgegenzusetzen und mit Beharrlichkeit eine eigene Handschrift zu entwickeln. Wir haben dieses Konzept der Nachhaltigkeit in Analogie zu anderen Lebensbereichen, etwa „slow food“ oder „slow cinema“, zur Philosophie der „slow science“ erhoben. Deren Ziel ist es, „dicke Bretter“ zu bohren, auch wenn dies zuweilen zu Lasten von schnell getakteten und hochrangigen Publikationen geht. So konnte etwa eine Arbeit aus dem IPEK nicht, wie die Veröffentlichung einer konkurrierenden Arbeitsgruppe in Science publiziert werden, sondern nur in einem spezialisierten Fachorgan, da aufgrund der gebotenen Zurückhaltung und Sorgfalt die dort erhobenen Befunde nicht bestätigt, vielmehr sogar widerlegt werden konnten. Andererseits werden am IPEK viele Projekte verfolgt und durchgeführt, die zum Teil sieben Jahre oder länger andauern und beinahe Generationen von Wissenschaftlern in Anspruch nehmen, von Proteomik bis Strukturbiologie, Modellierung und biophysikalischen Techniken bis hin zu höchstauflösender Nanoskopie und transgenen Tiermodellen. All dies wird hoffentlich dazu beitragen, durch bessere Übertragbarkeit der Befunde in die Klinik auch für viele Patienten entscheidende Fortschritte erzielen zu können, welche von der biotechnologischen oder pharmazeutischen Industrie, wie in einigen Beispielen am IPEK bereits geschehen, aufgegriffen und bis zu einer Marktreife hin weiterentwickelt werden. So sollte sich auch „slow science“ zum Wohle aller Beteiligten auswirken.

Inhaltsverzeichnis

Institutsdirektor

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

Prof. Christian Weber hat wegweisende Beiträge zu einem besseren Verständnis der Pathogenese der Atherosklerose als chronisch-inflammatorische Erkrankung und als Grundlage für neue Therapieformen geleistet. Auf Basis seiner Arbeit und Initiative als Koordinator und Gründungssprecher wurde erstmals ein Sonderforschungsbereich zum Thema „Atherosklerose und therapeutische Zielstrukturen" eingerichtet, der von den Gutachtern als herausragend beurteilt worden ist und als weltweit einzigartig angesehen wurde. Die Forschung von Herrn Weber ist maßgeblich für das heutige Verständnis der entzündlichen Pathogenese der Atherosklerose, insbesondere durch die Entdeckung der Rolle von Entzündungsmediatoren, wie Chemokinen und verwandten Zytokinen, bei der Rekrutierung von Leukozyten in die Gefäßwand und der protektiven Funktion regulatorischer microRNAs. Die mechanistische Aufklärung dieser Prozesse durch Herrn Weber hat dabei eine Reihe bahnbrechender Ergebnisse hervorgebracht, die eine Umsetzung neu identifizierter molekularer Zielstrukturen in therapeutisch anwendbare Ansätze erlauben, z.B. auf Basis zyklischer Peptide oder microRNA Mimetika. Damit gilt Herr Weber als einer der weltweit führenden Experten für die Rolle von Chemokinen, verwandten Zytokinen und microRNAs in der Atherosklerose.

Die Arbeiten von Herrn Weber sind in ihrer Gesamtheit hochinnovativ, bedienen sich modernster genetischer Tiermodelle und Mikroskopietechniken und sind von maßgeblicher Bedeutung für das molekulare Verständnis der Pathogenese und therapeutischer Zielstrukturen der Atherosklerose. Die Konzepte zur nebenwirkungsarmen Intervention im Chemokin-Interaktom und zu Bindungsstrukturen von MIF haben zu zahlreichen Patentanmeldungen und Patenten geführt, welche die Basis für die Ausgründung der Biopharmafirma *Carolus Therapeutics Inc.* gebildet haben. Da bislang keine selektiven Therapieoptionen für die Atherosklerose verfügbar sind, stellen die Befunde von Prof. Weber eine wichtige Innovation dar. Gerade die Entwicklung anti-entzündlicher Biologika ohne Nebenwirkungen auf das Immun- oder Gerinnungssystem wären ein wesentlicher Fortschritt mit erheblichem Potential für eine kontinuierliche Therapie. Diese Ansätze wurden unter anderem mit dem Paul-Martini-Preis 2008 und dem Galenus-von-Pergamon-Preis 2009 für Grundlagen der Medikamentenentwicklung ausgezeichnet. In Allianz mit *Incardia Therapeutics* steht CT-2009 als erster Kandidat kurz vor dem Eintritt in die klinische Studienphase.

Seit 1991 hat Herr Weber 285 Originalia und 170 Übersichtsarbeiten in *peer-reviewed* Zeitschriften mit einer Gesamt-Impactsumme von >3.300 veröffentlicht. Seine Publikationen wurden bisher ca. 23.500-mal zitiert, davon 2015 >2.800-mal mit steigender Tendenz, und haben einen h-Index von 84 (*Scopus*) und m-Index von 3,4 (*Web of Science*) erzielt. Allein 70 Publikationen wurden >100-mal zitiert. Diese Daten weisen Herrn Weber als international herausragenden Wissenschaftler mit wegweisenden Beiträgen in seinem Fachgebiet aus, der den Zenit seiner Produktivität noch nicht erreicht hat. In *Nat Med* 2011 (>500 Zitationen) hat er die Pathogenese und Therapieoptionen der Atherosklerose zusammengefasst.

Die Forschung von Herrn Weber wird seit 1995 kontinuierlich durch die DFG gefördert, u.a. in den Sonderforschungsbereichen SFB542, TRR5, SFB914 und SFB1054. Herr Weber war Sprecher der Forschergruppe 809 *Chemokine und Adhäsionsmoleküle in der kardiovaskulären Pathogenese* und des Internationalen Graduiertenkollegs 1508 *Arterial Remodeling.* Zudem fungiert er als Ko-Koordinator der Munich Heart Alliance im Deutschen Zentrum für Herz-Kreislauf-Forschung (DZHK). Herr Weber wurde für seine Arbeit mit einer Reihe wichtiger Preise, z.B. dem GlaxoSmithKline Wissenschaftspreis 2003, dem Arthur-Weber Preis 2004, dem Forßmann-Preis 2005, dem Hauss-Preis 2008, dem *ESC Outstanding Achievement Award* 2008, dem *Special Recognition Award* 2009 der *American Heart Association* und dem Alexander-Schmidt-Preis der GTH 2015 für seine Verdienste um die Atheroskleroseforschung ausgezeichnet. Neben der Tätigkeit in Editorial Boards zahlreicher wissenschaftlicher Fachzeitschriften dient Herr Weber seit 2010 als *Editor-in-Chief* des Fachorgans *Thrombosis & Haemostasis,* seit 2012 als Senior Associate Editor für Arteriosclerosis *Thrombosis & Vascular Biology* und seit 2014 als Consulting Editor für *Circulation Research.*
Auf europäischer Ebene ist hervorzuheben, dass Herrn Weber als einem von wenigen Lebenswissenschaftlern ein zweiter *ERC Advanced Investigator Grant* (Atheroprotect) des *European Research Council* und der VICI Preis der *Nederlandse Organisatie voor Wetenschappelijk Onderzoek* zugesprochen wurde. Zudem ist er der europäische Koordinator des Leducq Transatlantic Network of Excellence CVGeneF(x). Neben diversen eingeladenen Vorträgen auf Gordon und Keystone Konferenzen ist seine internationale Reputation durch Rufe auf Lehrstühle der University of Virginia, des King's College London, der RWTH Aachen, der Heinrich-Heine-Universität Düsseldorf, der Westfälischen Wilhelms-Universität Münster sowie die Ernennung zum Gastprofessor der Universität Maastricht unterstrichen worden. Nach dem Aufbau des Instituts für Molekulare Herz-Kreislaufforschung an der RWTH Aachen ist er seit 2010 Inhaber des Lehrstuhls für Vaskuläre Medizin an der Ludwig-Maximilians-Universität München.

Die erfolgreiche Einrichtung des Sonderforschungsbereichs SFB1123 *Atherosklerose – Neue Mechanismen und Netzwerke therapeutischer Zielstrukturen* durch die DFG stellt einen weiteren Meilenstein dar, mit dem auch die Arbeit von Prof. Weber eine besondere

Würdigung erfahren hat. Hier ist es gelungen, eine Reihe namhafter Wissenschaftler zusammenzuführen, die sich gemeinsam dieser Thematik interdisziplinär und mit komplementärer Expertise widmen werden. Mittels neuer optoakustischer und nanoskopisch auflösender Bildgebungstechnologien, einer Reihe transgener und konditionaler Mausmodelle sowie bioinformatischer Netzwerkanalysen soll die pathogenetische Komplexizität adäquat abgebildet werden, um so die Interaktion molekularer Mechanismen und individueller Zielstrukturen zu identifizieren. Damit sollen die Standards für die Entdeckung und Validierung therapeutischer Zielstrukturen neu definiert werden.

Biosketch (english)

Christian Weber is Director of the Institute for Cardiovascular Prevention and the Chair in Vascular Medicine at Ludwig-Maximilians-University (LMU) in 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 serves as a 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. Among many other awards, he is a double ERC Advanced Grant Recipient with > 460 publications, more than 24.000 citations and an h-index of 84 and serves as the Editor-in-Chief of *Thrombosis & Haemostasis,* Senior Associate Editor of *Arterisclerosis,Thrombosis & Vascular Biology* and 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 fünfzehn Arbeitsgruppenleiter, darunter zwei C3-Professoren, drei W2-Professoren und drei außerplanmäßige Professoren thematisch eigenständige Arbeitsgruppen. Des Weiteren umfasst das Institut die DFG-Forschergruppe 809, ist Sprechereinrichtung des Sonderforschungsbereichs 1123 sowie Editorial Office des Journals Thrombosis & Haemostasis und ist eine der Mitgliederinstitutionen des DZHK-Standortes München.

Organigramm der August-Lenz-Stiftung

Durch den Chefarzt und zwei Oberärzte werden mehrere internistische Teilgebietsschwerpunkte abgedeckt. Zudem wurden die Patienten durch eine Assistenzärztin und den Emeritus betreut. Die Laboranalytik und die Durchführung spezieller Untersuchungen am Patienten werden durch mehrere MTAs vorgenommen.

Adressen

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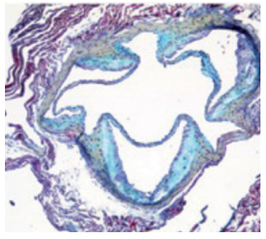
Januar 2014

Zu viel schädliches Cholesterin im Blut ist ein wichtiger Risikofaktor für Gefäßerkrankungen. LMU-Wissenschaftler identifizierten nun einen Schalter für den Cholesterinspiegel – möglicherweise werden so neue therapeutische Möglichkeiten eröffnet. Die Verwendung von synthetischen CXCR7-Reaktionspartnern könnte daher eine neue therapeutische Strategie bei zu hohen Cholesterin-Spiegeln im Blut darstellen, wie sie etwa im Rahmen des Metabolischen Syndroms vorkommen. (*Circulation 2014*)



Im Rahmen des Vascular Biology Symposiums am 24. Januar 2014 in Wien wurde Dipl.-Biol. Martin Schmitt der mit 2.000 Euro dotierte Bernd R. Binder Publication Prize 2013 verliehen. Herr Schmitt erhielt den Preis für seine exzellente Publikation *in Circulation* auf dem Forschungsgebiet der vaskulären Biologie und Thromboseforschung, die im Rahmen seiner Promotionsarbeit entstanden ist.

März 2014

IPEK scientists revealed the role of two microRNAs called miR-126-3p and miR-126-5p in atherosclerosis. The results of the study are highly relevant for future approaches to the treatment of atherosclerosis.
The therapeutic procedure already devised is the subject of a patent application, and its further development is underway at the German Center for Cardiovascular Research, in collaboration with interested biotechnology firms.

Mai 2014

New Collaborative Research Centers Atherosclerosis and general homeostasis. LMU researchers coordinate the work of two new Collaborative Research Centers, for which funding has now been approved by the *Deutsche Forschungsgemeinschaft* (DFG).
In order to develop more effective strategies for the prevention and treatment of arterial disease, a better understanding of the pathogenesis and progression of atherosclerosis is crucial. This is where the new Collaborative Research Center (CRC) aims to make a difference. "We plan to characterize the molecular mechanisms that underlie atherosclerosis in detail to enable more efficient and reliable identification and validation of potential drug targets for therapeutic interventions", explains Professor Christian Weber, Director of LMU's Institute for Cardiovascular Prevention (IPEK) and Coordinator of the new CRC.

The new Munich-based CRC started on 1. October 2014, and has received funding amounting to around 11 million euros for the period up to 2018. In addition to LMU as coordinating university, the Technical University Munich, the Helmholtz Center Munich and the Max Planck Institute for Biochemistry are partners in the project.

Juli 2014

Für ihre in *Nature Medicine* publizierte Arbeit zur Rolle von miRNA-126-5p in der Atherosklerose wurden Dr. rer. nat. Maliheh Nazari-Jahantigh und Prof. Dr. med. Andreas Schober mit dem hochdotierten Rolf-Becker-Preis der LMU ausgezeichnet. Der für Erstautoren herausragender Originalarbeiten ausgelobte Preis wurde auf dem Sommerfest der Medizinischen Fakultät am 19.07.2014 in Wildbad Kreuth verliehen. Die Laudatio hielt Prof. Dr. Gerhard Steinbeck, Emeritus für Kardiologie.

September 2014

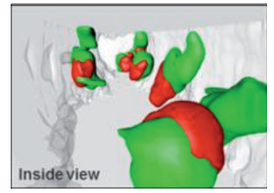
Prof. Dr. Andreas Schober hat den Outstanding Achievement Award der European Society of Cardiology (ESC) / Council for Basic Cardiovascular Research auf dem diesjährigen Kongress der ESC in Barcelona erhalten. Dieser Preis würdigt Grundlagenwissenschaftler, die herausragende Leistungen in der frühen Phase ihrer Karriere erbracht haben.

Oktober 2014

Als Direktor des IPEK gehört Prof. Christian Weber auf dem Gebiet der Herz-Kreislauf-Forschung zu den Besten seines Fachs, wie nun ein Ranking des *Laborjournals* bestätigt. In der aktuellen Ausgabe veröffentlicht das Magazin die 50 in den Jahren 2008 - 2012 am häufigsten zitierten Herz-Kreislauf-Forscher aus Deutschland, Österreich und der Schweiz. Die Häufigkeit, mit der eine wissenschaftliche Originalarbeit zitiert wird, gibt einen Hinweis auf die Relevanz der darin vorgestellten Ergebnisse.
Als einer von wenigen in der Grundlagenwissenschaft aktiven Kardiologen belegt Prof. Weber in diesem Ranking den 25. Platz. Im Zentrum seiner Arbeit steht die Aufklärung der zellulären und molekularen Mechanismen, die der Atherosklerose zugrunde liegen und so neue therapeutische Optionen bei koronarer Herzerkrankung eröffnen. Diese Ansätze von Prof. Weber haben sich in bisher 400 Publikationen und ca. 20.000 Zitationen niedergeschlagen und werden u.a. im gerade eingerichteten Sonderforschungsbereich 1123 weiter verfolgt.

Dezember 2014

In a study published in *Science* Professor Andreas Hidalgo and his group at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) Madrid and the Institute for Cardiovascular Prevention (IPEK) report that mouse neutrophils rely on platelets to help find sites of inflammation. Image shows: Neutrophils (green) extend protrusions into blood vessels. When these protrusions come into contact with platelets (red), the neutrophils migrate into the surrounding tissue to carry out their inflammatory functions. Preventing these neutrophil-platelet interactions can alleviate collateral inflammatory damage to tissues in several injury models in mice.



Februar 2015

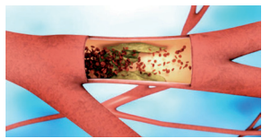
Der Alexander-Schmidt-Preis 2015 der GTH wurde an den Direktor des IPEK, Prof. Dr. Christian Weber, verliehen. Bei dem mit 15.000 Euro dotierten Preis handelt es sich um die wichtigste wissenschaftliche Anerkennung, welche die Gesellschaft für Thrombose- und Hämostaseforschung (GTH) vergibt. Mit dem Preis wurde das Lebenswerk von Prof. Weber, aber auch jüngere Arbeiten zur Rolle der Endothelproliferation in der Atherosklerose gewürdigt.

April 2015

Der Franz-Maximilian-Groedel-Forschungspreis 2015 der Deutschen Gesellschaft für Kardiologie wurde an Frau Dr. Rabea Hinkel aus dem IPEK verliehen. Mit dem mit 5.000 Euro dotierten Preis werden theoretisch und klinisch tätige Wissenschaftler ausgezeichnet, deren wissenschaftliche Arbeiten sich mit Fragen der Herz- und Kreislaufforschung beschäftigen. Mit diesem Preis wurde eine im Juni 2014 in Nature Communications veröffentlichte Arbeit: *MRTF-A controls vessel growth and maturation by increasing the expression of CCN1 and CCN2* gewürdigt, die sich mit dem down-stream signaling von Thymosin ß4 in der therapeutischen Neovaskularisierung beschäftigt.

Juni 2015

Blutgerinnsel in Schlagadern – sogenannte arterielle Thrombosen – gehören zu den häufigsten Ursachen für Herzinfarkte und Schlaganfälle. Sie entstehen durch Verletzungen der Blutgefäße, etwa wenn atherosklerotische Plaques an den Gefäßinnenwänden aufreißen und die in den Gefäßen zirkulierenden Thrombozyten (Blutplättchen) aggregieren. Pharmakologische Thrombozytenhemmer wie Aspirin hemmen diesen Prozess und können vor Thrombosen schützen.



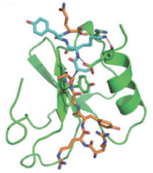
Allerdings wirken sie nur begrenzt, außerdem hemmen sie die Blutplättchen im gesamten Körper und können deswegen Blutungen verursachen. „Daher ist es unser Ziel, antithrombotische Medikamente zu entwickeln, die einerseits wirksamer sind, und andererseits weniger Nebenwirkungen haben" sagt Professor Wolfgang Siess (IPEK), dessen Team nun die Wirksamkeit zweier neuer Strategien der Thrombozytenhemmung verglichen hat. Über ihre Ergebnisse berichten die Wissenschaftler im Fachmagazin *JACC (Journal of the American College of Cardiology).*

Juli 2015

Atherosklerose entsteht, wenn Ablagerungen in der Gefäßinnenwand – sogenannte atherosklerotische Plaques – zu chronischen Entzündungen führen und die Blutgefäße verengen. Plaques behindern den Blutfluss und blockieren ihn schließlich vollständig, was einen Herzinfarkt oder Schlaganfall auslöst. Verursacht werden die chronischen Entzündungen durch eine außer Kontrolle geratene Reaktion des Immunsystems. „Aber das Immunsystem kann an den betroffenen Arterien die überschießende Immunreaktion auch dämpfen", sagt Professor Andreas Habenicht (Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten, Direktor Professor Christian Weber). Das Team von Habenicht konnte nun in Kooperation mit nationalen und internationalen Forschergruppen zeigen, dass sogenannte arterielle tertiäre Lymphorgane (ATLOs) auf den Gefäßaußenwänden den Entzündungen entgegen wirken können. Über ihre Ergebnisse berichten die Wissenschaftler in der Fachzeitschrift *Immunity*.

Dezember 2015

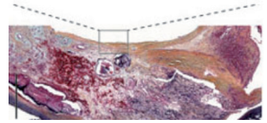
IPEK researchers led by Professor Oliver Söhnlein have developed a short peptide able to inhibit the signal pathway activation in monocytes allowing their adhesion to endothelial cells and penetration in sites of acute inflammation. Their findings appeared in the latest issue of the journal *Science Translational Medicine*.



Februar 2016

Ein Herzinfarkt führt zum Absterben einer großen Zahl an Herzmuskelzellen. Durch das Absterben wird ein Reparaturprozess ausgelöst, der letztendlich zur Narbenbildung und Dilatation des Herzmuskels führt. Häufig kommt es zu Folgeerscheinungen, wie Herzinsuffizienz, die eine dauerhafte Nachbehandlung erfordern und mit hohen Kosten verbunden sind. Die Arbeitsgruppe von Professor Sabine Steffens (Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten, Direktor Professor Christian Weber) beschäftigt sich daher mit der Aufklärung der Pathomechanismen, die an der Infarktheilung beteiligt sind. Eine gerade veröffentlichte Studie der Arbeitsgruppe Steffens im *European Heart Journal* zeigt nun, dass die Neutrophilen eine entscheidende Rolle in der Infarktheilung spielen. Dabei setzen Neutrophile Faktoren frei, welche die Entwicklung von Makrophagen begünstigen, die den Reparaturprozess vorantreiben. „Die Ergebnisse sind insofern überraschend, als man den Neutrophilen bislang lediglich eine schädliche Wirkung nach akutem Herzinfarkt zugeordnet hat", so Prof. Steffens. „Denn Neutrophile wandern unmittelbar nach Infarkt in den geschädigten Herzmuskel ein und fördern eine akute Endzündungsreaktion. Aber Endzündung ist nicht unbedingt nur schädlich, sondern für den Ablauf einer geordneten Wundheilung in Maßen sogar notwendig. Es kommt allerdings auf das richtige Gleichgewicht an."

A team from the Institute for Cardiovascular Prevention at the LMU Medical Center, led by Andreas Schober, has discovered that an enzyme called Dicer plays a central role in the activation of the endothelial cells.



The researchers characterized the mechanism underlying the activation process and identified a new potential target for the therapy of atherosclerosis. The results of the study have been recently published in the journal *Nature Communications*.

Forschung

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

Forschungsbericht 2014

Anzahl der Planstellen für wissenschaftliche Mitarbeiter: 18
Anzahl der Planstellen für Nicht-wissenschaftliche Mitarbeiter: 17
Anzahl aller drittmittelfinanzierten Mitarbeiter: 70

Drittmittelausgaben (in €):

	Anzahl Projekte	Ausgaben 2014 laut Verwaltung
DFG (einschließlich STED Mikroskop)	26	1.998.656
BMBF, StMWFK, EU	10	1.079.905
Stiftungen (Humboldt, Fondation Leducq, etc.	12	419.751
LMU excellent	5	334.712
Summe begutachtete externe Drittmittel		**3.833.024**

	Anzahl Projekte	Ausgaben 2014 laut Verwaltung
FöFoLe	8	60.907
Lebmit (Invest.)	9	23.726
Summe interne Drittmittel		**84.633**
Gesamtsumme verausgabte Drittmittel		**3.917.657**

Publikationen:

	Anzahl	ungewichteter IF
Im WoS gelistete Originalarbeiten	41	324.8
Im WoS gelistete Reviews und Editorials	23	179.1
Beiträge in Lehr-/Handbüchern, Monographien		
Gesamtsumme	**64**	**503.9**

Forschungsbericht 2015

Anzahl der Planstellen für wissenschaftliche Mitarbeiter: 18
Anzahl der Planstellen für Nicht-wissenschaftliche Mitarbeiter: 17
Anzahl aller drittmittelfinanzierten Mitarbeiter: 73

Drittmittelausgaben (in €):

	Anzahl Projekte	Ausgaben 2015 laut Verwaltung
DFG	28	2.461.840
BMBF, StMWFK, EU	26	1.244.029
Stiftungen (Humboldt, Fondation Leducq, etc.)	13	398.534
LMU excellent	5	366.779
Summe begutachtete externe Drittmittel		**4.471.182**

	Anzahl Projekte	Ausgaben 2015 laut Verwaltung
FöFoLe	3	46.651
Lebmit (Invest.)	7	44.200
Promotionsstipendien	2	32.000
Summe interne Drittmittel		**122.851**
Gesamtsumme verausgabte Drittmittel		**4.594.033**

Publikationen:

	Anzahl	ungewichteter IF
Im WoS gelistete Originalarbeiten	39	343.3
Im WoS gelistete Reviews, Editorials	33	166.4
Beiträge in Lehr-/Handbüchern, Monographien	1	
Gesamtsumme	**73**	**509.7**

Arbeitsgruppen (Principal Investigators)

GPVI-targeted inhibition of acute atherothrombosis

Prof. Dr. Wolfgang Siess

Group members
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Arterial thrombi develop when atherosclerotic plaques erode or rupture. Circulating platelets are the first to stick to the site of injury, and they initiate the formation of an intraluminal growing thrombus that can precipitate myocardial infarction and ischemic stroke, leading causes of death worldwide. Decisive thrombogenic plaque components are collagen type I and III fibers, which trigger platelet deposition under static and flow conditions by activating the glycoprotein VI (GPVI) collagen receptor. The alternative platelet collagen receptor, $\alpha_2\beta_1$-integrin, is not involved in plaque-induced platelet aggregation. Therefore, targeting GPVI might preferentially inhibit atherosclerotic plaque-induced thrombosis (atherothrombosis) and should not affect other cells as GPVI expression is restricted to platelets and megakaryocytes. Present antithrombotic drugs target physiological platelet activation mechanisms and coagulation factors thereby increasing the risk of bleeding. In addition, plaque-induced platelet thrombus formation is not efficiently inhibited by current dual antiplatelet therapy (aspirin and a $P2Y_{12}$ receptor antagonist). The long-term goal of our research is to understand the mechanisms of atherothrombosis in order to inhibit atherothrombosis specifically without interfering with physiological hemostatic mechanisms.

We compared in various static and flow models of human plaque-induced thrombus formation by applying advanced microscopic techniques (two-photon laser scanning microscopy, structural illumination microscopy, stimulated emission depletion microscopy) the anti-thrombotic effects of different monoclonal antibodies directed against platelet GPVI with that of a recombinant dimeric GPVI-Fc fusion protein (Revacept ®) masking GPVI binding sites on collagen. It was found that anti-GPVI antibodies inhibit atherosclerotic plaque-induced platelet aggregation under static and flow conditions more effectively than GPVI-Fc. However, potent platelet inhibition by GPVI-Fc at higher arterial shear rate (1,500/s) suggested localized antithrombotic efficacy at denuded or fissured stenotic high-risk lesions without systemic bleeding.

As inhibition of plaque-induced platelet aggregation by GPVI-Fc was inferior to anti-GPVI antibodies, we aimed to increase its anti-atherothrombotic potential. GPVI-Fc was incubated with equimolar concentrations of anti-human Fc antibodies to cross-link the Fc tails of GPVI-Fc. Cross-linking yielded oligomeric GPVI-Fc complexes, which inhibited atherosclerotic plaque- induced platelet aggregation in static and flow assays as efficiently as antibodies blocking GPVI receptors on platelets without increasing bleeding time in vitro. Advanced optical imaging revealed a rapid and stable sheath-like coverage of collagen fibers by cross-linked GPVI-Fc complexes preventing platelet attachment to collagen. It was concluded that transformation of GPVI into multivalent GPVI complexes may provide a novel strategy to effectively suppress atherothrombosis without increasing systemic bleeding risk.

Leukocyte Biology: Myeloid Cells in Vascular Inflammation and Therapy

Prof. Dr. Dr. 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. However, neutrophil granulocytes, the most abundant circulating white blood cell in humans, were so far rarely associated with atherosclerosis. The group led by Oliver Söhnlein focuses on inflammatory processes instructed by neutrophils and aims at developing strategies to combat neutrophil-driven inflammation.

Chemokine-controlled arterial leukocyte recruitment is a crucial process in atherosclerosis. We previously reported the importance of various chemokine receptors including CCR2, CCR5, and CXCR2 during arterial myeloid cell recruitment (Drechsler et al., Circulation, 2010; Soehnlein et al., EMBO Mol Med, 2013; Döring et al., Circ Res, 2014). Formyl peptide receptor 2 (FPR2) is a chemoattractant receptor that recognizes proinflammatory and proresolving ligands. With the ambivalence of FPR2 ligands we initiated a study to assess the role of FPR2 in atherosclerosis (Drechsler et al., Circ Res, 2015). Employing hypercholesterolemic mice, we found that deletion of FPR2 or its ligand Annexin A1 enhances atherosclerotic lesion formation, arterial myeloid cell adhesion, and recruitment. Mechanistically, we identified Annexin A1 as an endogenous inhibitor of integrin activation evoked by the chemokines CCL5, CCL2, and CXCL1. Specifically, the Annexin A1 fragment Ac2-26 counteracts conformational activation and clustering of integrins on myeloid cells evoked by CCL5, CCL2, and CXCL1 through inhibiting activation of the small GTPase Rap1.

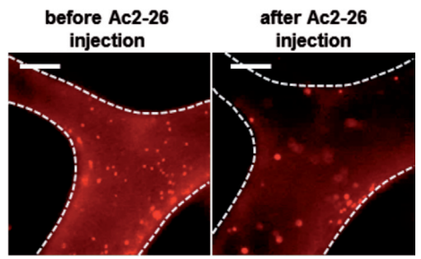

Figure 1: Ac2-26 inhibits arterial leukocyte adhesion. Apoe$^{-/-}$ mice were fed a high-fat diet (HFD) for 4 weeks. Intravital microscopy of the carotid artery was used for assessment of luminal leukocyte endothelial interactions. Myeloid cells were identified by intravenous injection of an antibody to CD11b. Scale bar, 100 µm.

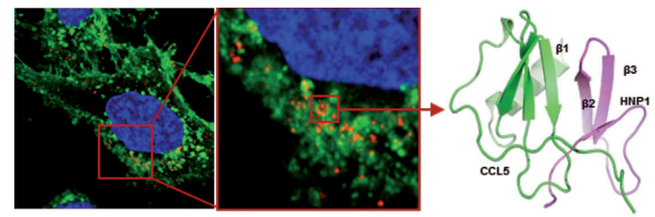

Figure 2: HNP1 and CCL5 form heteromers on endothelial cells. Proximity ligation assay on endothelial cells incubated with HNP1 (10 µg/ml) and CCL5 (1µg/ml). Cells were probed with antibodies to HNP1 and CCL5. Representative images of STED nanoscopy. Scale bar indicates 5 µm. Model of heteromer conformation between CCL5 (green) and HNP1 (magenta). Note interaction between β-strand 1 of CCL5 and β-strand 2-3 of HNP1.

In vivo administration of Ac2-26 largely diminishes arterial recruitment of myeloid cells in a FPR2-dependent fashion (Figure 1). This effect is also observed in the presence of selective antagonists to CCR5, CCR2, or CXCR2, whereas Ac2-26 was without effect when all 3 chemokine receptors were antagonized simultaneously. Finally, repeated treatment with Ac2-26 reduces atherosclerotic lesion sizes and lesional macrophage accumulation. Thus, instructing the Annexin A1-FPR2 axis harbors a novel approach to target arterial leukocyte recruitment. With the ability of Ac2-26 to counteract integrin activation exerted by various chemokines, delivery of Ac2-26 may be superior in inhibition of arterial leukocyte recruitment when compared with blocking individual chemokine receptors.

In acute inflammatory and chronic inflammation, neutrophils and monocytes form a tight partnership, where neutrophils can orchestrate monocyte recruitment by release of preformed chemotactic molecules (Soehnlein & Lindbom, Nat Rev Immunol, 2010; Wantha et al., Circ Res, 2013). Interestingly, platelets have also been shown to seed monocyte-chemoattractants on endothelial cells. As neutrophils and platelets are often activated simultaneously we investigated how secretory products of neutrophils and platelets synergize to enhance the recruitment of monocytes. We found that neutrophil-borne human neutrophil peptide 1 (HNP1, α-defensin) and platelet-derived CCL5 form heteromers (Figure 2). These heteromers stimulate monocyte adhesion through CCR5 ligation. We further determined structural features of HNP1-CCL5 heteromers and designed a stable peptide that could disturb proinflammatory HNP1-CCL5 interactions. This peptide attenuated monocyte and macrophage recruitment in a mouse model of myocardial infarction. These results establish the in vivo relevance of heteromers formed between proteins released from neutrophils and platelets and show the potential of targeting heteromer formation to resolve acute or chronic inflammation.

Clinical Pathobiochemistry - Lipid signaling in cardiovascular disease

Prof. Dr. Sabine Steffens

Our group focuses on the pathophysiological role of endocannabinoids and related N-acylethanolamines in atherosclerosis. The endocannabinoid system is an endogenous lipid signaling system that comprises at least two distinct membrane receptors, CB1 and CB2, their endogenous ligands (named endocannabinoids) as well as enzymes for ligand biosynthesis and inactivation. Previously it was thought that CB2 receptors are mainly expressed in immune and hematopoietic cells thereby mediating various immunomodulatory effects, while CB1 receptors are primarily distributed in the central nervous system and are responsible for neuromodulatory properties. More recent studies have confirmed CB1 and CB2 expression in various peripheral tissues (including myocardium, human coronary artery endothelial and smooth muscle cells). Endocannabinoids are produced ''on demand'' by the cleavage of membrane fatty acids from various cells and tissues, including immune cells and brain. Endocannabinoids are chemotactic and contribute to the recruitment of other inflammatory cells for pathogen removal and induction of an adaptive immune response. Tissue and circulating levels of endocannabinoids and fatty acid amide analogues are increased in atherosclerosis and its related cardiovascular risk factors, obesity, dyslipidemia, diabetes and endothelial dysfunction. However, the pathophysiological effect of this elevated tone in cardiovascular disease is not well understood. Our group therefore aims to clarify the precise pathophysiological relevance of its receptors and ligands in atherosclerosis **(project 1).**

Another focus of our group is to investigate the inflammatory mechanisms of myocardial infarction healing **(project 2).** A myocardial infarction results in the death of large numbers of cardiac muscle cells. This induces an acute inflammatory response and rapid infiltration of neutrophils. These cells contribute to tissue damage after acute myocardial ischemia and reperfusion, but their role in infarct healing has been underestimated so far. Because neutrophil-derived granule proteins mediate classical monocyte recruitment in acute inflammation, we hypothesized that neutrophil depletion during the acute inflammatory phase will improve infarct healing by reducing the proinflammatory monocyte response in the heart. Surprisingly, we found that neutrophil depletion resulted in an imbalanced inflammatory response, insufficient resolution of inflammation and maladaptive remodeling associated with progressive decline of cardiac function. Our data indicate that neutrophils represent a key regulator in post-MI remodeling by fine-tuning the balance between inflammation and reparative state (Horckmans et al. European Heart Journal 2016). The new findings confirm that the function of neutrophils is not yet fully understood.

Additional findings from our own group suggest that there might be a threshold value at which the positive impact of the neutrophils is adversely affected. The clinical application of anti-inflammatory therapies inhibiting neutrophil recruitment may end up by actually impeding the repair process. It might therefore be a better idea to try and boost the development of reparative macrophages that promote repair. We therefore aim to identify and dissect the signal pathways and regulatory mechanisms that stimulate the differentiation

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of these cells after myocardial infarction. In particular, we aim to clarify the implication of endocannabinoid levels and their receptors in this process.

In a **third project,** 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. Between 30-50% of all drugs work directly or indirectly via the approximately 350 non-odorant members of this group for which endogenous ligands have been identified. In recent years it has been appreciated that the signaling of a GPCR does not only occur via the activation of its cognate G proteins but also via the simultaneous activation or inhibition of G protein-independent pathways. How these different pathways of a specific GPCR become affected and regulated - and thus the final outcome for the cell and the whole organism - may strongly vary with the kind of (synthetic) receptor ligand applied and with the type of cell under consideration.
In this context, our group aims to identify in cell culture models differences in the activation, signaling and regulation mechanisms of certain GPCRs (cannabinoid, bradykinin and chemokine receptors) and their specific ligands that may help to understand on a cellular level the observed pro- or anti-inflammatory effects upon application of these ligands (i.e. cannabinoids) in animal models. We have developed a set of tools that enables us to study the regulation of GPCRs with regard to expression, G protein-dependent and -independent signal transduction and trafficking. Using Flp-In TRex HEK293 cells that permit the isogenic expression of (receptor) constructs, we established reporter cell lines for several signaling pathways (CRE, NFAT, NFkB, AP-1, TCF/LEF). We can study the role of GRK2-6 in the regulation of a GPCR in detail through stable (but regulatable) or transient expression of GRK WT or mutant constructs. As a long term goal, a deeper insight in the regulatory processes of GPCRs should result in the generation of even more specifically working drugs with fewer side effects.

Experimental Vascular Medicine – Tiny complexity: microRNAs drive inflammation in blood vessels

Prof. Dr. Andreas Schober

The cellular response to environmental stress is controlled by small, non-coding RNAs (microRNAs), which negatively regulate post-transcriptional gene expression and are essential for the fine-tuning of stress-induced gene transcription.
Endothelial cells are lining the inner surface of blood vessels and are perfectly adapted to high shear stress. At bifurcations of arteries, however, blood flow is naturally disturbed and endothelial cells constantly damaged by low shear stress (*Schober A, Nazari-Jahantigh M, Weber C.* Nat Rev Cardiol 2015). This damage predisposes endothelial cells to additional damage by hyperlipidemia due to impaired regenerative capability. We found that downregulation of the microRNA miR-126-5p by low shear stress plays a crucial role in the reduced regenerative response of endothelial cells to hyperlipidemia and for the development of atherosclerosis (*Schober A, Nazari-Jahantigh M., et al,* Nat Med 2014). Dr Schober and Dr Nazari-Jahantigh have been awarded with the Rolf-Becker-Award from the Medical Faculty of the LMU and the Foundation "Rufzeichen Gesundheit" in August 2014. In 2015, Dr Schober and Dr Nazari-Jahantigh were nominated for the Galenus-von-Pergamon-Award and received the second price in the Herman Rein Award session. Moreover, Dr Nazari-Jahantigh was one out of five applicants who received a post-doctoral grant from the German Centre for Cardiovascular Research in 2015 to continue her research.

In addition, Dr Schober and his group demonstrated for the first time a crucial role of the hypoxia-inducible transcription factor HIF-1a in the inflammatory activation of endothelial cells (*Akhtar S., Hartmann P,* et al. Hypertension 2015). Conditional deletion of the HIF-1a gene in endothelial cells reduced the development of atherosclerosis and the expression of pro-inflammatory chemokines such as CXCL1. MicroRNA expression profiling showed that HIF-1a specifically regulated the expression of miR-19a, which activates inflammatory signaling via NF-kB in endothelial cells and triggers CXCL1-mediated monocyte adhesion.

Another focus of the Dr Schober's lab is the role of the miR-155 in macrophages on the development of atherosclerosis. In addition to previous findings of his group, Dr Yuanyuan Wei has shown that the effect of miR-155 on lesional macrophages differs between early and advanced atherosclerotic lesions (Wei et al. Arterioscler Thromb Vasc Biol 2015). Whereas miR-155 inhibits macrophage proliferation in early lesions mainly by suppressing the receptor for the macrophage growth factor M-CSF, miR-155 promotes advanced lesions by targeting the anti-inflammatory transcription factor BCL6. This change of the miR-155 effect during the progression of atherosclerosis is accompanied by the upregulation of miR-155 in lipid-laden macrophages. These results demonstrate

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that therapeutic targeting of miR-155 in atherosclerosis needs to be tailored to specific targets of miR-155.

For his sustained outstanding productivity over several years and his significant contribution to his field, Dr. Schober was awarded in 2014 by the European Society of Cardiology Council for Basic Cardiovascular Science with the Outstanding Achievement Award.

Prof. Schober (left) received the ESC Outstanding Achievement Award from Prof. Axel Pries (right) at the ESC Congress 2014 in Barcelona

Autoimmune Responses in Atherosclerosis

Andreas J.R. Habenicht, MD

Group members
Andreas Habenicht, Professor Dr. med.
Sarajo Mohanta, Dr. rer.nat.
Changjun Yin, Dr. rer.nat.
Zhe Ma, PhD student
Yuanfang Li, PhD student

Earlier studies from our laboratory identified *artery tertiary lymphoid organs* (ATLOs) in the abdominal adventitia of aged hyperlipidemic apolipoprotein E-deficient (Apoe-/-) mice. These studies provided support for the hypothesis that atherosclerosis may be associated with the generation of autoreactive T and B cells and that autoimmune responses against atherosclerosis-specific antigens are organized within the arterial wall.

Progress in atherosclerosis T cell biology

We observed that ATLOs organize T cell recruitment into the arterial wall followed by activation, proliferation, and formation of T memory cells. CD4+ T cells - that had been recruited into ATLOs - were converted into induced T regulatory cells. In transgenic mice that were deficient in the lymphotoxin β receptor in smooth muscle cells ($Apoe^{-/-fl/fl}$/Tagln-cre), ATLOs were smaller, showed a disrupted morphology, and atherosclerosis was more pronounced. These data supported our previous hypothesis that vascular smooth muscle cells can adopt features of lymphoid tissue organizer cells that are required for lymphoid tissue neogenesis during ontogeny and by the same token for ATLO neogenesis in atherosclerosis. They also supported the conclusion that ATLOs – under steady state conditions – are atheroprotective. In assays of exogenous antigen application, our data revealed that an unusual set of ATLO cells including B cells, several subtypes of dendritic cells, and monocytes/macrophages are capable of antigen presentation to T cells.

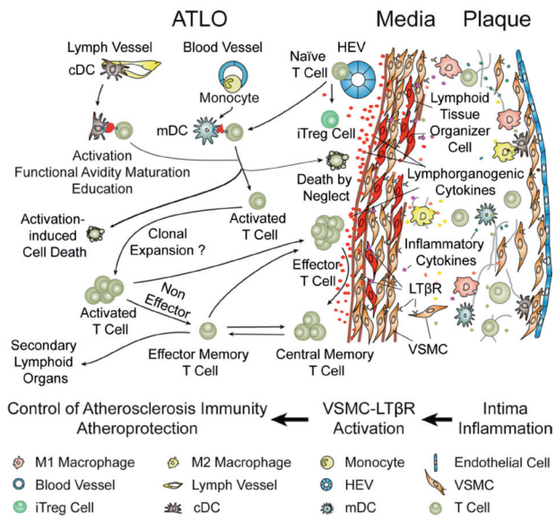

Figure 1. ATLOs emerge during atherosclerosis progression in aged hyperlipidemic mice. We observed that atherosclerosis immune responses are controlled by ATLOs in the adventitial connective tissue adjoining arteries. These lymphocyte aggregates arise through vascular smooth muscle cell lymphotoxin β receptor signaling and act as powerhouses of protective atherosclerosis immunity. Adopted from Hu et al. 2015. Immunity Jun 16;42(6):1100-15

Progress in atherosclerosis B cell biology

Together with Prasad Srikakulapu, a former graduate student in the Habenicht group and now at the University of Virginia, USA), B cell subtypes in ATLOs of aged hyperlipidemic mice were characterized. Transcript maps, FACS, immunofluorescence analyses, cell transfers, and Ig-ELISPOT assays showed multi-layered atherosclerosis B cell responses in ATLOs. Aging-associated aorta B cell-related transcriptomes were identified and transcript atlases revealed highly territorialized B cell responses in ATLOs versus atherosclerotic lesions: ATLOs showed upregulation of bona fide B cell genes including Cd19, Ms4a1 (Cd20), Cd79a/b, and Ighm though intima plaques preferentially expressed molecules involved in non-B effector responses towards B cell-derived mediators, i.e. Fcgr3 (Cd16), Fcer1g (Cd23), and the C1q family. ATLOs promoted B cell recruitment. ATLO B-2 B cells included naïve, transitional, follicular, germinal center, switched IgG1+, IgA+, and IgE+ memory cells, plasmablasts, and long-lived plasma cells (PCs). ATLOs recruited large numbers of B-1 cells whose subtypes were skewed towards IL-10+ B-1b cells versus IL-10- B-1a cells. ATLO B-1 cells and PCs constitutively produced IgM and IgG and a fraction of PCs expressed IL-10. Moreover, Apoe-/- mice showed increased germinal center B cells in renal lymph nodes, IgM-producing PCs in the bone marrow, and higher IgM and anti-MDA-LDL IgG serum titers. These data indicated that ATLOs orchestrate dichotomic, territorialized, and multi-layered B cell responses in the diseased aorta. ATLO germinal center reactions suggest generation of autoimmune B cells within the diseased arterial wall (Arterioscler. Thromb. Vasc. Biol., in revision).

Immune modulation in atherosclerosis and obesity

Prof. Dr. Esther Lutgens / Dr. Norbert Gerdes

Co-stimulatory molecules

Research Interests (background)

Atherosclerosis is a chronic inflammatory disease of the large and middle-sized arteries and is the underlying cause of the majority of cardiovascular diseases. Both the innate and adaptive immune system play a major role in its pathogenesis, and communication between the different immune cells is key to atherosclerotic plaque development. Understanding of the modulation of this communication is therefore of paramount importance to understand the atherogenic process and to develop potential therapeutic targets for atherosclerosis, but also other chronic inflammatory diseases. Co-stimulatory molecules are a special group of molecules mediating this communication in the immune system (Zirlik and Lutgens, Hamostaseologie 2015). In 1999 (*Lutgens et al, Nat Med*) and 2010 (Lutgens et al, J Exp Med), we found that inhibition of CD40L-CD40 interactions, a co-stimulatory dyad from the TNF(R) family, turned out to be one of the most potent plaque-reducing and plaque-stabilizing strategies known. Most of our research since has focused on co-stimulatory molecules and its related immunological pathways.

Group members

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Sigrid Reim, CTA
Tobias Badmann, MTA
Sandra Auer, B.S.

Highlights in 2014/2015

Investigation of the CD40-downstream pathways in atherosclerosis.

CD40 has no intrinsic signalling and needs adaptor molecules, 'TNF receptor associated factors', TRAFs, to signal. CD40 has 2 TRAF binding sites on its cytoplasmic tail, a TRAF2 binding site, which indirectly binds TRAF3 and 5, and a TRAF6 binding site. By mutating these binding sites, we generated mice that are deficient in CD40-TRAF2/3/5, CD40-TRAF6, or CD40-TRAF2/3/5/6 signalling and could show that interruption of CD40-TRAF6 resulted in a decrease in atherosclerosis (Lutgens et al, J Exp Med 2010).

Based on these findings we designed small molecules against the potential CD40-binding domain on TRAF6 using computational modelling. Since the TRAF6 homotrimer has not been solved to atomic detail yet, we have modelled the homotrimer structure of TRAF6 on the basis of TRAF2 by comparative modelling techniques. Besides the earlier identified drugable sites on the TRAF6 monomer, we have additionally identified putative drugable sites on the surface of the TRAF6 trimer. Based on these structures, we designed and optimized our compounds using in silico drug discovery platform, and we were able to generate a family of compounds inhibiting CD40-TRAF6 interactions (Zarzycka et al, J Chem Inf Model 2015).

Eventually, we found 7 CD40-TRAF6 inhibitors (which we coined "TRAF-STOPs") that are specific to block CD40-TRAF6. Two of them were tested in atherosclerosis and are very powerful in reducing CD40-induced inflammation in vitro. Intravital microscopy demonstrated that the compounds indeed reduced the recruitment of leukocytes, especially of monocytes and granulocytes, to the arterial wall of hyperlipidemic apolipoprotein E deficient ($Apoe^{-/-}$) mice. These results are currently summarized in a manuscript.

Investigation of the contribution of CD40-CD40L-signaling in and between the different plaque cell-types to atherosclerotic plaque stability.

Although the overall pro-atherogenic function of CD40-CD40L interaction is long-established it remains elusive which particular cell types mediate this effect. Previously, we reported a role for platelet-expressed CD40L in atherosclerosis (Lievens et al, Blood, 2010). Interestingly, platelets have recently gained considerable attention as mediators of inflammation (Ahmadsei et al, Curr Opin Lipidol 2015). However, platelets also contain CD40 (Kuijpers et al, Arterioscler Thromb Vasc Biol 2015), yet, no data are available on its precise role in inflammation and atherosclerosis. We found that in both mice and humans, platelet CD40 mediates the formation of platelet-leukocyte aggregates and the release of chemokine (C-X-C motif) ligand 4 (Gerdes et al, Arterioscler Thromb Vasc Biol 2016). Leukocytes were also less prone to adhere to CD40-deficient thrombi. However, platelet CD40 was not involved in platelet aggregation. Lack of CD40 on injected platelets led to reduced leukocyte recruitment to the carotid artery as assayed by intravital microscopy. When atherosclerotic Apoe-/- mice were repeatedly injected with platelets deficient in CD40, we found that platelet-specific deficiency of CD40 slowed the acceleration of atherosclerosis induced by activated platelets. Thus, our data show that platelet CD40 plays a crucial role in inflammation by stimulating leukocyte activation and recruitment and activation of endothelial cells, thereby promoting atherosclerosis. (Gerdes et al, ATVB 2016).

Adoptive transfer of cells or bone marrow transplantation is one way to look at cell-type specific actions of the CD40-CD40L system. However, not all cell-types can be studied this way. Therefore, we generated models which allow cell type-specific ablation of CD40 or CD40L, respectively.

These so-called floxed CD40 and floxed CD40L mice were backcrossed to a mouse strain cell-type-specifically expressing the recombinase Cre. By Cre-mediated deletion of CD40 or CD40L, respectively, we are able to study the role of CD40 and CD40L in various cell types including endothelial cells, smooth muscle cells, T cells, dendritic cells, macrophages and adipocytes.

Preliminary data indicate that CD40L on T lymphocytes is crucial for the development of atherosclerosis. Mice lacking CD40L on T cells develop smaller atherosclerotic plaques. In contrary, mice that are deficient for CD40 on dendritic cells develop similar sized atherosclerotic plaques. These models are currently under intense analytical investigation.

Investigation of the contribution of CD40-CD40L signalling in other inflammatory disorders: obesity

Excessive obesity appears to promote adipose tissue inflammation which can lead to metabolic dysregulation (Seijkens et al, Diabetes, 2014). Although not exhibiting increased weight gain, male $Cd40^{-/-}$ mice in diet-induced obesity (DIO) displayed worsened insulin resistance, compared to wild-type mice. This metabolic dysregulation was associated with excessive inflammation of adipose tissue (AT), characterized by increased accumulation of CD8(+) T cells and M1 macrophages and enhanced hepatosteatosis (Chatzigeorgiou et al, Proc Natl Acad Sci U S A 2014). Mice with deficient CD40-TRAF2/3/5 signaling in MHCII+ cells exhibited a similar phenotype in DIO as Cd40-/- mice. In contrast, mice with deficient CD40-TRAF6 signaling in v cells displayed no insulin resistance and showed a reduction in both AT inflammation and hepatosteatosis in DIO. To prove the therapeutic potential of inhibition of CD40-TRAF6 in obesity, DIO mice were treated with a TRAF-STOP that we designed to specifically block CD40-TRAF6 interactions. This compound improved insulin sensitivity, reduced AT inflammation, and decreased hepatosteatosis (van den Berg SM et al, Int J Obes 2015). Our studies reveal that the CD40-TRAF2/3/5 signaling pathway in MHCII+ cells protects against AT inflammation and metabolic complications associated with obesity whereas CD40-TRAF6 interactions in MHCII+ cells aggravate these complications (Chatzigeorgiou et al, Proc Natl Acad Sci U S A 2014). Inhibition of CD40-TRAF6 signaling by our compound may provide a therapeutic option in obesity-associated insulin resistance.

Other publications:

We collaborated with two other groups working on epigenetic manipulations mediated through histone deacetylases (HDACs) and their impact on atherosclerosis. In one publication HDAC9 was shown to limit atherosclerosis in a mouse model of atherosclerosis. This effect appeared to be mediated mainly by enhancing the function of regulatory T cells (Azghandi et al, Stroke, 2015). On the other hand, macrophage-specific targeting of HDAC3 leads to stabilized atherosclerotic lesions (Hoeksema et al, EMBO Mol Med 2014).

In a long-lasting collaborative effort we were involved in a study identifying a previously unsuspected protein critically involved in signaling of the cytokine Interleukin-18 (IL-18) (Wang et al, Nat Med, 2015). This Na-Cl co-transporter (NCC), a 12-transmembrane-domain ion transporter protein preferentially expressed in the kidney, co-localizes to the classical IL-18 receptor in atherosclerotic lesions. Interestingly, NCC can, independently from IL-18R bind IL-18 and confer cellular signaling and function. Development of atherosclerosis was not affected in mice lacking either IL-18R or NCC, while only combined deficiency of NCC/IL-18R recapitulated the atherosclerotic phenotype observed in IL-18-deficient mice (Wang et al, Nat Med 2015).

Additional collaboration within the SFB1054 and the Department for Immunology defined a critical role for CD40 on thymic B cells presenting self-antigens to confer induction of central T cell tolerance (Yamano et al, Immunity. 2015). Lastly, we also participated in demonstrating a role for the CD40L/CD40 axis in mast cell-driven expansion of IL-10-competent B cells in vitro and highlighting the importance of mast cell CD40L signaling in the colon (Mion et al, J Immunol, 2014).

Outlook

We currently focus our efforts to investigate the phenotype and function of T cell subsets in different stages of atherosclerosis while exploring the kinetics of their appearance. Mechanistic studies will try to reveal the underlying mechanisms and unexpected consequences, such as changes in lipid metabolism, will be investigated. In addition, we examine the function of the non-classical co-stimulatory molecules CD27, CD70, GITR, and CTLA-4 in different stages and models of atherosclerosis. These studies are mainly completed and, at least partly, in revision at high-ranking journals. Lastly, the biology of CD40/CD40L interaction, it cellular origin, and signaling pathways continue to be a major focus of our research endeavors.

Platelet Chemokines and Atherosclerosis

Dr. Philipp von Hundelshausen / PD Dr. Rory Koenen

Group members
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Dr. He Li, PhD
Dr. rer nat. Martin Schmitt
Veit Eckardt, cand. med.
Julian Leberzammer, cand. med.

Lusine Saroyan, MTA
Sabine Streicher
Christiane Gimpfl

Platelets play a crucial role for repair mechanisms after injuries causing vessel disintegration. Coming into contact with various proteins and mediators of the vessel wall platelets get activated and lead to the occlusion of the injured site by aggregation and complex formation with macromolecules such as von Willebrand Factor, collagen and fibrinogen preventing blood loss. In addition to this vital function the scientific interest, spurred by novel findings involving platelets in inflammation, has increased to investigate the relatively new role of platelets in inflammatory and immune responses. Atherosclerosis is a disease, which develops slowly but is characterized by a strong inflammatory component. As a result atherosclerotic plaques may lead to progressively increasing blood flow obstructions resulting in chronic ischemia and stable angina pectoris or may result in an acute myocardial infarction if an instable plaque ruptures and instantly occludes a coronary artery. Therefore in the centre of our interest are cellular and molecular mechanisms that initiate and sustain the development of atherosclerosis and processes which trigger the rupture of a plaque. Although virtually all cell types have been detected in atherosclerotic lesions, monocytes are the most prominent inflammatory cell type representing an important link to the principal cardiovascular risk factor hypercholesterolemia and lipid metabolism. Being generated in the bone marrow, monocytes emigrate into the circulation and are recruited under conditions involving altered blood flow patterns and directional cues into the vascular tissue, guided by adhesion molecules and chemokines attracting activated inflammatory cells.

Our team investigates the role of chemokines which may be derived from platelets in enhancing vascular monocyte recruitment and atherosclerosis. The projects range from biochemical basic science to clinical studies. We have shown that activated platelets release the CC-chemokine RANTES which will be deposited on endothelial cells. From there flowing and rolling monocytes bearing RANTES receptors will come into contact with endothelium and get subsequently activated which leads to adhesion and transendothelial migration. The rolling movement of activated platelets on the endothelium is mediated by P-selectin and this close contact facilitates the deposition of RANTES (CCL5). Mouse models of atherosclerosis indeed show that the injection of activated platelets leads, dependent on the presence of P-selectin, to CCL5 immobilisation on endothelium and exacerbates atherosclerosis. CCL5 is not the only platelet released chemokine and mediator. Platelet factor 4 (PF4, CXCL4) a selective abundant platelet chemokine has the capacity to increase monocyte recruitment, but only in the presence of CCL5. The enhancement of CCL5-triggered monocyte adhesion by CXCL4 was due to a direct binding of RANTES and PF4. This interaction was further analyzed with surface plasmon resonance and modelled with NMR studies revealing the formation of a PF4-RANTES-herterodimer of a CC-type which helped to design peptides interfering with the interface blocking heterodimer formation. These peptides were tested in murine models of atherosclerosis revealing a substantial anti-atherosclerotic effect due to a decreased monocyte infiltration (*Koenen et al,* Nat Med 2009).

Besides their essential role in hemostasis, platelets also have functions in inflammation. On platelets, junctional adhesion molecule (JAM-)A, is abundantly expressed. Recently, platelet-JAM-A was identified as an inhibitor of integrin α2bβ3-mwediated outside-in signaling and its absence in platelets resulted in hyperreactivity. In this study, this gain-of-function was specifically exploited to investigate the role of platelet hyperreactivity in plaque development. Mice with or without platelet-specific (tr)JAM-A-deficiency were crossed in an apolipoprotein e (Apoe–/–) background and fed a high-fat diet weeks. During flow, trJAM-A$^{-/-}$ Apoe$^{-/-}$ platelets showed increased collagen adhesion and α2bβ3 integrin expression. After up to 12 weeks of diet, trJAM-A$^{-/-}$ Apoe$^{-/-}$ mice showed increased plaque formation in the aorta compared with trJAM-A$^{+/+}$ Apoe$^{-/-}$ controls and these differences were most evident at early time points. At 2 weeks, the plaques of the trJAM-A$^{-/-}$ Apoe$^{-/-}$ animals showed increased macrophage, T cell and smooth muscle cell content Interestingly, the plasma levels of chemokines CCL5 and CXCL4 were increased in the trJAM-A$^{-/-}$ Apoe$^{-/-}$ mice and JAM-A–deficient platelets showed increased binding to monocytes and leukocytes. Finally, whole-blood perfusion experiments in vitro and intravital microscopy in vivo revealed increased recruitment of monocytes to the endothelium in blood of trJAM-A$^{-/-}$ Apoe$^{-/-}$ mice compared to controls.

Conclusions - Deletion of JAM-A causes a gain-of-function in platelets, with lower activation thresholds and increased inflammatory activities. This leads to an increase of plaque formation, particularly in early stages of the disease.

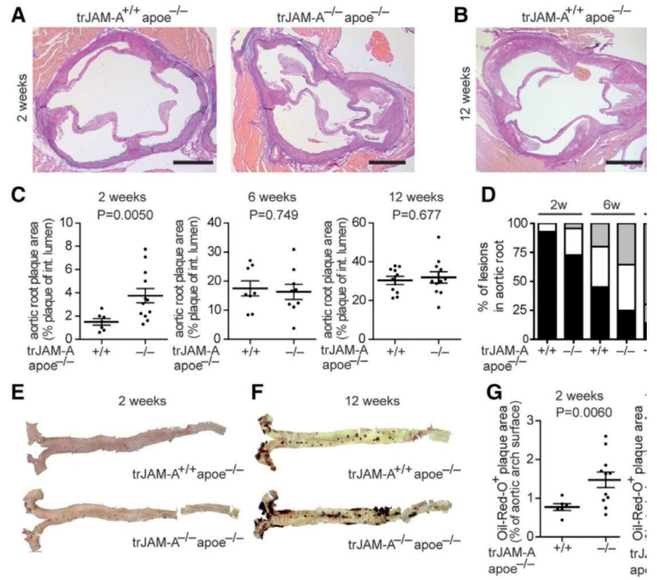


Figure 1: Specific role of JAM-A on platelets during atherogenesis. trJAM-A$^{+/+}$ Apoe$^{-/-}$ and trJAM-A$^{-/-}$ Apoe$^{-/-}$ mice were fed a high-fat diet (HFD) for 2 weeks (A-C, F), 6 weeks (D,G) and 12 weeks (A,B,E,H), as indicated. Representative pictures display the atherosclerotic areas in aortic roots (A) and in whole aortae (B) of trJAM-A$^{+/+}$ Apoe$^{-/-}$ and trJAM-A$^{-/-}$ Apoe$^{-/-}$ mice after 2 weeks and 12 weeks HFD, as indicated. Scale bar=500µm. Lesional areas were quantified in the whole aorta after Oil-Red-O staining (B-E) and in the aortic roots after EVG-staining (A,F-H).

Flow Cytometry and Cell Sorting

PD Dr. Michael Hristov

Our research focusses on multicolor flow cytometry, cell sorting and human monocyte biology. A BD FACSAria III sorter (funded by DFG/LMU) is available at IPEK. This instrument allows high-performance analysis of up to 12 parameters and aseptic high-speed sorting for a wide range of particles. Simultaneous sorting of up to 4 populations, well preserved cell viability and adaptable options for collection of sorted cells in tubes, on plates or glass slides enable flexible experimental setups. So far, our expertise has substantially contributed to numerous studies aiming to separate mouse lymphocytes or CD11b+ subsets from blood, bone marrow, lymph nodes, spleen and other tissues. Further applications include the sorting of mouse HSC, human monocytes, neutrophils and T-cells next to cultured cells, transfected cell lines (GFP+, YFP+, iRFP+) and apoptotic microvesicles. Sorted cells were used for transfer in experimental animals, extraction of protein, lipids or RNA, functional in vitro assays, microscopy and clonal expansion. These studies were performed primarily by IPEK and the Division of Clinical Pharmacology at LMU.

In terms of clinically related translational research, we investigate the prognostic value of monocyte subsets in patients with metabolic disease. Ongoing clinical trials intend to consider a potential relation of these cells to lipid disorder and lipid lowering therapy. We consider further the subset-specific development, differentiation and recruitment of human CD14/CD16 monocytes. Our recent data revealed that the monocyte pool in human bone marrow mainly match the CD14++CD16+ intermediate phenotype suggesting that the definitive signature of monocyte subsets appears first in the bloodstream.

Biophysics of Microscopy - Cardiovascular Imaging Technologies

Dr. Remco Megens

Group members

Remco Megens, PhD

Mariaelvy Bianchini, MSc

In order to further elucidate the processes involved in initiation and progression of atherosclerosis, insight in cardiovascular structure and function is essential. The IPEK working group on biophysics of microscopy focusses on the application of advanced optical fluorescence microscopic and nanoscopic imaging techniques for (molecular) imaging of atherosclerotic structures and processes in cardiovascular samples. Available modalities are dual channel intravital microscopy, confocal (CLSM) and two-photon laser scanning microscopy (TPLSM), and Stimulated Emission Depletion (STED).

CLSM allows 3D microscopic imaging of thin samples or isolated/cultured cells at sub micrometer resolution (≈ 250nm) and great specificity whereas STED offers improved nanometer resolution (≈ 30nm) thereby strongly improving the possibilities of imaging of intracellular processes. TPLSM enables studying of biological structures and processes directly at sites of occurrence: i.e. the intact large arteries in vivo and ex vivo.

Application of CLSM/STED (Leica SP8 3X) in cardiovascular research contributed to unraveling processes and distribution of targets such as fluorescently marked proteins or chemokines, outside and inside cells while offering highly specific multichannel imaging in 3D over time. Furthermore, tissue sections can be visualized with strongly improved image quality and resolution. Finally, video rate image acquisition speed enables studying of cell properties or cell-cell interactions in (arterial) flow assays. Application of TPLSM (Leica SP5IIMP) enabled imaging of structures deep in the large arterial wall in up to four dimensions due to its improved acquisition speed, depth penetration, and optical sectioning properties. For *in vivo* imaging of atherosclerosis, the impact of arterial movement on imaging could be circumvented by usage of TPLSM imaging triggered on the heart and respiration cycle of the animal under subject or artery stabilization.

The Megens laboratory functions as an optical imaging core facility for internal and external collaborators. Moreover, the Megens group aims to further develop CLSM, STED, and TPLSM applications for imaging in (diseased) cardiovascular targets and utilize them for projects studying the structure and dynamics of atherosclerosis in *in vitro, ex vivo, or in vivo* models as well as vessel wall morphology and functionality.

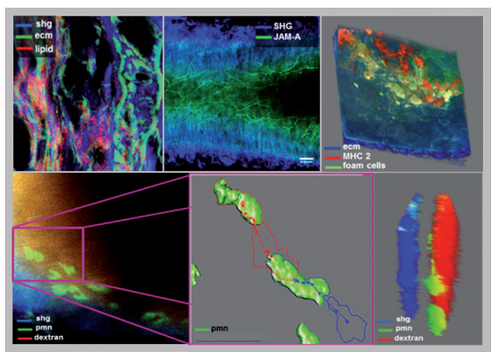


Figure1: examples of CLSM and STED in mouse cardiovascular tissue. Top part: 3D comparison of CLSM and STED for structural imaging of two types of collagen. Middle panel: 3D visualization of In vitro cultured endothelial cells where intracellular matrix bound proteins (red) and the membrane (green) are stained. Lower panel: 3D visualization of intracellular (blue/green) and extracellular structures in stimulated inflammatory cells.

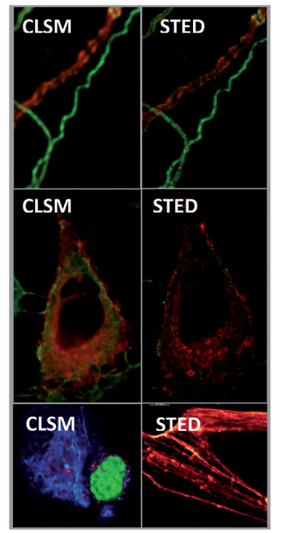


Figure2: examples TPLSM in mouse cardiovascular tissue: top left; intrinsic fluorescence signal (autofluorescence, SHG) derived from a plaque section. Top middle: Junctional adhesion molecule-A in endothelial cell junctions of an ex vivo mounted mouse carotid artery (*Schmitt et al,* Circulation 2014). Top right; ex vivo atherosclerotic plaque foam cells (green/ red); Lower panel; three dimensional dynamics of neutrophils in in a carotid artery of Apoe-/-LysMeGFP mouse visualized in vivo using artery stabilization and triggering (lumen in red, collagen of vessel wall in blue, neutrophils in green) thereby enabling tracking of cells (lower middle) and 3D analyses (lower right) of vessel wall -leukocyte interactions (*Chevre et al,* Circ Res 2014).

Innovative therapeutic strategies for sulfur mustard-evoked skin injuries: modulation of HIF-1 signaling and microRNA regulated pathways

PD Dr. Christian Ries

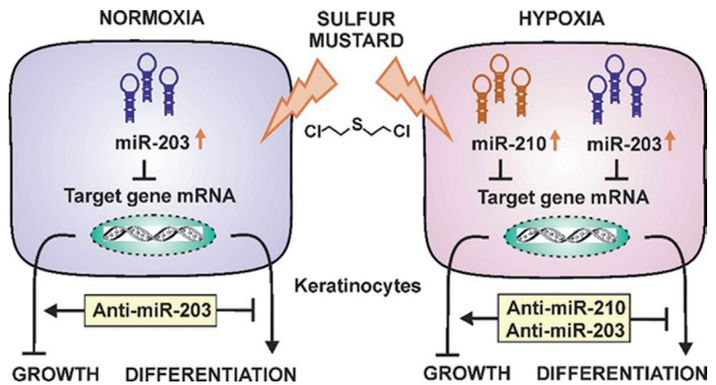
Sulfur mustard (2,2´-dichlordiethylsulfide; SM) is an alkylating, highly toxic chemical agent that after exposure to humans causes severe inflammation and extensive blistering in skin and lung within several hours. The acute symptoms are followed by long term effects including impaired wound healing. SM has been used as a chemical warfare agent in various military conflicts during the twentieth century. Its relative ease of production and stockpiling together with its multiple incapacitating health effects make mustard gas a continuing threat by military conflicts and terrorist attacks. Identification of effective therapies for SM-induced injuries is the focus of research worldwide.

The results of our previous research projects supported by the German Federal Ministry of Defense provided insight into molecular and cellular mechanisms that may contribute to the pathogenesis of SM injury. Our *in vitro* studies demonstrated that SM upregulates the secretion of proteinases from various skin cells. Remarkably, SM exposure of keratinocytes was shown to trigger the release of soluble factors from the cells which then induce an enhanced secretion of matrix metalloproteinase 9 (MMP-9) from fibroblasts. This may represent a SM-mediated pathomechanism that can lead to an increased degradation of basement membranes and thereby facilitate blister formation in skin (Ries et al., Toxicology, 2009). Moreover, our findings indicated that SM triggers premature differentiation in keratinocytes via p38 MAP kinase activity which is negatively influenced by ERK1/2. These events may contribute to the impaired regeneration capacity of skin after exposure to SM (Popp T. et al., Toxicology Letters, 2011). Together, our results suggest the usefulness of MMP-9 and p38 MAP kinase-inhibitors when applied in a timely differentiated manner for the treatment of SM-induced acute and chronic symptoms.

Calcium (Ca^{2+}) is an important regulator of keratinocyte differentiation in the epidermis. Investigating the underlying molecular mechanisms we discovered that Wnt5a/α-catenin signaling is involved in this process. Binding of Ca^{2+} to the calcium-sensing receptor on the cell surface elevates free intracellular Ca^{2+} and upregulates the expression and secretion of Wnt5a in these cells. Wnt5a then acts as an autocrine stimulus by increasing β-catenin stability and signaling activity that promotes keratinocyte differentiation. Importantly, our results show that application of Wnt5a to the cells and stimulation of β-catenin activity accelerates differentiation of keratinocytes (Popp *et al.,* J Invest Dermatol, 2014).

In a continuing project we investigated the importance of oxygen-deficiency (hypoxia), especially the role of HIF-1α and microRNAs in the pathophysiology of SM. Under normal physiological conditions, wound-associated hypoxia is a timely-limited situation that acts as an important stimulus for proper healing and regeneration in skin. Hypoxia controls the function and behaviour of keratinocytes and fibroblasts by influencing the expression of various regulatory molecules including cytokines and proteinases. In this context, HIF-1αplays a key role because it is significantly upregulated during hypoxic conditions in the skin and thereby stimulates various processes including cell proliferation, migration, autophagy, and angiogenesis that facilitate wound healing. The results of our studies provide evidence that SM attenuates hypoxia-induced HIF-1α accumulation and target gene expression in human primary keratinocytes and dermal fibroblasts, thereby impeding the migratory potential of these cells. Furthermore we demonstrate, that the addition of IOX2, a synthetic inhibitor of PHD-2 activity, fully restores HIF-1α stability and cell funtionality in SM-intoxicated keratinocytes and fibroblasts (Deppe *et al.*, Arch Toxicol, 2015).

microRNAs (miRNAs) are a group of small non-coding RNA molecules that play key roles in the regulation of numerous physiological and pathological processes. In wound healing, miRNAs are involved in the control of inflammation, angiogenesis, and apoptosis especially by influencing the functions of keratinocytes and fibroblasts. We hypothesized, that SM influences miRNA expression profiles in keratinocytes which may contribute to defects in functions of these cells essential in normal wound healing. Our studies demonstrate for the first time that SM induces miR-203 expression in primary keratinocytes independent of oxygen levels, and augments miR-210 in these cells under a hypoxic state. We show that upregulation of these miRNAs contribute to SM-induced deficiencies in cellular viability, proliferation, and differentiation of keratinocytes. Furthermore, our results suggest that application of specific inhibitors of miR-203 and miR-210 (antagomirs) might be useful to counterbalance disturbances of these processes under pathological conditions. Our findings may have implications for the development of novel therapies to improve re-epithelialization and wound healing in skin lesions of patients after exposure to SM (Deppe *et al.,* Tox Letters, 2015).



Funded by contracts from the German Federal Ministry of Defense (research projects M/SAB1/A001, M/SABX/8A002, and M/SABX/BA003).

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Janina Deppe, Dipl. Biol.
Thomas Pitsch, MTA

Head Veterinarian and Animal Welfare Officer

Dr. Annalena Riedasch and Prof. Dr. Frank Richter

Dr. Riedasch and Prof. Richter ensure that all animal experiments are performed according to highest possible standards of animal welfare and oversee respective applications for approval by the local authorities. In addition, they are in charge of operating the central animal facility (ZVH) and ensuring its high quality standards.

Drittmittelförderungen

P 1: MIF in der Atherosklerose

Projektleiter:	J. Bernhagen / C. Weber
Förderer:	DFG (BE1977/4-1, FOR809-TP1)
Bewilligungszeitraum:	01/2011-12/2014

P 2: Interaktionen thrombozytärer Chemokine

Projektleiter:	P. v. Hundelshausen / C. Weber
Förderer:	DFG (WE1913/5-2, HU1618/1-2, FOR809-TP2)
Bewilligungszeitraum:	01/2011-12/2014

P 3: Dendritische Zellen in der Atherosklerose

Projektleiter:	A. Zernecke
Förderer:	DFG (ZE827/1-2, FOR809-TP3)
Bewilligungszeitraum:	01/2011-12/2014

P 4: SDF-1 und vaskuläre Vorläuferzellen

Projektleiter:	C. Weber / A. Schober
Förderer:	DFG (WE1913/7-2, WE1913/11-2, FOR809-TP4)
Bewilligungszeitraum:	01/2011-12/2014
Kooperationen:	R. Adams, MPI Münster

P 5: JAM-A und vaskuläre Entzündung

Projektleiter:	R. Koenen / C. Weber
Förderer:	DFG (WE1913/9-2), (KO2948/1-2), (FOR809-TP6)
Bewilligungszeitraum:	01/2011-12/2014
Kooperationen:	E. Dejana, Mario Negri-Institut

P 6: DFG Forschergruppe TP 09

Projektleiter:	O. Söhnlein
Förderer:	DFG (SO 876/4-1)
Bewilligungszeitraum:	01/2011-09/2014
Kooperationen:	J.J. Oppenheim & P.M. Murphy, NIH

P 7: DFG Forschergruppe TP 10

Projektleiter:	M. Hristov
Förderer:	DFG (HR18/1-1)
Bewilligungszeitraum:	01/2011-06/2014
Kooperationen:	N.Marx, Kardiologie, RWTH Aachen

P 8: DFG Forschergruppe TP 11
Projektleiter: E. Lutgens
Förderer: DFG (LU 1643/1-1)
Bewilligungszeitraum: 01/2011-06/2014

P 9: Transgene Mausmodelle
Projektleiter: C. Weber
Förderer: DFG (WE1913/12-2, FOR809-ZP)
Bewilligungszeitraum: 01/2011-12/2014
Kooperationen: R.Naumann, MPI Dresden

P 10: Differential recruitment of monocyte subsets
Projektleiter: C. Weber / O. Söhnlein
Förderer: DFG (SFB914-B08)
Bewilligungszeitraum: 06/2011-06/2015
Kooperationen: diverse

P 11: Induktion der Entzündungsresolution in der Atherosklerose
Projektleiter: O. Söhnlein
Förderer: DFG (SO 876/6-1)
Bewilligungszeitraum: 02/2013-02/2016

P 12: Chemokinrezeptor-vermittelte Kontrolle von T-Zell- und DC-Plastizität bei chronischer Entzündung
Projektleiter: C. Weber
Förderer: DFG (SFB1054/1-B04)
Bewilligungszeitraum: 01/2013-12/2016

P 13: Die Wirkung von Hypercholesterinämie auf die Funktion kostimulatorischer Moleküle: Von Stamm- und Vorläuferzellen zum reifen Immunsystem
Projektleiter: E. Lutgens
Förderer: DFG (SFB1054/1-B08)
Bewilligungszeitraum: 01/2013-12/2016

P 14: Role of LPA in atherosclerosis
Projektleiter: A. Schober
Förderer: DFG (SFB1054/3)
Bewilligungszeitraum: 01/2013-12/2016

P 15: Molekulare und funktionelle Charakterisierung von T-und B-Zell Autoimmunreaktionen der Atherosklerose in Hyperlipidämischen Mäusen
Projektleiter: A. Habenicht
Förderer: DFG (HA 1083/15-3)
Bewilligungszeitraum: 11/2012-04/2016

P 16: Neutrophil apoptosis in atherosclerosis
Projektleiter: O. Söhnlein
Förderer: LMUexcellent
Bewilligungszeitraum: 06/2013-06/2014

P 17: Munich Heart Alliance
Projektleiter: C. Weber
Förderer: BMBF / StMWFK
Bewilligungszeitraum: 01/2011-12/2015

P 18: Vaskuläre Immuntherapie
Projektleiter: C. Weber
Förderer: BMBF DZHK MHA VD1.2
Bewilligungszeitraum: 10/2011-12/2015

P 19: IntenC Research Grant Lipotoxic Stress
Projektleiter: C. Weber / E. Erbay
Förderer: BMBF (TUR10/I13)
Bewilligungszeitraum: 10/2011-09/2014

P 20: Verbund miR-A
Projektleiter: A. Schober
Förderer: BMBF DLR (01KU1213A)
Bewilligungszeitraum: 04/2012-03/2015

P 21: Verbund miR-A
Projektleiter: C. Weber
Förderer: BMBF DLR (01KU1213B)
Bewilligungszeitraum: 04/2012-03/2015

P22: ERC Advanced Investigator Grant Atheroprotect
Projektleiter: C. Weber
Förderer: European Research Council
Bewilligungszeitraum: 01/2011-12/2015
Kooperationen: K. Mayo, University of Minnesota

P 23: Leducq Transatlantic Network of Excellence CVGeneF(x)Differential recruitment of monocyte subsets
Projektleiter: C. Weber
Förderer: Leducq Foundation
Bewilligungszeitraum: 01/2011-12/2015
Kooperationen: D. Rader, University of Pennsylvania

P 24: NWO VICI Grant
Projektleiter: C. Weber
Förderer: NWO
Bewilligungszeitraum: 04/2010-03/2016
Kooperationen: diverse

P 25: Kostimulation via CD40 in der Atherosklerose
Projektleiter: E. Lutgens
Förderer: Humboldt-Stiftung
Bewilligungszeitraum: 12/2008-12/2014

P 26: Atheroprotektion durch α-Defensine
Projektleiter: O. Söhnlein
Förderer: Else-Kröner-Fresenius Stiftung 2012_A36
Bewilligungszeitraum: 07/2012-02/2015

P 27: Role of serotonin receptors in atherosclerosis
Projektleiter: S. Steffens
Förderer: Friedrich-Baur Stiftung 45/13
Bewilligungszeitraum: 06/2013-06/2014

P 28: Die Rolle des peripheren Serotoninsystems in der Atherosklerose
Projektleiter: S. Steffens
Förderer: Else-Kröner-Fresenius Stiftung 2013_A114
Bewilligungszeitraum: 07/2013-07/2016

P 29: Neutrophils and platelets cooperate during monocyte recruitment
Projektleiter: Söhnlein, Weber
Förderer: DFG
Geschäftszeichen: SFB914, TP B08
Bewilligungszeitraum: 2011-2019
Kooperationspartner: Gerry Nicolaes, Tilman Hackeng

P 30: Alarmins mediating homeostatic leukocyte alterations in atherosclerosis
Projektleiter: Söhnlein, Drechsler
Förderer: DFG, SFB1123, TP A6
Bewilligungszeitraum: 07/2014-06/2018
Kooperationspartner: Andres Hidalgo

P 31: Role of NETs in atherogenesis
Projektleiter: Söhnlein, Döring
Förderer: DFG, SFB1123, TP B5
Bewilligungszeitraum: 07/2014-06/2018
Kooperationspartner: Steffen Massberg

P 32: Apoptotic neutrophils in atherosclerosis
Projektleiter: Oliver Söhnlein
Förderer: NWO
Bewilligungszeitraum: 2012-2017
Kooperationspartner: Mat Daemen, Esther Lutgens

P 33: Entzündungsresolution in der Atherosklerose
Projektleiter: Oliver Söhnlein
Förderer: LMUexcellent
Bewilligungszeitraum: 2013-2017
Kooperationspartner: Nicolas Cenac, Mauro Perretti

P 34: Apoptotische Neutrophile in der Atherogenese
Projektleiter: Oliver Söhnlein
Förderer: DFG, SO876/6-1
Bewilligungszeitraum: 2014-2017
Kooperationspartner: Christian Kupatt, Nicolas Cenac, Mauro Perretti

P 35: European Vascular Interventions and Therapeutic Innovation Network
Projektleiter: Oliver Söhnlein
Förderer: EU
Bewilligungszeitraum: 2014-2018
Kooperationspartner: Mauro Perretti

P 36: Investigating the role of FPR2/ALX in myocardial repair
Projektleiter: Söhnlein, Leoni
Förderer: EU, WHRI Academy
Bewilligungszeitraum: 2014-2017
Kooperationspartner: Mauro Perretti

P 37: Atheroprotection by alpha-defensins
Projektleiter: Oliver Söhnlein
Förderer: EKFS
Bewilligungszeitraum: 2012-2015
Kooperationspartner: Patrick Rensen, Khalil Bdeir

P 38: The role of MFG-E8 in atherosclerosis
Projektleiter: Joana Viola
Förderer: LMU FöFoLe
Bewilligungszeitraum: 03/2014-09/2015

P 39: Neutrophils in advanced atherosclerosis
Projektleiter: Carlos Silvestre-Roig
Förderer: LMU FöFoLe
Bewilligungszeitraum: 2015-2016

P 40: Kleintierultraschall
Projektleiter: Söhnlein
Förderer: BMBF/DZHK
Bewilligungszeitraum: seit 2015

P 41: Neutrophils in plaque destabilization
Projektleiter: Oliver Söhnlein
Förderer: DFG, SO876/11-1
Zeitraum: 2015-2018
Kooperationspartner: Mat Daemen, Esther Lutgens

P 42: Rolle von PMN in der Aufweichung der fibrösen Kappe
Projektleiter: Oliver Söhnlein
Förderer: B. Braun Stiftung
Bewilligungszeitraum: 2015

P 43: Cxcl12 und Cxcr4/7 in der Atherosklerose
Projektleiter: Weber, Döring
Förderer: DFG, SFB1123, TP A01
Bewilligungszeitraum: 07/2014-08/2018

P 44: Molecular mechanisms linking the CXCL12 pathway to atherosclerosis
Projektleiter: Weber, Döring
Förderer: NIH
Bewilligungszeitraum: 2015-2018
Kooperationspartner: D. Saleheen, Univ. Philadelphia

P 45: Study of the role of endothelial and smooth muscle cell CXCR4 in regulating vascular tone
Projektleiter: Weber, Döring
Förderer: BMBF/DZHK
Bewilligungszeitraum: 2014-2015

P 46: Study of the role of endothelial CXCR4 in vascular permeability
Projektleiter: Weber, Döring
Förderer: BMBF/DZHK
Bewilligungszeitraum: 2014-2015

P 47: DC und T-Zell-Funktion in der Atherosklerose
Projektleiter: Christian Weber
Förderer: DFG, SFB1054, B04
Bewilligungszeitraum: 01/2013-1220/16
Kooperationspartner: diverse

P 48: Ko-stimulatorische Moleküle bei Adipositas
Projektleiter: Esther Lutgens
Förderer: DFG, SFB1054, B08
Bewilligungszeitraum: 01/2013-12/2016
Kooperationspartner: diverse

P 49: Effect of the AMPK alpha2 subunit on neutrophil recruitment and function in atherosclerosis
Projektleiter: Oliver Söhnlein
Förderer: DZHK/BMBF
Geschäftszeichen: DZHK B 14-020 SE
Zeitraum: 2014
Kooperationspartner: Beate Fisslthaler

P 50: Annexin A1 prevents arterial leukocyte recruitment – mechanistic insights
Projektleiter: Oliver Söhnlein
Förderer: DZHK/BMBF
Zeitraum: 2014-2015
Kooperationspartner: Alexander Zarbock

P 51: Proteomic analysis of the resolving macrophage in cardiovascular inflammation
Projektleiter: Oliver Söhnlein
Förderer: DZHK/BMBF
Zeitraum: 2015-2016
Kooperationspartner: Gunnar Dittmar

P 52: Ko-stimulatorische Moleküle in der Atherosklerose
Projektleiter: Esther Lutgens
Förderer: DFG, SFB1123, TP A05
Bewilligungszeitraum: 07/2014-08/2018

P 53: Rolle des peripheren Endocannabinoidsystems in der Atherosklerose
Projektleiter: Sabine Steffens
Förderer: DFG
Bewilligungszeitraum: 07/2014 bis 06/2017

P 54: Rolle des Endocannabinoidsystems und des zirkadianen Rhythmus in der Wundheilung nach Herzinfarkt
Projektleiter: Sabine Steffens
Förderer: DFG
Bewilligungszeitraum: 12/2015 bis 11/2018

P 55: Rolle des peripheren Serotoninsystems in der Atherosklerose
Projektleiter: Sabine Steffens
Förderer: EKFS
Bewilligungszeitraum: 10/2013 bis 02/2017

P 56: Rolle des neuen Cannabinoidrezeptors GPR55 in der Wundheilung nach Herzinfarkt
Projektleiter: Sabine Steffens
Förderer: FöFoLe
Bewilligungszeitraum: 04/ 2016 bis 09/2017

P 57: Specific contribution of vascular and macrophage cannabinoid receptor CB1 signaling to the cardiometabolic effects of endocannabinoids
Projektleiter: Sabine Steffens
Förderer: DZHK/BMBF
Bewilligungszeitraum: 01/2015 bis 12/2016
Kooperationspartner: Ulrich Kintscher, Charite Berlin

P 58: Funktionelle Chrakterisierung von T- und B-Zell Autoimmunreaktionen der Atherosklerose in hyperlipidämischen Mäusen
Projektleiter: Andreas Habenicht
Förderer: DFG
Bewilligungszeitraum: 01/2013 – 03/2017
Kooperationspartner: Prof. Rudolf Manz, Institut für Systemische Entzündungsforschung ISEF der Universität Lübeck

P 59: Atherosklerosis B Cell Autoimmunity in Aged Hyperlipidemic Mice
Projektleiter: Andreas Habenicht
Förderer: DFG
Bewilligungszeitraum: 01/2016 – 12/2019
Kooperationspartner: Dr. Klaus Dornmair, Institute of Clinical Neuroimmunology, LMU Munich; Prof. Rudolph Manz, Institut für Systemische Entzündungsforschung ISEF

P 60: Immune Injury of the Central Nervous System in Aged Humanized Transgenic apolipoprotein E Isoform-specific Knockin Mice
Projektleiter: Changjun Yin
Förderer: DFG
Bewilligungszeitraum: 2016 - 2019
Kooperationspartner: Prof. Christine Skerka and Prof. Dr. Peter Zipfel, Leibniz Institute for Natural Product Research and Infection Biology e.V. Hans-Knöll-Institute (HKI), Jena, Germany ; Dr. Arthur Liesz and Prof. Dr. Martin Dichgans, Institute for Stroke and Dementia Research (ISD), Ludwig-Maximilians-University (LMU), Munich, Germany.

P 61: Atherosclerosis Peripheral Nervous System Crosstalk in Apolipoprotein E-deficient and Human Apolipoprotein E Isoform-specific Knock-in Mice
Projektleiter: Saroj Mohanta
Förderer: DFG
Bewilligungszeitraum: 01/2016 - 12/2019
Kooperationspartner: Winfried Neuhuber, Institut für Anatomie I, Friedrich-Alexander Universität, Erlangen; Arthur Liesz, Institute for Stroke and Dementia Research, LMU Munich; Bernhard W. Renz, Department of Surgery, KUM Munich; Christoph Scheiermann, LMU Munich; Michael Schemann, Department of human biology; TU München; Thomas C. Mettenleiter, Friedrich-Loeffler-Institut, Greifswald-Insel Riems; Heike Heuer, Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany

P 62: Optical imaging platform
Projektleiter: Remco Megens
Förderer: DFG, SFB1123, TP Z01
Bewilligungszeitraum: 07/2014-06/2018

P 63: Chemokine-Heteromers in atherosclerosis
Projektleiter: Philipp von Hundelshausen
Förderer: DFG, SFB1123, TP A02
Bewilligungszeitraum: 07/2014-06/2018

P 64: miRNA in atherosclerosis
Projektleiter: Schober, Weber
Förderer: DFG, SFB1123, B04
Bewilligungszeitraum: 07/2014-06/2018

P 65: LPA in atherosclerosis
Projektleiter: Siess, Schober
Förderer: DFG, SFB1123, B08
Bewilligungszeitraum: 07/2014-06/2018

P 66: LMU excellent Investitionsfond
Projektleiter: Prof. Weber
Förderer: LMU
Geschäftszeichen: Excellent/ERCAdG
Bewilligungszeitraum: 2015

P 67: LMU excellent/DFG Mittel über STED
Projektleiter: Prof. Weber
Förderer: LMU
Geschäftszeichen: INST 409/150-1 FUGG
Bewilligungszeitraum: 2015

Preise und Auszeichnungen

Jahr : 2014
Auszeichnung: Prof. Christian Weber gehört zu den Besten seines Fachs auf dem Gebiet der Herz-Kreislauf-Forschung, wie ein Ranking des *Laborjournals* bestätigt

Jahr : 2014
Preis: Rolf-Becker-Preis der Medizinischen Fakultät der LMU
Maliheh Nazari-Jahantigh und Andreas Schober

Jahr : 2014
Preis: Outstanding Achievement Award der European Society of Cardiology (ESC)
Andreas Schober

Jahr : 2015
Preis: Franz-Maximilian-Groedel-Forschungspreis Preis 2015 der Deutsche Gesellschaft für Kardiologie
Rabea Hinkel

Jahr : 2015
Preis: Alexander-Schmidt-Preis 2015 der Gesellschaft für Thrombose- und Hämostaseforschung
Christian Weber

Jahr : 2015
Preis: Borchers-Plakette der RWTH Aachen und CARIM Dissertation Award für herausragende Promotionen
Martin Schmitt

Thrombosis & Haemostasis

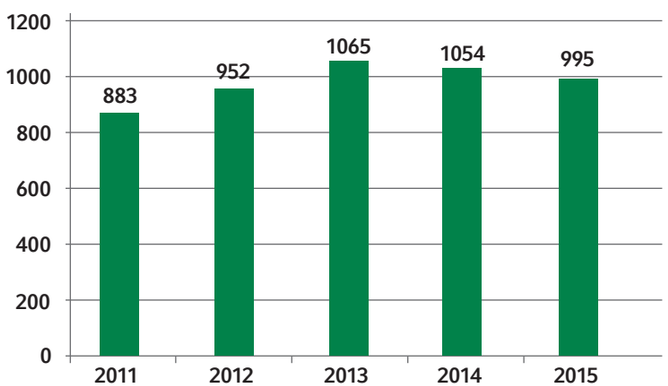
Haemostasis is a leading journal of the Schattauer Group, it publishes reports on basic and clinical research dedicated to novel results and highest quality in any area of thrombosis and haemostasis, vascular biology and medicine, inflammation and infection, platelet and leukocyte biology, from genetic, molecular & cellular studies, diagnostic, therapeutic & preventative studies to high-level translational and clinical research.
Target group: Haematologists, clinical pharmatologists, cardiologists, surgeons, gynaecologists, internal specialists and laboratory physicians. The journal successfully carries out its mission being a forum for the exchange of ideas and concepts fostering cross-disciplinary insights in basic and clinical research. Thrombosis and Haemostasis provides position and guideline papers, state-of-the-art papers, expert analysis and commentaries, and dedicated Theme issues covering recent developments and key topics in the field. Prof. Weber serves as the Editor-in-Chief (Basic Sciences) since 2009.

General Information

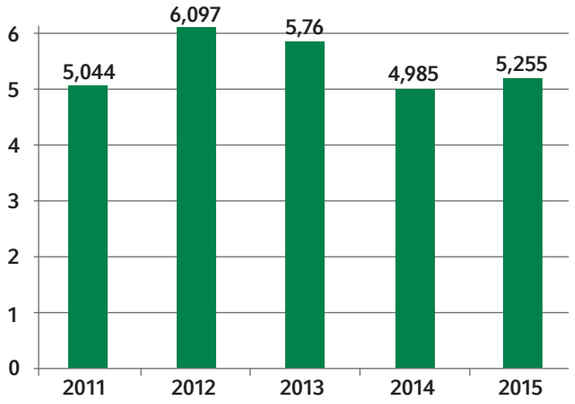
The journal is published monthly in print (ISSN 0340–6245) and online (www.thrombosis-online.com) and is covered in the main abstracting and indexing services worldwide. The journal continues serving as a link journal for the European Society of Cardiology Working Groups on Thrombosis and Atherosclerosis & Vascular Biology, as the official journal of the Spanish Sociedad Española de Trombosis y Hemostasia (SETH), the Italian Societa Italiana per lo Studio dell'Emostasi e della Thrombosi (SISET) societies on Thrombosis and Haemostasis and the Australian Vascular Biology Society (AVBS).

Highlights 2014-2015

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 Haemostasis has again risen to 5.255 terms representing one of the leading journals in its field.



In 2015 the Journal received a little makeover: the categories have been revised and new ones have been introduced, while colour was added to the Table of Contents. Highlighted by colour-indexing were the Basic, Clinical and Translational areas of research. The eight new subcategories of Original Articles since 2015 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.
Due to the mentioned changes our issues have obtained better structure, categories are better balanced and the colours have not only vividly brightened the pages, but also allow for improved navigation through the topics.

Editor-in-Chief (Basic Science)

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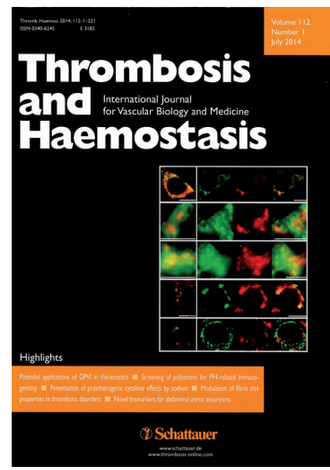
In 2014 the Journal has got the own Internet-page: http://th.schattauer.de/en/home.html and in 2015 appeared in Facebook: https://www.facebook.com/thrombosisandhaemostasis.



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.

Patientenbetreuung

Team des patientenversorgenden Bereiches im Rahmen der August-Lenz-Stiftung.

Im Rahmen der August-Lenz-Stiftung kümmert sich das IPEK neben Forschung und Weiterentwicklung von Projekten auch um die Versorgung von Studienpatienten. Wie der Name *Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten* nahe legt, geht es dabei schwerpunktmäßig um Studien im Rahmen von Herz-Kreislauferkrankungen und die Entwicklung neuer diagnostischer Parameter, die eine frühzeitige Demaskierung und entsprechende Behandlung einer Atherosklerose ermöglichen.

Oft sind die Herz-Kreislauferkrankungen jedoch nicht die einzigen Beschwerden, denen in der Praxis durch die Einbeziehung weiterer Facharztdisziplinen Rechnung getragen wird. So setzt sich das Team aus folgenden Mitarbeitern zusammen: einem Chefarzt für Innere Medizin und Kardiologie, einem Oberarzt, ebenfalls mit dem Schwerpunk Innere Medizin und Kardiologie, einem weiteren Oberarzt mit den Bezeichnungen Innere Medizin, Gastroenterologie und Nephrologie, sowie einer Assistenzärztin. Des Weiteren wird das Team durch eine study nurse und zwei technische Assistentinnen unterstützt, sowie zwei Verwaltungsangestellten, die die Terminabsprachen koordinieren.

Hintergrund

Herz-Kreislaufkrankheiten machen mit 48% den Hauptanteil der Todesursachen in Deutschland aus (siehe Graphik unten) und liegen damit deutlich vor Krebserkrankungen, die in 25% der Todesfälle verantwortlich sind.

Trotz zahlreicher Aufklärungsmaßnahmen und der starken Präsenz des Themas in den Medien, fragen sich viele Patienten, wie sie Herz-Kreislauferkrankungen gegenübertreten sollen und was sie zur Vorsorge tun können.
Neben den regulären Untersuchungen beim Hausarzt oder Internisten gibt es mittlerweile zusätzliche, spezifische Check-ups, die ganz gezielt das Herz und Gefäßsystem unter die Lupe nehmen. Mit Hilfe dieser Ergebnisse kann der Arzt frühzeitig eine individuelle Diagnose stellen und die Erkrankung behandeln oder dem Patienten weitere Empfehlungen geben, wie er Erkrankungen wie Herzinfarkt oder Schlaganfall effektiv vorbeugen kann.

Prävention

Eine reguläre Vorsorge-Untersuchung umfasst zunächst ein eingehendes und ausführliches Gespräch mit der Patientin bzw. dem Patienten. Dabei werden familiäre Vorerkrankungen genauso berücksichtigt wie die aktuelle Lebenssituation und mögliche Belastungsfaktoren. Uns ist es besonders wichtig, ein vertrauensvolles Verhältnis zu unseren Patienten aufzubauen, da wir davon überzeugt sind, dass eine ganzheitliche Arzt-Patienten-Beziehung die Grundlage für jede erfolgreiche Behandlung ist. In Abhängigkeit der individuellen Fragestellung bieten wir neben der Anamnese und körperlichen Untersuchung folgende Diagnostik an:

- serielle Blutdruckmessung manuell und oszillometrisch
- Blutentnahme, u.a. zur Bestimmung der Cholesterin- und Lipidwerte
- EKG-Ableitung
- Belastungs-EKG
- Herz-Ultraschall (UKG)
- Ultraschalluntersuchung der Halsschlagader (Arteria carotis)
- Messung der Pulswellengeschwindigkeit (PWV) als Maß für die Gefäßsteifigkeit
- 24-Stunden-Blutdruck- oder 24-Stunden-EKG-Messung

Weiter bieten wir spezielle Untersuchungen an:

- Bestimmung genetischer Risikofaktoren
- Messung von inflammatorischen Zellpopulationen

Anmeldungs- und Öffnungszeiten

Die Anmeldung erfolgt über das Sekretariat, z. B. per Telefon über die Nummer der August-Lenz-Stiftung: +49 (0)89 / 53 93 31 oder mittels elektronischer Terminanfrage über die E-mail-Adresse: kreislaufinstitut@med.uni-muenchen.de.

Terminvereinbarungen sind telefonisch oder persönlich möglich zu folgenden Zeiten:
Mo, Di, Mi, Do: 8:30 Uhr bis 17:00 Uhr
Fr: 8:30 Uhr bis 15:30 Uhr

Die **Öffnungszeiten** entsprechen regulär
Mo, Di, Do: 8:00 Uhr bis 13:00 Uhr
Mi: 8:00 Uhr bis 17:00 Uhr (Studientag)
können aber nach Vereinbarung auch zu anderen Zeiten wahrgenommen werden.

Carolus Therapeutics

Carolus Therapeutics ist ein amerikanisches, biopharmakologisches Unternehmen, dessen Schwerpunkt auf Arzneimittelentwicklungen zur Behandlung von akuten oder chronischen, inflammatorischen Prozessen liegt. Im Fokus stehen neue Medikamente und Strategien, die nicht-invasiv Interaktionen von Chemokinen hemmen und so einer Entzündungsreaktion vorbeugen bzw. eine bestehende Inflammation heilen können. Das Unternehmen hat zu diesem Zweck bereits mehrere Patente aufgekauft und leitet nun weitere Entwicklungen in Zusammenarbeit mit den Forschungslaboren.

Auch die Forschungsarbeiten am IPEK stellen für *Carolus Therapeutics* ein interessantes Gebiet dar. Die Firma hat ausdrückliches Interesse an der Chemokin- und RANTES-PF4-Forschung und das Unternehmen wurde auch mit Hilfe der vielversprechenden Forschung Rund um das MIF-Projekt zu Aachener Zeiten gegründet.

RANTES und PF4

RANTES ist ein lösliches Chemokin, das von vielen unterschiedlichen Zellen gebildet und sezerniert wird. Blutplättchen speichern RANTES in ihren alpha-Granula und schütten es bei einer akuten Entzündung aus. RANTES ist ein potenter, chemischer Lockstoff für T-Zellen, Monozyten, natürliche Killerzellen, Basophile und Eosinophile und spielt eine ausschlaggebende Rolle bei zellulären Infiltrationen, die verschiedenen Erkrankungsprozessen, wie z. B. auch der Atherosklerose und Atemwegserkrankungen, zugrunde liegen.

Plättchenfaktor 4 (PF4) ist ein kleines Zytokin, welches aus den alpha-Granulae aktivierter Thrombozyten bei deren Aggregation ausgeschüttet wird. Es bindet Heparin an der endothelialen Gefäßwand mit hoher Affinität und fördert so die Blutgerinnung. Im Weiteren ist PF4 ein starker, chemischer Lockstoff für Neutrophile und Fibroblasten und spielt eine Rolle in der Monozyten- und Plättchenrekrutierung bei der Entstehung einer atherosklerotischen Plaque oder der Wundreperatur.

In Tiermodellen führte die Elimination von PF4 aus den Thrombozyten zu einer Reduktion der Atherosklerose. Die Interaktion von PF4 mit RANTES und Heterodimere aus PF4-RANTES verstärkten die Rekrutierung von Monozyten und die Adhäsion an entzündliches Endothel.

Wissenschaftliche Entwicklungen unter Carolus Therapeutics konnten zeigen, dass eine Spaltung des PF4-RANTES Heterodimers durch einen hochaffinen Peptidliganden zu einer Verlangsamung atherosklerotischer Plaquebildung aber auch der Ausbildung abdominaler Aortenaneurysmen im Mausmodel führt (Koenen, Nat Med, 2009). Das Unternehmen hat die Vorteile dieser Entwicklung aufgegriffen und entwickelt diese therapeutischen Peptide zur Behandlung diverser inflammatorischer insbesondere auch pulmonaler Erkrankungen, bei denen RANTES-PF4 mit einer Exazerbation im Krankheitsverlauf assoziiert ist.
Gemeinsam mit der alpha-1 Stiftung ist hier eine klinische Phase I Studie bei Patienten mit α-1 Antitrypsin Mangel oder zystischer Fibrose geplant, während mit der Firma BioScale Inc. neue diagnostische Assays entwickelt werden.

MIF

Der *macrophage migration inhibiting factor* (MIF) ist ein entscheidender Mediator der angeborenen, zellvermittelnden Immunität, der Immunregulation und der Inflammation. MIF hat in der Regulation der Makrophagenfunktion bei der Körperabwehr durch die Suppression antiinflammatorischer Effekte auf Glukokortikoide eine Schlüsselrolle. Beim Menschen ist MIF während verschiedener, entzündlicher Prozesse im Körper erhöht, so z.B. auch bei Atherosklerose, Rheumatoider Arthritis, Multipler Sklerose oder Atemwegserkrankungen und im Blut von Patienten mit schwerer Sepsis. Allgemein gehalten korreliert die Konzentration an MIF mit dem Schweregrad der Erkrankung.

Exogen zugeführtes MIF wirkt proinflammatorisch und verschlimmert eine Erkrankung. Die Neutralisierung von MIF mittels Antiserum oder die Eliminierung durch genetische Veränderung führen zu einer Hemmung der inflammatorischen Antwort und vermindern die Progression der Erkrankung in verschiedenen Tiermodellen. Anti-MIF-Antikörper supprimieren zudem das Tumorwachstum und reduzieren die tumorassoziierte Angiogenese effektiv.

MIF geht TNF-alpha in der Entzündungskaskade voraus. Eine Herunterregulation von MIF führt somit direkt zu verminderten Spiegeln an TNF-alpha und anderen proinflammatorischen Faktoren.

Wissenschaftler haben im Rahmen von *Carolus Therapeutics* die Chemokinrezeptoren CXCR2 und CXCR4 als Bindungsstellen für MIF identifiziert. Über diese beiden Rezeptoren triggert MIF unmittelbar die Migration, Rekrutierung und den Arrest von Leukozyten. Durch die Aktivierung beider Rezeptoren wirkt das Molekül als Hauptregulator bei entzündlicher Zellrekrutierung und Atherogenese. Die Blockade von MIF führt zur Reduktion von Plaques und vermindert zusätzlich den Anteil an T-Zellen und Monozyten im Plaqueinneren bei Tieren mit vermehrter Atherosklerose.

Ausblick

Das Unternehmen strebt den Einsatz der entwickelten Medikamente am Patienten an.

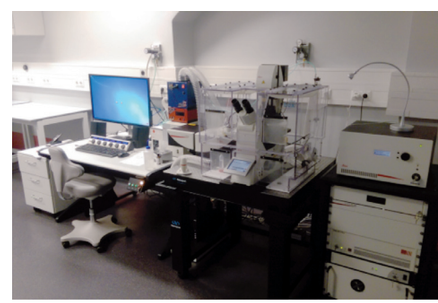
Bauliche Entwicklungen

Sanierungsarbeiten Gartenpavillon

Im Gebäude an der Goethestr. 69 wurden vor allem gründliche und aufwändige Kanalsanierungsarbeiten durchgeführt. Diese waren dringend erforderlich, um die zahlreichen undichten Stellen an den alten Abflüssen zu sanieren und dadurch entstandene Dauerprobleme mit Feuchtigkeit an Wänden und Fundament konsequent zu beheben. Rund um das Gebäude wurden neue Abflussrohre und Schächte errichtet. Alle Abflussleitungen inkl. Regenwasser mussten entsprechend abgedichtet bzw. umgeleitet oder neu verlegt werden. Spülbecken und die Eismaschine im Zelllabor mussten neu verlegt werden. Ferner wurden die Waschräume sowie der Bodenbelag inkl. Estrich und der Wandanstrich im Aufenthaltsraum erneuert. Abschließend wurde der Außenbereich vor dem Gebäude angehoben und neu asphaltiert. Zusätzlich erfolgte eine weitere Optimierung der Laborsicherheit. Dazu wurden zwei neue Notduschen angebracht.

STED Einbringung in der ZVH

Im Rahmen der Neuanschaffung eines Stimulated Emission Depletion Microscope (STED; Leica SP8 3X) in 2014 wurde der beherbergende Raum BU.05 in der ZVH im Untergeschoss der Chirurgischen Klinik, Nußbaumstr. 20, Anfang 2015 vollständig umgebaut. Der ehemalige Lagerraum wurde saniert und anschließend als S1-Labor komplett neu gestaltet. Für die optimale Nutzung als solches wurden eine Klimaanlage, neue Gas- und Stromanschlüsse sowie neue Labormöbel eingebaut. Diese Baumaßnahmen wurden unter Leitung des Architekten Heribert Eibicht vom Staatlichen Bauamt koordiniert. Damit erfüllt dieser neu entstandene Raum mit ca. 25 m2 Laborfläche alle Anforderungen der high-end Mikroskopie (siehe Bilder)



Forschungsverbünde und Projektförderungen

Forschungsverbünde

DFG Forschergruppe 809

Chemokines and adhesion molecules in cardiovascular pathogenesis

Atherosclerosis is a chronic inflammatory disease destroying the inner layers of the blood vessel walls. These damages cause vascular occlusion and thrombosis progression resulting in heart attacks and strokes, which are responsible worldwide for almost 30% of all cases of death and hold the first place in the list. Only in 2006 around 7 million people died in North America and Europe due to cardiac and vascular diseases, the tendency shows constant progression. It is important to understand the mechanisms of development and destabilization of vascular pathological changes to detect the disease on early stages and offer appropriate medical help in time.

Until the end of 2014 the research group 809 investigated new ways to dissolve plaque in the arteries, as well as to prevent their formation. Atherosclerosis is caused by chronic inflammation in the vessel wall. According to current understanding the onset of atherosclerosis is sparked by metabolic dysbalance along with other factors causing endothelial dysfunction. Later different leukocytes subtypes start infiltration in endothelial and vascular smooth musculature. This in turn initiates the formation of atherosclerotic plaques and accompanying pathophysiological changes. Migration of immune cells, particularly T cells and monocytes plays a crucial role in the process (Weber et al, Nat Rev Immunol 2008; Nat Rev Drug Discov 2010; Nat Med 2011). Though some studies point on the involvement in atherosclerosis of chemokines, related to cytokines (e.g MIF) and activated by their receptors adhesion molecules (e.g. P-selectin), junctional adhesion molecules (e.g. JAM-A) and possibly adhesions contra-player (e.g. Del-1), the molecular signals that are launching and coordinating cellular inflammatory response in complicated interaction are still understood rather poor. The apparent redundancy in the expression and function of various chemokines and adhesion molecules during the progression of atherosclerosis could be explained in different ways. One model could be based on possible involvement of chemokines in certain stages of recruiting cascade, e.g. arrest vs diapedese, as well as in kinetics of development of stages (new formation vs complex plaque). The other concept arises from detected tendency at least in some cases for certain mononuclear cell populations, e.g. CXCR6 or monocytes subpopulations to dominate. That builds in turn complicated interaction and co-influence with proarterogenic and protective functions of different mononuclear cell populations in systemic and local immune response in plaque, such as anti-inflammatory properties of regulatory T cells and, unexpectedly, proatherogenic function of neutrophils. The mission of research group 809 was to carry out the detailed study of each mononuclear cell population along with their secretory products involvement in atherosclerosis and chemokines role in the recruitment and progression of plaques.

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

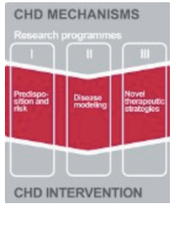
It has long been known that blood levels of lipids like cholesterol are important risk factors for atherosclerotic cardiovascular disease. Lipid levels and atherosclerosis both run in families, but how these traits are genetically determined is poorly understood. Genome-wide association studies (GWAS) 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.

Munich Heart Alliance (MHA)

Munich Heart Alliance

The Munich Heart Alliance Centre (MHA Centre) as 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

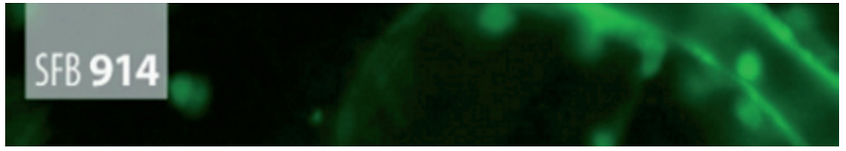
The **Munich research area** is the ideal site to address these goals, as it combines excellent basic and clinical research on the disease mechanisms and interventions to prevent and treat CHD. In particular, Munich provides the nation's leading cardiovascular framework with regards to the conduct of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

German Federal Ministry of Defense research project M/SABX/8A002/BA003

Innovative therapeutic strategies in the treatment of sulfur mustard (SM)-affected skin: modulation of HIF 1α signaling and microRNA regulated pathways. Its relative ease of production and stockpiling together with its multiple incapacitating health effects make mustard gas a continuing threat. Identification of effective therapies for SM-induced injuries is the focus of research worldwide.
In a further project (M/SABX/8A002/BA003) we currently investigate the importance of oxygen-deficiency (hypoxia), especially the role of HIF-1α and microRNAs in the pathophysiology of SM. Under normal physiological conditions, wound-associated hypoxia is a timely-limited situation that acts as an important stimulus for proper healing and regeneration in skin. Hypoxia controls the function and behavior of keratinocytes and fibroblasts by influencing the expression of various regulatory molecules including cytokines and proteinases. In this context, HIF-1α plays a key role because it is upregulated during hypoxic conditions in the skin and thereby stimulates various processes including cell proliferation, migration, autophagy, and angiogenesis that facilitate wound healing. We hypothesize that SM causes dysregulation in HIF-1α-mediated signal transduction pathways which contributes to the pathophysiology of impaired tissue regeneration in SM-injured skin. The elucidation of SM-evoked malfunctions in keratinocytes and/or fibroblasts provoked by a disturbance of HIF-1α cell signaling would provide new therapeutic strategies of intervention including the application of specific agents that inhibit or stabilize HIF-1α activity. Autophagy is a tightly regulated catabolic process important in cell growth and development. Under stress conditions such as nutrient deficiency, autophagy facilitates cell survival by degradation of subcellular components through the lysosomal machinery, or initiates apoptosis. Our studies aim to explore whether SM exposure to skin cells interferes with the balance between survival and apoptosis in keratinocytes which may result in delayed wound healing.
MicroRNAs are a group of small non-coding RNA molecules that play key roles in the regulation of numerous physiological and pathological processes. In wound healing, microRNAs are involved in the control of inflammation, angiogenesis, and apoptosis especially by influencing the functions of keratinocytes and fibroblasts. Interestingly, specific microRNAs seem to be regulated by HIF-1α signaling. Therefore, a major part of our project aims to analyze the influence of SM on microRNA expression profiles in keratinocytes and fibroblasts. SM-mediated alterations in cellular microRNA signatures may indicate defects in the functions of these cells essential in normal wound healing. These findings could provide the opportunity for the development of innovative therapeutic concepts such as the topical application of microRNA inhibitors or microRNA agonists in the treatment of SM-injured skin.

BMBF Förderung des translationalen Verbundprojektes miR-A am IPEK Metabolic Syndrome and Atherosclerosis: Role of microRNAs

Vascular disease, such as atherosclerosis, is highly prevalent in the Metabolic Syndrome (MetS). This is due, at least in part, to the enhanced adipocyte and vascular inflammation that occurs in MetS. Understanding the complex etiology of vascular disease in MetS will allow the design of effective therapies to prevent and treat this debilitating disease. Recently, microRNAs (miRs) have been shown to be altered in atherosclerosis. For example, we found using a miRNomics approach that several microRNAs (miR-126, miR-146, miR-155) are enhanced in atherosclerosis plaques, while others are down-regulated (miR-181a). Additionally, we have found that a subset of miRs are packaged in secreted microvesicles (MVs) and have evidence that this packaging may be altered in disease states. We also identified a single nucleotide polymorphism (SNP) in miR-146a that was associated with disease in a large coronary artery disease patient population (>5500 patients, our unpublished results). MicroRNAs are attractive targets for therapeutic modulation. However, the functional role of individual miRs in the development of atherosclerotic lesions is largely unknown. This collaborative project will exploit our miRNomics data to test the functional role of four miRs (miR-126, miR-146, miR-155, and miR-181a) in the pathogenesis of atherosclerosis in the context of MetS. This includes the analysis of pro- and anti-atherogenic effects of miRs on the inflammatory response in macrophages. In addition, the contribution of these miRs to endothelial dysfunction, which is important in early atherosclerosis, in response to atherogenic stimuli will be evaluated. Furthermore, the role and molecular mechanism of dysfunctional miR packaging into endothelial MVs in MetS-associated atherosclerosis will be studied. The identification of miRs that are involved in accelerated atherosclerosis promises to become a completely new class of targets in the treatment and prevention of this detrimental sequela of the MetS.

Projektförderungen

ERC Advanced Grant

Professor Christian Weber (Director of the Institute for Prophylaxis and Epidemiology of Cardiovascular Diseases and Chair of Preventive Vascular Medicine) has just received an Advanced Investigator Grant from the European Research Council (ERC). Weber's ERC project begins in January 2011. The generously endowed ERC Advanced Grants are intended to give European researchers who have already produced outstanding work the freedom to undertake imaginative and unconventional new projects.

Cardiovascular disease remains the leading cause of death in Western societies. The most common cause is atherosclerosis, popularly known as "hardening of the arteries." Indeed, the medical term refers to the progressive thickening of the walls of the arteries due to the accumulation of fatty deposits or "plaques". This results in chronic inflammation that exacerbates plaque growth, ultimately leading to obstruction of blood flow, which can trigger heart attacks and strokes. Professor Christian Weber was the first to show that a molecular complex formed by two small signal proteins, called chemokines, regulates the migration of immune cells into the inflamed tissue and so facilitates the growth of atherosclerotic plaques.

In his *Atheroprotect* project, for which the ERC will provide some 2.5 million Euros, Professor Weber plans to analyse further the biological significance of such interactions between chemokines for the fine tuning of the inflammation process in mice. He also hopes to develop new strategies to prevent or reverse the formation of chemokine complexes – once again using the mouse as a model. "The development of specific inhibitors of chemokine action could provide new opportunities for targeted therapy of the obstructive lesions in the vasculature", says Weber. "This would provide a entirely new basis for the treatment of atherosclerosis, but also of other inflammatory conditions such as multiple sclerosis."

Professor Christian Weber (b. 1967) studied medicine at LMU, obtaining his MD degree in 1994. He went on to do research at Harvard University in Boston (USA) and completed his Habilitation at LMU, before taking up a professorship in Maastricht (Netherlands). In 2005 he was appointed Chairman and Director of the Institute of Molecular Cardiovascular Research (IMCAR) at the RWTH in Aachen. He was named Director of the Institute for Prophylaxis and Epidemiology of Cardiovascular Diseases at LMU Munich University Hospital in November 2010. Weber has received several prizes for his research work, among them an Outstanding Achievement Award from the European Society of Cardiology and the Galen of Pergamon Prize.

ERC Advanced Investigator Grants

ERC Advanced Investigator Grants are designed to support highly innovative research, which has the potential to extend significantly the frontiers of existing fields and pioneer the investigation of new areas. Projects are assessed solely on the basis of the scientific stature of their authors and the originality and quality of the proposed research program.

VICI award granted by NWO

Prof. Dr. Christian Weber also holds a part-time professorship at the Cardiovascular Research Institute Maastricht (CARIM) was awarded VICI award granted for his project 'Putting the brakes on arteriosclerosis' by the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO).

A healthy body has a very clever mechanism for clearing out detrimental substances. For instance, if there is too much fat in the blood vessels, white blood cells (macrophages) will actually eat this excess fat. "You can already see this in babies who drink fatty mother's milk", says Weber. "If everything goes according to plan, the macrophages simply do their job and then disappear again."

Macrophages are controlled by chemokines, which are small proteins. The problem arises when these chemokines tell the macrophages to settle in the vascular wall instead of disappearing from the blood vessel. The macrophages form plaques, which may cause clots that roam around through the bloodstream. A blood clot can become so big that it closes off the entire blood vessel, exactly where the plaque is. The consequence: a heart attack, a stroke or a pulmonary embolism. Scientists have the important task of finding out why those chemokines give off the wrong signals, and how this can be prevented. "Of course you can fight them with antibodies", Weber suggests, "but this will also affect the good signals that chemokines give off. As a side effect, the immune system will stop functioning. So we're on the hunt for a treatment that eliminates the bad qualities of the chemokines, but not the good ones."

There are approximately 50 chemokines. Why so many? Do these proteins all have a specific task or function? Weber and his colleagues published an article on this in the scientific journal Nature Medicine: "Certain chemokines appear to reinforce one another; they have what you might call a synergetic interaction. They form the compound units known as 'heteromers'. In certain infections, for instance, a cocktail of ten chemokines is active. We focus on these heteromers. First we analyse their structure, then we add peptides. Peptides are molecules that can serve as a building block for proteins. The key is to establish where in the structure those peptides are active. The ultimate goal is to fight and prevent arteriosclerosis."

The first results are positive and the industry has shown interest, according to Weber. "We've set up a small business called Carolus Therapeutics. It's important that we capture the peptides in small molecular units, wrapped in a synthetic structure. From there, the step to actually creating a medication is a very small one. We're still doing tests on mice, and the preliminary results are looking good. We hope to do our first tests on humans in 2011."

DFG Sonderforschungsbereich 1123

Atherosclerosis - Mechanisms and Networks of Novel Therapeutic Targets

SFB 1123 - Zusammenfassung

Arterielle Gefäßerkrankungen, wie koronare Herzkrankheit (KHK) und Schlafanfall, bleiben die welt-weit führende Todesursache trotz Fortschritten in der interventionellen und sekundären Therapie. So verursacht die KHK enorme und weiter steigende sozioökonomischen Kosten in den Europäischen Gesundheitssystemen. Dieses Dilemma könnte durch eine verbesserte vaskuläre Prävention und Therapie gelindert werden, was eine tiefere mechanistischere Durchdringung der Atherosklerose als zugrundeliegender Pathologie voraussetzt, um eine effizientere und verlässlichere Identifizierung und Verifizierung möglicher therapeutischer Zielstrukturen zu ermöglichen. Daher ist es die Mission des geplanten SFB1123, ein detaillierteres Verständnis der molekularen Netzwerke in der Athero-genese, Atheroprogression und Atherothrombose als pathologischer Sequenz der KHK auszubilden. Die Identifizierung lohnender therapeutische Zielstrukturen innerhalb solcher Netzwerke erfordert die unvoreingenommene Prüfung und Auslese von Kandidaten auf solider pathogenetischer Basis und die Analyse ihrer Interaktionen in relevanten Modellsystemen *in vivo*. Wir planen eine systematische Ausarbeitung der Verknüpfung von molekularen Mechanismen verschiedener Zielstrukturfamilien (Zytokine, Signalproteine, Nukleinsäuren und Lipidmediatoren) als einem ausreichend breiten und doch kohärenten Spektrums. Die Validierung werden wir mittels neuer optoakustischer und nanoskopisch auflösender Bildgebungstechnologien und einer Reihe transgener und konditionaler knockout Mausmodelle zur Gendeletion, Insertion funktioneller Mutanten und fluoreszenter Markierung vorantreiben. Wir werden harmonisierte Modellsysteme und standardisierte Protokolle implementieren und bioinformatische Netzwerkanalysen anwenden, um die pathogenetische Komplexizität adäquat zu kartieren und so die Kommunikation und Interaktion neuer molekularer Mechanismen und indivi-dueller Zielstrukturen zu identifizieren. Dies wird es ermöglichen, den Standard die Entdeckung und Validierung therpauetischer Zielstrukturen wesentlich zu verfeinern und neue Optionen zu eröffnen.

Academic profile of the Collaborative Research Centre

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

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

Atherogenesis is driven by a disturbed equilibrium of lipid accumulation, maladaptive immune responses and their clearance, entailing chronic inflammation of the artery wall, crosstalk with pro-coagulant pathways and culminating in plaque rupture and thrombosis. New **atherogenic and/or protective pathways mutually linking lipid, inflammation and coagulation biology** have been discovered, and profiling studies, namely genome-wide association studies (GWAS), unveiled risk **genetic variants and epigenetic factors** for CAD. This multitude of variables gives rise to complex network effects creating specific signatures for this disease. Bioinformatics analysis, next generation sequencing (NGS) and omics tools will be instrumental for the discovery of **biologicals** for vascular disease, which will gain importance over classical drug candidate or high-throughput approaches, since their **structure-function relationship** can be more readily probed, while off-target effects and toxicity can be better anticipated. An identification of worthwhile targets within such networks requires unbiased screening of different targets, a thorough pathogenic basis and analysis of their interactions in relevant model systems *in vivo*. We aim to systematically elaborate such intricately linked molecular mechanisms for different target families (cytokines, signal

proteins, nucleic acids and lipid mediators), some of which have been verified in relevance by GWAS, allowing for a sufficiently broad yet coherent spectrum. We will propagate their validation by **molecular imaging technologies** in human tissue or animal models, e.g. using an array of **transgenic and knockout mouse models** of cell-specifically inducible gene deletion, 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 **chronic inflammatory reaction and maladaptive immune response** features effector cells of both innate and adaptive immunity, for instance neutrophils, dendritic cells and their interactions identified by our group members. The growing appreciation of the inflammatory processes and mediators involved has uncovered an intriguing diversity of targetable mechanisms that could be exploited to complement lipid-lowering therapies. In the planned CRC, we aim to implement **harmonized model systems and standardized protocols and to employ bioinformatic network analyses,** which reflect the multifactorial and complex nature of this disease, to identify the cross-talk and interaction of the molecular mechanisms and individual targets. In particular, we see an important **triad** emerging that links chronic inflammation to **lipid mediators and metabolism, to procoagulative/ thrombogenic pathways** and to **genetic/epigenetic risk factors.** These pathways are represented in two target areas with **signal proteins and cytokines (area A)** and **nucleic acids and lipid mediators (area B),** wherein multiple projects exemplify the cross-talk of inflammation with lipid biology or with coagulation and thrombogenicity **(Fig. 1).**

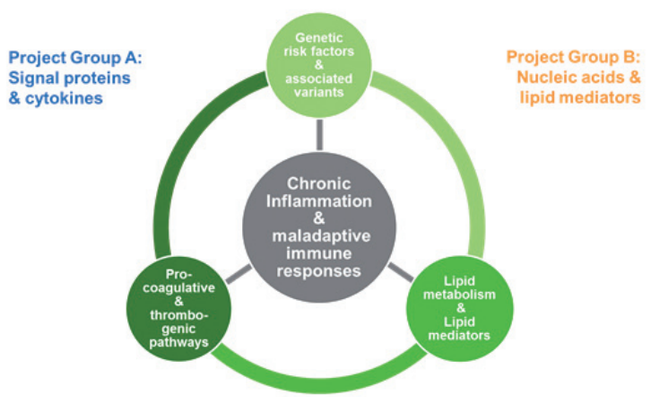


Figure 1: Pathogenesis of atherosclerosis: creating mechanistic links between target families/pathways

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.

Summary - CRC 1123

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 understanding of molecular networks in atherogenesis, atheroprogression and atherothrombosis as the pathological 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 31.12.2015	Drittmittelfinanzierung 31.12.2015
Institutsdirektor	1	1	
Professoren	6	6	
Arbeitsgruppenleiter	9	7	2
Post-Doktoranden	16	4	12
Doktoranden	43	0	43
nichtwissenschaftliche Mitarbeiter	27	17	10
Gesamt	**102**	**35**	**67**

Zahlen im Bereich klinisch tätigen Personals

Berufsbezeichnung	Gesamtzahl	Haushaltsfinanzierung 31.12.2015	Drittmittelfinanzierung 31.12.2015
Chefarzt	1	1	
Oberärzte	2	2	
Assistenzärzte	1	1	
nichtärztliche Mitarbeiter	4	3	1
Gesamt	**8**	**7**	**1**

Aufgrund von überlappenden Aufgabenverteilungen in hauptsächlich wissenschaftlich tätigem oder vornehmlich klinisch arbeitendem Personal, beläuft sich die Gesamtzahl der Mitarbeiter auf 110 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
Auer, Sandra

Baatsch, Isabelle
Badmann, Tobias
Bianchini, Mariaelvy
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Blanchet, Xavier, PhD
Blay, Richard, M. Phil.
Brauner, Janine
Böhlig, Barbara
Braster, Quinte
Bretzke, Eva
Bürger, Christina
Busygina, Kristina

Clados, Adelheid, Dr. med.
Corbalán Campos, Judit

Deininger, Matthias
de Jong, Renske
Deppe, Janina
Döring, Yvonne, Dr. rer. nat.
Drechsler, Maik, Dr. rer. nat.
Duchene, Johan

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

Faußner, Alexander, PD Dr. rer. nat.
Ferraro, Bartolo

Geißler, Claudia
Gerdes, Norbert, Dr. rer. nat.
Gimpfl, Christiane
Gippner-Steppert, Cornelia
Gomez, Lorena
Gurung, Rashmi

Habenicht, Andreas
Haberbosch, Markus
Hartmann, Petra, Dipl. Troph.
Herrle, Corinna
Heyll, Kathrin
Horckmans, Michael, Dr. biol.
Hristov, Michael, PD Dr. med.

Jamasbi, Janina, Apothekerin
Jansen, Yvonne

Kaczmarek, Veronika
Karshovska, Ela, Dr. rer. biol. hum.
Kurz, Alexandra

Lemnitzer, Patricia
Leoni, Giovana
Li, He, Dr.
Lorenz, Reinhard, Univ.-Prof. Dr. med.
Lutgens, Esther, Prof. Dr. med., PhD

Ma, Zhe
Mahl, Christian
Mandl, Manuela
Megens, Remco T.A., PhD
Mohanta, Sarajo
Mojica, Ann
Moshkova, Irina, Dipl.-Ing.

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

Ortega Gomez, Almudena, Dr.

Paulin, Nicole
Pawig, Lukas
Pilz, Veronika
Pitsch, Thomas

Rami, Martina
Reim, Sigrid
Richter, Elmar, Prof. Dr. med. vet.
Riedasch, Annalena, Dr. med. vet.
Ries, Christian, PD Dr. rer. nat.
Ring, Larisa
Rinne, Petteri
Rodrigues Viola, Joana, Dr. rer. nat.
Rügamer-Biese, Karola
Ruiz-Heinrich, Lourdes

Santovito, Donato, Dr. med.
Saroyan, Lusine
Schloss, Maximilian
Schmitt, Martin, Dipl. Biol.
Schober, Andreas, Univ.-Prof. Dr. med.
Schumski, Ariane
Seidl, Cornelia
Siess, Wolfgang, Univ.-Prof. Dr. med.
Silvestre-Roig, Carlos, PhD
Simion, Verena
Simon, Stefan
Söhnlein, Oliver, Univ.-Prof. Dr. Dr. med.
Spitz, Charlotte
Steffens, Sabine, Univ.-Prof. Dr. rer. nat.

Stöger, Brigitte
Streicher, Sabine

Thurmann, Lucie

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

Wagner, Diana
Wade, Orsolya Kimbu
Weber, Christian, Univ.-Prof. Dr. med.
Wei, Yuanyuan, PhD
Winkels, Holger

Yin, Changjun, Dr. rer. nat.

Zahedi, Farima, MSc
Zhao, Zhen
Zhu, Mengyu, MSc
Zimmer, Brigitte
Zimmermann, Christof

Publikationen

2014

	n	IF Summe	IF Mittelwert
Gesamt	64	503.9	7.9
Erst-/Seniorautorschaften IPEK	38	290.1	7.6

	n	IF Summe	IF Mittelwert
Originalarbeiten	41	324.8	7.9
Erst-/Seniorautorschaften IPEK	28	146.5	8.1

	n	IF Summe	IF Mittelwert
Übersichtsarbeiten	23	179.1	7.8
Erst-/Seniorautorschaften IPEK	20	143.6	7.2

Original Articles

Aoqui C, Chmielewski S, Scherer E, Eißler R, Sollinger D, Heid I, Braren R, Schmaderer C, Megens RT, Weber C, Heemann U, Tschöp M, Baumann M. Microvascular dysfunction in the course of metabolic syndrome induced by high-fat diet. Cardiovasc Diabetol 2014;13:31. IF 4.015

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Wildhagen KC, Schrijver R, Beckers L, Ten Cate H, Reutelingsperger CP, Lutgens E, Nicolaes GA. Effects of exogenous recombinant APC in mouse models of ischemia reperfusion injury and of atherosclerosis. PLoS One 2014;9:e101446. IF 3.234

Review articles and Commentaries

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2015

	n	IF Summe	IF Mittelwert
Gesamt	72	509.7	7.1
Erst-/Seniorautorschaften IPEK	48	321.3	6.7

	n	IF Summe	IF Mittelwert
Originalarbeiten	39	343.3	8.8

	n	IF Summe	IF Mittelwert
Übersichtsarbeiten	33	166.4	5.0
Erst-/Seniorautorschaften IPEK	33	166.4	5.0

	n
Beiträge in Lehr-/Handbüchern, Monographien	1

Original articles

Akhtar S, Hartmann P, Karshovska E, Rinderknecht FA, Subramanian P, Gremse F, Grommes J, Jacobs M, Kiessling F, Weber C, Steffens S, Schober A. Endothelial hypoxia-inducible factor-1α promotes atherosclerosis and monocyte recruitment by upregulating microRNA-19a. Hypertension 2015:66:1220-6. (IF 6.499)

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