LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

2012/2013

JAHRESBERICHT

Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten (IPEK)

Vorwort

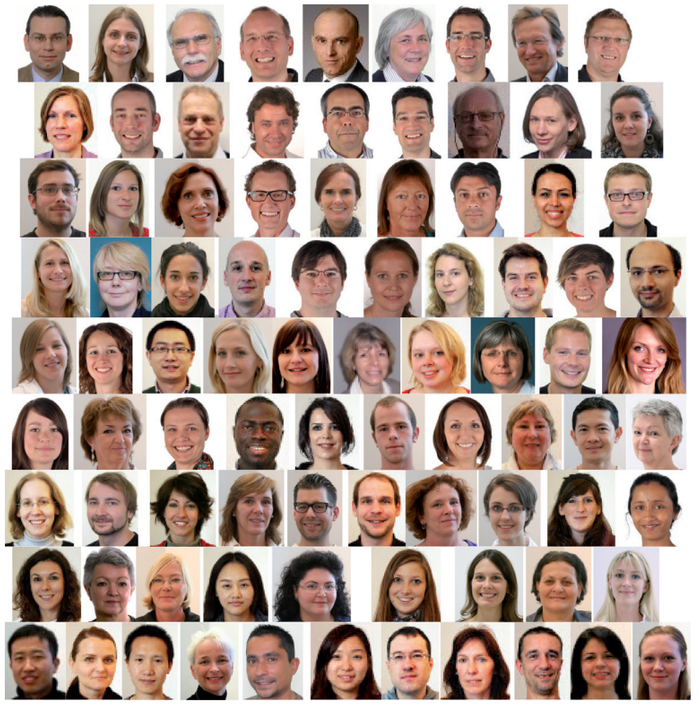
Nach nunmehr dreieinhalb Jahren seit der Wiederbesetzung des Lehrstuhls für Gefäßmedizin am Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten (IPEK) zeichnen sich nun erste Akzente und Erfolge der Neuausrichtung sowie der Intensivierung und Ausweitung des wissenschaftlichen Fokus ab. Ein guter Zeitpunkt um diese Entwicklung Revue passieren zu lassen und die seither implementierten Strukturen zusammenfassend abzubilden.

Die Ihnen vorliegende Ausgabe des Jahresberichtes 2012/2013 soll einen Einblick hinter die Kulissen des Instituts geben, die Strukturen verdeutlichen und die erbrachten Leistungen rekapitulieren. Zudem finden Sie alle wichtigen Ansprechpartner, Adressen und Telefonnummern, die für eine Zusammenarbeit mit dem IPEK relevant sind.

Wir hoffen, dass wir Ihr Interesse mit diesem Jahresbericht geweckt haben und Ihnen einen anschaulichen Leitfaden bezüglich unserer wissenschaftlichen und klinischen Tätigkeiten mit an die Hand geben können.

Im Namen des gesamten IPEK-Teams

Prof. Dr. Christian Weber
Ordinarius und Institutsdirektor



Editorial

Das Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten versteht sich als Einrichtung für die Vorbeugung und Behandlung von Kreislaufkrankheiten. Als besonders effektiv und zukunftsweisend ist dabei die enge Verzahnung zwischen Forschung und Klinik hervorzuheben, die es ermöglicht, die Beschwerden von Patienten zu beobachten und sie als Anreiz für die Forschung aufzugreifen. Neben dieser unmittelbaren Motivation und der Möglichkeit, klinische Studien direkt an geeigneten und dazu einwilligenden Patienten durchzuführen, profitieren diese im Gegenzug unmittelbar von Forschungserfolgen und den neusten Entwicklungen in der Wissenschaft.

Dieses Prinzip der direkten Verbindung von Theorie und Praxis wird zudem durch das breite Spektrum der Mitarbeiter ergänzt, die zum Einen aus unterschiedlichen Generationen stammend sich gegenseitig bereichern und zum Anderen durch sehr unterschiedliche, fachliche Hintergründe eine Spezialisierung auf vielen verschiedenen Gebieten und deren Kombination erlauben. Auf diese Weise ist es möglich, eine große Bandbreite an Fragestellungen abzudecken, den wissenschaftlichen Nachwuchs auszubilden und zugleich innovative Forschung mit großer Synergie zu betreiben.

Hinter alledem stehen hoch motivierte Mitarbeiter, ein kompetentes Team und der Idealismus jedes Einzelnen, nicht nur die Arbeitsgruppen und Patienten des Instituts voranzubringen, sondern Menschen mit koronarer Herzkrankheit weltweit die Hoffnung auf Verbesserung ihrer Therapie geben zu können. Bescheidenheit ist die Kunst, unter der egalitären Asche die elitäre Glut zu hüten. Mit dieser dem Philosophen und Zeitdiagnostiger Peter Sloterdijk zugeschriebenen Sentenz ist unser Bemühen sehr pointiert umschrieben, auf meritokratische Weise sowie unter Respektierung der ebenso notwendigen Resilienz und Persistenz nach neuen und richtungsweisenden wissenschaftlichen Erkenntnissen zu streben, ohne sich dabei in den Vordergrund zu drängen. Jeder wirkliche Erkenntnisgewinn folgt somit unserem Credo “per aspera ad astra“.

Inhaltsverzeichnis

Institutsdirektor

Als Nachfolger von Prof. Dr. Peter C. Weber ist Univ.-Prof. Dr. med. Christian Weber seit 01.11.2010 Ordinarius für Gefäßmedizin an der Ludwig-Maximilians-Universität München und Direktor des Instituts für Prophylaxe und Epidemiologie der Kreislaufkrankheiten (IPEK) am Klinikum der Universität München (KUM).

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

Das Institut umfasst als international sichtbare Forschungseinrichtung den Lehrstuhl für Präventive Vaskuläre Medizin, der mit mehreren Professuren und Arbeitsgruppen eine Reihe koordinierter Forschungsschwerpunkte mit kardiovaskulärer und pathobiochemischer Ausrichtung abbildet, sowie eine von der August-Lenz-Stiftung getragene Patientenambulanz, deren Schwerpunkt auf internistisch-kardiologischen Erkrankungen liegt und so den Rahmen für zukünftige klinische Studien bildet.

Seine weithin anerkannte Expertise zur Pathogenese, Diagnostik, Therapie und Prävention der Atherosklerose bezieht Prof. Weber aus jahrelanger Erfahrung in der klinischen Medizin und der kardiovaskulären Grundlagenforschung. Nach dem Studium der Humanmedizin an der Ludwig-Maximilians-Universität (LMU) München promovierte er 1994 bei Prof. Dr. Peter C. Weber mit „summa cum laude“. Es folgte ein mehrjähriger Aufenthalt als DFG-Stipendiat am Center for Blood Research der Harvard Medical School in Boston. Anschließend übernahm er am IPEK die Leitung einer DFG-Nachwuchsgruppe in den Biowissenschaften. Zeitgleich war er als wissenschaftlicher Assistent an der Medizinischen Poliklinik und am Gefäßzentrum des KUM bei Prof. Dr. Detlef Schlöndorff tätig. Ende 1999 erfolgte die Habilitation für Experimentelle Innere Medizin.

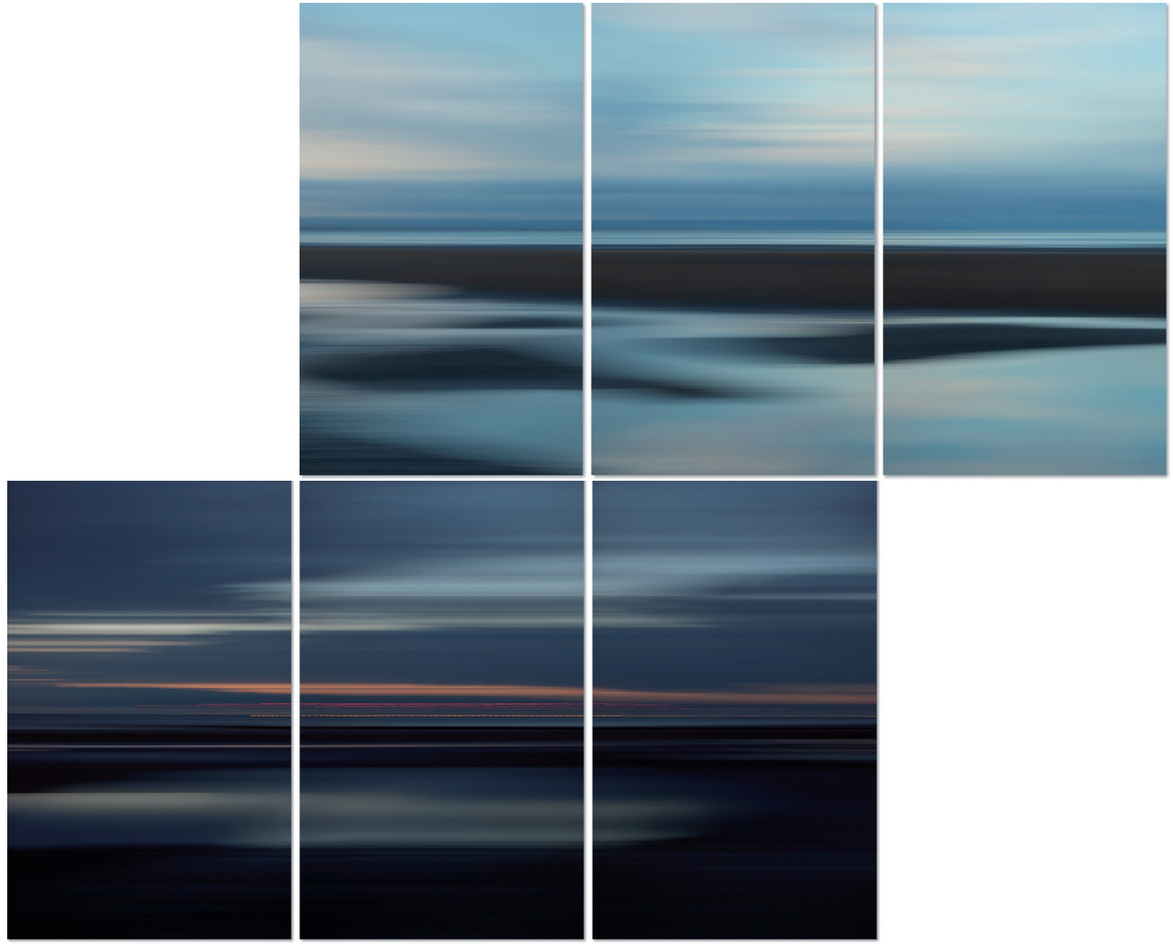
Als Universitätsprofessor (C3) für Kardiovaskuläre Molekularbiologie wurde er 2001 an die Rhein-Westfälische Technische Hochschule (RWTH) Aachen berufen. Gleichzeitig vervollständigte Prof. Weber die klinische Weiterbildung in der Inneren Medizin am Universitätsklinikum Aachen in der Medizinischen Klinik I bei Prof. Dr. Peter Hanrath, wo er 2003 die Gebietsbezeichnung Innere Medizin sowie die Schwerpunktbezeichnung Kardiologie erlangte.

Neben der Koordination eines interdisziplinären Zentrums für Klinische Forschung (IZKF) und der Organisation internationaler Symposien erhielt er Rufe auf Lehrstühle für Kardiologie an der *University of Virginia* und dem *King´s College London* und wurde 2005 zum Universitäts-professor (W3) und Direktor des Instituts für Molekulare Herz-Kreislaufforschung (IMCAR) und der Präventionsambulanz am Uniklinikum Aachen ernannt. Ein Jahr später erfolgte die Ernennung zum Professor am *Cardiovascular Research Institute Maastricht (CARIM)* der Universität Maastricht. Seit 1995 wurde die Forschung von Prof. Weber kontinuierlich durch die Deutsche Forschungsgemeinschaft (DFG) gefördert (z.B. SFB542, SFB914, SFB1054). Weiter ist er seit 2007 Sprecher der DFG Forschergruppe

FOR809 *Chemokine in der kardiovaskulären Pathogenese* und etablierte 2008 als Sprecher das Internationale Graduiertenkolleg GRK1508 *Arterial Remodeling* (EuCAR). Als einer von wenigen Lebenswissenschaftlern in Deutschland erhielt er 2010 den ERC Advanced Investigator Grant. Zahlreiche weitere Auszeichnungen, wie der GlaxoSmithKline Preis 2003, der Arthur-Weber-Preis 2004, der Forßmann-Preis 2005, der Paul-Martini-Preis 2008, der ESC Outstanding Achievement Award 2008, der Galenus von Pergamon-Preis 2009, der AHA Special Recognition Award Arteriosclerosis 2009 oder der VICI Award 2010 der *Nederlandse Organisatie voor Wetenschappelijk Onderzoek* unterstreichen die Bedeutung seiner Forschungsarbeit. Mit einem h-Index von 72 und über 18.000 Zitationen zählt Prof. Weber zu den weltweit meist zitierten Biomedizinern. Nach weiteren Rufen auf Lehrstühle an der Heinrich-Heine-Universität Düsseldorf und die Westfälische Wilhelms-Universität Münster erfolgte im November 2010 die Ernennung zum Ordinarius und Universitätsprofessor (W3) für Vaskuläre Medizin an der LMU München.

Seither ist die Zahl der Mitarbeiter an seinem Lehrstuhl auf deutlich über 100 angewachsen. Diese treiben in der Forschung die wissenschaftlichen Entwicklungen voran oder widmen sich als Ärzte der ambulanten Betreuung von Studienpatienten. Weiterhin ist Prof. Weber als Herausgeber für die renommierte Zeitschrift *Thrombosis & Haemostasis* verantwortlich, im Editorial Board Mitglied zahlreicher, hochkarätiger Journals tätig, u.a. als Senior Editor für *Arteriosclerosis, Thrombosis & Vascular Biology,* und übt verschiedene Funktionen in internationalen Fachgesellschaften aus, wie z.B. als Chairman der European Society of Cardiology (ESC) Working Group on Atherosclerosis. Auf internationaler Ebene dient er seit 2011 als Koordinator des Leducq Transatlantic Network of Excellence CVGeneF(x) und auf nationaler Ebene koordiniert er gemeinsam mit Prof. Dr. Stefan Engelhardt die Munich Heart Alliance (MHA) im Deutschen Zentrum für Herz-Kreislauf-Forschung (DZHK). Wie vielversprechend und anwendungsnah die Forschungsergebnisse der Arbeitsgruppen um Prof. Weber sind, zeigen auch zahlreiche Patente und Anmeldungen, welche die Basis zur Gründung und erfolgreichen Entwicklung der Firma *Carolus Therapeutics Inc.* gelegt haben.

Für die Zukunft des Instituts lässt sich Prof. Weber von folgenden Zielen leiten. Zunächst soll die veritable Tradition des IPEK als Einrichtung zur Förderung translationaler Ansätze in der kardiovaskulären Diagnostik, Therapie und Prävention fortgesetzt werden. Weiter soll die Stellung als national und international beachtete Institution in der Atheroskleroseforschung ausgebaut werden. Neben Verbesserungen und Ergänzungen der Gebäudeinfrastruktur, der Etablierung moderner Ultraschallverfahren sowie der Lasermikrodissektion, Multiphotonen und hochauflösender STED-Mikroskopie konnte dies durch passgenaue Berufungsverfahren für die W2 Professur für Experimentelle Gefäßmedizin (Andreas Schober), für Vaskuläre Immuntherapie (Oliver Söhnlein) und Klinische Pathobiochemie (Sabine Steffens) erreicht werden, welche in den Institutsvorstand kooptiert sind und von der Optimierung der operativen Prozesssteuerung profitieren. Schließlich ist Prof. Weber dem Ziel, im Anschluss an die FOR809 an der LMU einen Sonderforschungsbereich der DFG zum Thema Atherosklerose aufzulegen, nach erfolgreicher Begutachtung des SFB1123 Einrichtungsantrages einen großen Schritt näher gekommen. Die überragende gesundheitsökonomische Bedeutung wird hoffentlich bald erstmals in dieser Förderlinie thematische Berücksichtigung finden. Dabei sollen neue und innovative molekulare Zielstrukturen, wie z.B. Chemokin-Peptide oder microRNAs identifiziert und validiert werden. In Kooperation mit dem DZHK soll die Übertragung therapeutischer Ansätze in die klinische Studienphase und Anwendung erfolgen, einschließlich einer angemessenen wirtschaftlichen Verwertung im hervorragenden Umfeld der Biotechnologieregion München.



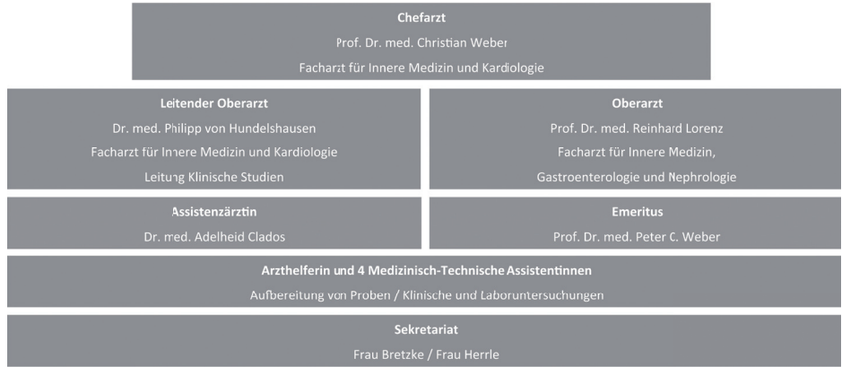
Übersicht

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-Forschungsgruppe 809 und das Journal Thrombosis & Haemostasis.

Organigramm der August-Lenz-Stiftung



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

Adressen

Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten (IPEK)

Direktion und wissenschaftliches Institut
Pettenkoferstraße 8a
80336 München
Tel.: +49 (0) 89/5160-4671
Fax: +49 (0) 89/5160-4352
Mail: kreislaufinstitut@med.uni-muenchen.de
Web: ipek.klinikum.uni-muenchen.de

Gentechnische Laboranlage
Gartenpavillon
Goethestraße 69
80336 München
Tel.: +49 (0) 89/5160-4373
+49 (0) 89/5160-4375
Fax: +49 (0) 89/5160-4382

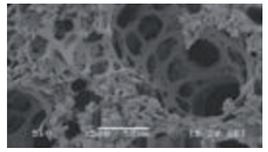
Internistische Ambulanz – Kardiologie
August – Lenz – Stiftung
Pettenkoferstraße 9
80336 München
Tel.: +49 (0) 89/5160-4351
Fax: +49 (0) 89/5160-4352

Experimentelle Gefäßmedizin
Klinische Pathobiochemie
Pettenkoferstraße 9b
80336 München
Tel.: +49 (0) 89/5160-2554
Fax: +49 (0) 89/5160-4740

Januar 2012

Keeping chemokines apart

Acute lung injury results from bacterial infection e.g. in sepsis or after aspiration. PD Dr. Oliver Söhnlein and his team using a murine model identified a promising strategy targeting chemokines for the prevention of lung damage (*Am J Resp Crit Care Med* 2012).



März 2012

Transnationales BMBF Verbundprojekt mir-A

Als transnationaler Forschungsverbund zur Pathophysiologie des metabolischen Syndroms und assoziierter Erkrankungen wird das Projekt zur Rolle von microRNAs (miR-A) von Prof. Andreas Schober (Koordinator), Prof. Chantal M. Boulanger (Paris), Prof. Jason Fish (Toronto) und Prof. Christian Weber (IPEK) mit einem Gesamtbudget von € 1,3 Mio. durch das Bundesministerium für Bildung und Forschung, die Agence National de la Recherche und die Canadian Institutes of Health Research gefördert.

April 2012

Antrittsvorlesung von Prof. Weber

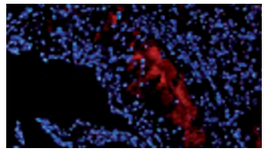
Am 30.04.2012 fand die feierliche Antrittsvorlesung von Prof. Dr. Christian Weber statt.

Nach der Begrüßung von Prof. Wolf Mutschler als Vorsitzendem des Ärztlichen Vereins folgten Grußworte von LMU-Vizepräsident Prof. Ulrich Pohl, Wissenschaftsminister Dr. Wolfgang Heubisch, eine Einführung des Dekans der Medizinischen Fakultät Prof. Maximilian Reiser und natürlich die Antrittsvorlesung zum Thema *„Atherosklerose: In Virchow veritas“*.

April 2012

A link between atherosclerosis and autoimmunity

Researchers at IPEK (Dr. Yvonne Döring) in collaboration with colleagues in Würzburg (Dr. Alma Zernecke) have shown how plasmacytoid dendritic cells contribute to early steps in the formation of atherosclerotic lesions in the blood vessels and explained why patients with autoimmune disorders such as psoriasis or systemic lupus erythematodes are predisposed to atherosclerosis (*Circulation* 2012).



Drei neue Arbeitsgruppen in IPEK

Nach Emeritierung der Leiterin der selbstständigen Abteilung Klinische Chemie und Klinische Biochemie, Frau Prof. Dr. Marianne Jochum, wurden drei verbliebene Arbeitsgruppen (PD Dr. Alexander Faussner, PD Dr. Peter Neth, PD Dr. Christian Ries) und die Forschungsflächen des Gebäudes in der Pettenkoferstrasse 9b erfolgreich in das IPEK integriert.

Juni 2012

International Vascular Biology Meeting (IVBM) in Wiesbaden

Prof. Weber served as one of the Organisers and Presidents of the biannual IVBM, the World Congress for experts in vascular biology and medicine. With 15 plenary talks and 30 scientific sessions, the congress became the premier vascular biology meeting in 2012. Selected topics were covered in a Theme issue of *Thrombosis & Haemostasis*.

August 2012

Dienstantritt von Prof. Schober

Prof. Dr. med. Andreas Schober hat die Professur für Experimentelle Gefäßmedizin am IPEK angetreten. Zuvor wirkte er als Kommissarischer Direktor des Instituts für Molekulare Herzkreislaufforschung an der RWTH Aachen. Seine Forschungsschwerpunkte umfassen die Stammzell-vermittelte Gefäßreparatur nach Stentimplantation. Außerdem liegt sein Augenmerk auf der Rolle von microRNAs in der Entstehung atherosklerotischer Gefäßveränderungen.

September 2012

Prof. Weber appointed Chairman of the ESC WG for Atherosclerosis

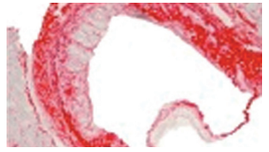
Prof. Weber was elected to become Chairman of the Working Group (WG) for Atherosclerosis and Vascular Biology of the European Society of Cardiology (ESC), as effective with the ESC 2012 Congress in Munich.

The WG is a platform for studying underlying mechanism of disease with a special focus on young cardiologists.

Oktober 2012

Involvement of TGF-β signaling in atherogenesis

Dirk Lievens and colleagues from IPEK have reported findings detailing the role of transforming growth factor-β (TGF-β) in dendritic cells for atherosclerotic plaque formation. The work has been published in the *European Heart Journal* 2013. The significance of this work was highlighted by Klaus Ley and Kevin Tse in an accompanying editorial commentary.



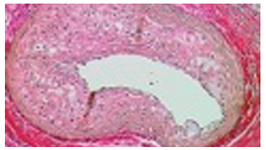
November 2012

Sonderforschungsbereich 1054 bewilligt

IPEK ist mit zwei immunologisch ausgerichteten Projekten (Prof. E. Lutgens und Prof. C. Weber) am von der Deutschen Forschungsgemeinschaft neu eingerichteten SFB 1054 *Kontrolle und Plastizität von Zelldifferenzierungsprozessen im Immunsystem* (Sprecher: Prof. T. Brocker) beteiligt.

Monocytes on the beaten track

IPEK scientists have reported an important role of neutrophil-derived cathelicidin for the adhesion of classical monocytes and elucidated a novel mechanism of neutrophil-mediated monocyte recruitment in conditions where such recruitment plays an unfavorable role, e.g. atherosclerosis.



Indeed, the authors have shown that lack of cathelicidin reduces monocyte recruitment and atherosclerotic lesion burden (*Circ Res* 2013). The significance of the work was underscored by an editorial commentary from Fil Swirski and Clinton Robbins.

Specific microRNAs promote inflammation

Prof. Andreas Schober and his team identified a microRNA, which initiates the inflammatory response in atherosclerosis.

They revealed miR-342-5p as an interesting target for new therapeutic approaches and managed to demonstrate in a mouse model that inhibition of miR-342-5p limits the progression of atherosclerosis (*Circulation* 2013). The researchers plan to develop microRNA inhibitors in collaboration with biotech companies.

Dienstantritt von Prof. Steffens

Prof. Dr. rer.nat. Sabine Steffens hat die Professur für Klinische Pathobiochemie am IPEK angetreten. Zuvor war sie als Arbeitsgruppenleiterin in der Kardiologie am Universitätsklinikum in Genf tätig. Ihre Forschungsschwerpunkte sind die Rolle der Endocannabinoide und verwandter Mediatoren in den entzündlichen Prozessen der Atherosklerose und Restenose.

Weitere Schwerpunkte sind die Erforschung der Mechanismen, die nach akutem Herzinfarkt zu einer Schädigung des Herzmuskels führen sowie bei der anschließenden Wundheilung eine Rolle spielen.

International Symposium Germany-China

The Chinese-German symposium Crossroads of *Vascular Inflammation, Obesity, and Autoimmunity in Brain Injury* was held in Munich. The symposium provided an opportunity to exchange multidisciplinary perspectives on atherosclerosis, its relationship to obesity and hyperlipidemia as well as to immune injury of the brain and vascular dementia. Organizers were Prof. Andreas Habenicht and Dr. Norbert Gerdes.

Phagocyte Workshop in Portugal

The Phagocyte Workshop 2013 was organised by PD Dr. Oliver Soehnlein, Principal Investigator and Groupleader at IPEK, at the 47th Annual Scientific Meeting of the European Society for Clinical Investigation in Albufeira, Portugal.

NMR facility within the Maastricht-Munich Centre

The new nuclear magnetic resonance (NMR) facility within the Maastricht-Munich Centre for Atherosclerosis Research (M-CAR) featuring a Bruker Ascend 700 instrument was opened in an official ceremony.

Hematopoietic rhythms

In a new publication, Andres Hidalgo and colleagues from IPEK discovered that the clearance of aged neutrophils from the circulation by macrophages in the bone marrow is coupled to the systemic egress of hematopoietic precursors from their niche (*Cell* 2013).

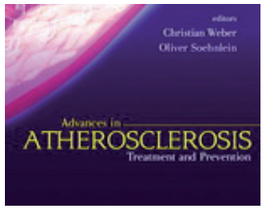
Denber-Pinard Forschungspreis für Prof. Steffens

In einer feierlichen Zeremonie wurde Prof. Sabine Steffens der Denber-Pinard Forschungspreis der Medizinischen Fakultät der Universität Genf für ihre Habilitationsschrift zum Thema *Role of the endocannabinoid system in atherosclerosis* überreicht. Der Preis ist mit Euro 8.000 dotiert.

July 2013

Book on novel treatment options for atherosclerosis

Oliver Soehnlein and Christian Weber have compiled a book that bridges between the various aspects of recent advances in understanding the disease mechanisms underlying atherosclerosis and atherothrombosis and possible clinical applications that can be derived thereof.



IPEK successful in the LMU Excellence Initiative

The Governing Board of the LMU has granted funding to IPEK scientists in the third line of the Excellence Initiative at LMU. The Investment Fund supports the implementation of stimulated emission depletion (STED) nanoscopic imaging in Munich (Dr. Remco Megens and Prof. Dr. Christian Weber) and a Junior Researcher Fund for studies on neutrophils and atherosclerosis was granted to PD Dr. Oliver Söhnlein.

Oktober 2013

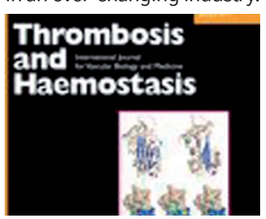
Dienstantritt von Prof. Söhnlein

Prof. Dr. med. Oliver Söhnlein hat die Professur für Vaskuläre Immuntherapie am IPEK angetreten. Die Professur ist Bestandteil des BMBF-geförderten Deutschen Zentrums für Herz-Kreislaufforschung. Der Forschungsschwerpunkt von Prof. Söhnlein ist die Rolle von neutrophilen Granulozyten bei entzündlichen Prozessen der Atherosklerose und Restenose.

Dezember 2013

Thrombosis & Haemostasis wins Journal Triathlon

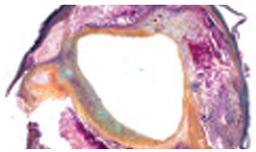
Thomson Reuters announced *Thrombosis & Haemostasis* as a winner in the Scholar One Journal Triathlon 2013 designed to have journals compete in three categories: agility - ability to accept the right papers; speed - fast implementing ways to increase efficiency; endurance - longevity of staying competitive in an ever-changing industry.



Januar 2014

A new regulator of cholesterol levels

High levels of cholesterol in blood are associated with increased risk for cardiovascular disease. Having identified the chemokine receptor CXCR7 as an endogenous regulator of serum cholesterol, Prof. Schober, Prof. Weber and their team open new therapeutic avenues for treating metabolic syndrome and atherosclerosis (*Circulation* 2014).



Verleihung des Binder Publication Prize 2013

Im Rahmen des Vascular Biology Symposiums 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 zur Rolle von JAM-A in der Atherosklerose (*Circulation* 2014), die im Rahmen seiner Promotionsarbeit entstanden ist.

Forschung

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

Forschungsbericht 2012

Anzahl der Planstellen für wissenschaftliche Mitarbeiter: 14
Anzahl der Planstellen für nicht-wissenschaftliche Mitarbeiter: 16
Anzahl aller drittmittelfinanzierten und sonstigen Mitarbeiter: 64

Drittmittelausgaben (in €):

	Anzahl Projekte	Ausgaben 2012 laut Verwaltung
DFG	16	888.383
BMBF, StMWFK, EU	6	751.434
Stiftungen (Humboldt, Fondation Leducq, etc.)	10	463.391
Summe begutachtete externe Drittmittel		**2.103.208**

	Anzahl Projekte	Ausgaben 2012 laut Verwaltung
FöFoLe	10	60.217
Lebmit	10	24.000
Summe interne Drittmittel		**84.217**

Gesamtsumme verausgabter Drittmittel		**2.187.425**

Publikationen:

	Anzahl	ungewichteter IF
Im WoS gelistete Originalarbeiten	32	180.3
Im WoS gelistete Reviews und Editorials	18	86.2
Beiträge in Lehr-/Handbüchern, Monographien	4	-
Gesamtsumme	**54**	**266.5**

Forschungsbericht 2013

Anzahl der Planstellen für wissenschaftliche Mitarbeiter: 18
Anzahl der Planstellen für nicht-wissenschaftliche Mitarbeiter: 14
Anzahl aller drittmittelfinanzierten und sonstigen Mitarbeiter: 68

Drittmittelausgaben (in €):

	Anzahl Projekte	Ausgaben 2013 laut Verwaltung
DFG	19	1.276.928
BMBF, StMWFK, EU	7	976.638
Stiftungen (Humboldt, Fondation Leducq, etc.)	12	570.656
Summe begutachtete externe Drittmittel		**2.824.222**

	Anzahl Projekte	Ausgaben 2013 laut Verwaltung
FöFoLe	12	106.386
Lebmit (Invest.)	12	12.288
Summe interne Drittmittel		**118.674**
Gesamtsumme verausgabter Drittmittel		**2.942.896**

Publikationen:

	Anzahl	ungewichteter IF
Im WoS gelistete Originalarbeiten	37	254.6
Im WoS gelistete Reviews und Editorials	20	115.5
Beiträge in Lehr-/Handbüchern, Monographien	2	1.0
Gesamtsumme	**56**	**373.1**

Arbeitsgruppen (Principal Investigators)

Experimental Vascular Medicine – The small RNA world and translational control in atherosclerosis

Univ.-Prof. Dr. Andreas Schober

Although the first small, non-coding RNAs were already discovered in 1992, the full impact of these regulatory molecules became only apparent during the last 10 years. Today we know hundreds of highly conserved microRNAs which fine tune almost every biological process in cells through networks of microRNA-mRNA interactions. Moreover, very effective pharmaceutical targeting by modified antisense oligonucleotides has been developed, which hold a great promise for future treatments of many diseases, including atherosclerosis.
Our group focused on the role of miRNAs in the inflammatory activation of macrophages during atherosclerosis. We determined the expression profile of hundreds of miRNAs in different stages of atherosclerosis is mice and found that two miRNAs, miR-155 and miR-342-5p, were up-regulated in lesional macrophages (*Nazari-Jahantigh et al,* J Clin Invest 2012; Wei et al, Circulation 2013). Our results show that these two miRNAs form a functional pair in macrophages that triggers their inflammatory activation. We identified two targets, BMPR2 and Akt1, which compete for the binding to miR-342-5p in macrophages. In resting macrophages, miR-342-5p suppresses mainly BMPR2 and thus increased expression of Akt1 inhibits the expression of miR-155. However, miR-342-5p primarily targets Akt1 following stimulation with LPS and IFN-g, because BMPR2 expression is transcriptionally downregulated. Consequently, the reduced Akt1 expression results in up-regulation of miR-155. We showed that miR-155 directly targets the anti-inflammatory transcription factor Bcl6 in macrophages and thus promotes the expression of pro-atherogenic factors, such as CCL2 or TNF-alpha, and enhances lesion formation. Accordingly, inhibition of miR-342-5p by systemic injection of antisense oligonucleotides reduced atherosclerosis and lesional miR-155 expression in mice.
In addition, we found that miR-126-5p, the sister strand of the atheroprotective miR-126-3p, plays an important role in endothelial regeneration in response to hyperlipidemic stress and vascular injury (*Schober et al,* Nat Med 2014). miR-126-5p targets the anti-proliferative Dlk1 in endothelial cells and thus generates a proliferative reserve at arterial sites that are protected from atherosclerosis. In contrast, disturbed flow at branching points, where atherosclerosis predominantly develops, down-regulates miR-126-5p and thus fine-tunes the increased proliferative response in these regions. Additional hyperlipidemic stress, however, further impairs endothelial proliferation, which can be compensated at non-predilection sites but not at predilection sites due to the differential expression of miR-126-5p. Accordingly, systemic treatment with miR-126-5p limits atherosclerosis and endothelial proliferation, indicating that miR-126-5p may potentially serve as a therapeutic tool in atherosclerosis.

In addition to miRNAs, the second main focus of our group is the effect of the chemokine CXCL12 and its alternative receptor CXCR7 in atherosclerosis. We found that treatment with CXCL12 induces the mobilization of vascular stem cells, which are recruited to the atherosclerotic lesions (*Akhtar et al,* Arterioscler Thromb Vasc Biol 2013). This recruitment results in a more stabilized lesion phenotype, which may help to avoid plaque rupture and its detrimental consequences, such as myocardial infarction and stroke. A completely different role, probably independent of CXCL12, plays CXCR7 in atherosclerosis. We discovered that CXCR7 mediates the uptake of cholesterol into adipose tissue, a major storage site for cholesterol in the body (*Li et al,* Circulation 2014). This effect of CXCR7 regulates the serum cholesterol levels, and activation of CXCR7 by a synthetic ligand (CCX771) reduces VLDL cholesterol levels, thus reducing the atherosclerotic burden in mice.

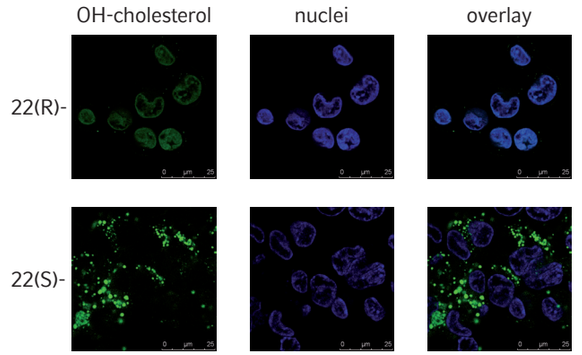
Group members
Prof. Dr. med. Andreas Schober
PD Dr. rer. nat. Peter Neth
Dr. rer. nat. Pallavi Subramanian
Dr. Yuanyuan Wei
Dipl. troph. Petra Hartmann
Maliheh Nazari Jahantigh, MSc
Lucia Natarelli, MSc
Mengyu Zhu, MSc
Farima Zahedi, MSc
Richard Blay, M.Phil.
Judit Corbalán Campos, MTA
Claudia Geissler, MTA
Kathrin Heyll, MTA
Lourdes Ruiz Heinrich, MTA
Karola Rügamer-Biese
Christof Zimmermann, stud. HK
Paula Pellicena, Praktikantin

LXR-related Mechanisms in Atherosclerosis

Univ.-Prof. Dr. Reinhard Lorenz

Group members
Prof. Dr. med. Reinhard Lorenz
Reinhard Brauner, oec. troph.
Stephanie Schaffer, app. Apothekerin

The nuclear transcription factors LXRalpha and LXRbeta function as cytoplasmatic cholesterol sensors. They are activated by specific oxysterols formed from excess cholesterol. Activated LXRs translocate to the nucleus and form a complex with the activated retinoic acid receptor RXR and additional co-activators or co-repressors. Thereby LXRs act as metabolic master regulator of genes relevant for cellular cholesterol homeostasis. Most prominently, LXR activation by specific oxysterols stimulates the expression of the major cellular cholesterol exporter ABCA1 that removes excess cholesterol from the cell. Simultaneously LXR suppresses genes of cellular cholesterol synthesis and cellular cholesterol uptake pathways.
Single cell cholesterol regulation by LXR is expressed in virtually all cells. Moreover, LXR in enterocytes, hepatocytes and macrophages controls sterol absorption, biliary sterol secretion and reverse cholesterol transport on the systemic level. We have shown that sterol selectivity and interaction, the low absorption of phytosterols from the diet and their inhibition of cholesterol absorption, is mediated by their interference with formation of 27OH-cholesterol in enterocytes. This acts as the key LXR-agonist in a self-priming mechanism of cholesterol absorption (*Brauner et al*, J Nutr 2012). Recently two synthetic LXR agonists were reported to inhibit collagen-induced platelet aggregation and thrombus formation in mice. This suggested that also non-transcriptional, non-metabolic effects of LXR-activation might be relevant in atherosclerosis. We therefore studied, whether natural LXR agonists inhibit platelet activation in man. The natural LXR activator 22(R)-OH-cholesterol, but not its LXR-inactive stereoisomer 22(S)-OH-cholesterol, inhibited collagen induced platelet shape change and aggregation similar to synthetic LXR agonists. 22(S)-OH-cholesterol prevented the inhibition of platelets by 22(R)-OH-cholesterol. The effects were very rapid and detectable at concentrations that may occur in plaque material. This offers a new mechanism that could limit platelet accretion onto denuded plaques that expose collagen and LXR agonistic oxysterols.



The 22(R)- and 22(S)OH-sterols were also prepared as fluorescence labelled 3OH-BODIPY esters with high yield and purity using the Steglich acylation. Labelled 22(R)- and 22(S)-OH-cholesterol esters retained the stereo specific bioactivity of their parent compounds, were metabolically stable and not cytotoxic at LXR agonistic concentrations. Life staining with labelled 22(R)- or 22(S)-OH-cholesterol esters demonstrated stereo specific inhibition of platelet spreading and stereo specific handling by macrophages reflecting LXR activation (*Schaffer et al,* Biocem Pharm 2013).
The synthesis of stable fluorescence labelled 22(R)- and 22(S)-OH-cholesterol analogues with preserved stereo specific bioactivity and staining characteristics provides a valuable tool for LXR related functional imaging and binding assays in pathophysiologic studies and drug development.

Mechanism and Inhibition of Acute Atherothrombosis

Univ.-Prof. Dr. Wolfgang Siess

Myocardial infarction and ischemic stroke are leading causes of morbidity and mortality. The trigger for ca. 70% of acute cardiac ischemic events is the rupture of vulnerable, lipid-rich atherosclerotic plaques, leading to the exposure of thrombogenic plaque material to circulating blood. Subsequent platelet activation and fibrin formation can lead to occlusive thrombosis, often with fatal consequences. Importantly, atherosclerotic plaques are more thrombogenic than the intima of healthy arteries. It should be therefore possible to inhibit atherothrombosis without impairing physiological haemostasis. Present antithrombotic drugs target, however, physiological coagulation factors and platelet activation mechanisms thereby increasing the risk of bleeding. In addition, own studies have shown that plaque-induced platelet thrombus formation is not efficiently inhibited by currently used platelet inhibitors (P2Y12 receptor antagonists, aspirin). The long-term goal of our investigations is to understand the mechanisms of atherothrombosis and to inhibit these specifically without interfering with physiological hemostatic mechanisms.

Upon plaque rupture, platelets in circulating blood get exposed to molecules of the ruptured cap and the lipid-rich core. Our previous studies have several platelet-activating plaque components and their platelet receptors. Main thrombogenic plaque components are diverse type I and III collagenous structures in the fibrous cap which induce platelet adhesion, secretion and aggregation in blood, under static and arterial flow conditions in blood, by acti-vating platelet glycoprotein VI (GPVI). Our present studies compare in various models of human plaque-induced thrombus formation the anti-thrombotic effects of different monoclonal antibodies directed against platelet GPVI and of recombinant GPVI-Fc fusion protein which binds to collagen. Plaque collagens undergoing a high turnover of synthesis and degradation are surrounded by lipids and other matrix proteins accumulating in atherosclerotic plaques. Plaque collagens might bind specific lipids and matrix proteins modifying their thrombogenic properties. By advanced microscopic techniques (2-photon microscopy, structural illumination microscopy) and inhibition of specific target molecules we aim to image and identify the primary platelet adhesion sites of atherosclerotic plaques.

As further anti-platelet strategy that specifically targets plaque-triggered platelet activation and leaves physiologic platelet activation intact we plan to inhibit early signalling steps downstream of GPVI. Collagen binds and activates two platelet receptors, the integrin $\alpha 2\beta 1$ and GPVI, whereas plaque activates only GPVI. In addition GPVI binding to and probably activation by plaque are less as compared to collagen. Early signaling steps after GPVI activation are the activation of Src-family tyrosine kinases and of the tyrosine kinase Syk. We currently test inhibitors of these kinases to explore whether platelet activation and thrombus for-mation induced by atherosclerotic plaques can be selectively reduced without affecting plate-let activation by physiological platelet stimuli.

Group members

Prof. Dr. med. Wolfgang Siess
Janina Jamasbi, Apothekerin
Gesa Feische, cand. dent. med
Kristyna Busygina, cand. med.
Kathrin von Oheimb, MTA

Leukocyte Biology: Myeloid Cells in Vascular Inflammation and Therapy

Univ.-Prof. Dr. Dr. Oliver Söhnlein

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 recruitment of neutrophils to large arteries and on the investigation of pro-atherogenic mechanisms promoted by these cells.

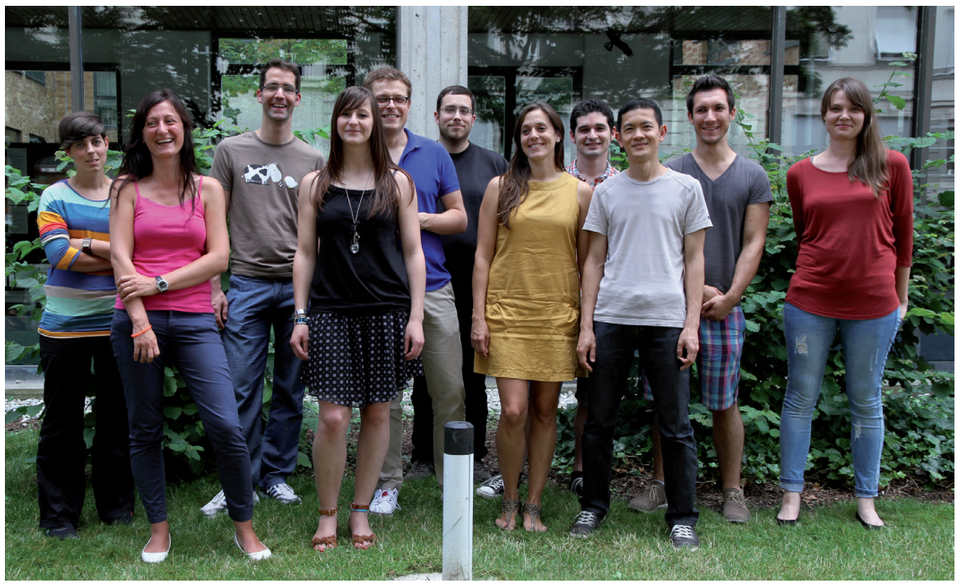
Hypercholesterolemia is a classical risk factor for atherosclerosis. Previous studies have shown that hypercholesterolemia induces a leukocytosis with increases in $Gr1^+/CD11b^+$ cells (*Swirski et al,* J Clin Invest 2007). In our own work we present clear evidence that hypercholesterolemia induces neutrophilia (*Drechsler et al,* Circulation 2010), which is attributable to enhanced granulopoiesis and increased mobilization from the bone marrow. The degree of hypercholesterolemia-induced neutrophilia is positively correlated with the extent of early atherosclerotic lesion formation thus suggesting that neutrophils play a causal role in early atherosclerotic lesion formation. In line, neutropenic mice display reduced plaque sizes at early but not late stages of atherosclerotic lesion formation. Flow cytometry of enzymatically digested aortas further shows altered cellular plaque composition in neutropenic mice with reduced numbers of inflammatory monocytes and macrophages. As mechanisms of neutrophil-driven arterial macrophage accumulation remained unclear we investigated the possibility that chemotactic proteins released from neutrophils directly induce adhesion and migration of monocytes and macrophages. A prime candidate for such response is cathelicidin (LL37 in humans, CRAMP in mice) which we have previously attributed chemotactic activity to (*Soehnlein et al*, Blood 2008). Hence, we crossed $Cramp^{-/-}$ mice with $Apoe^{-/-}$ mice and found a significant reduction in early atherosclerotic lesion formation accompanied by reduced lesional macrophage accumulation (*Wantha et al,* Circ Res 2013). CRAMP is a positively charged, neutrophil-derived molecule which we detected immobilized on the arterial endothelial cells. In this location CRAMP promotes adhesion of classical monocytes thus favoring their arterial recruitment (*Wantha et al,* Circ Res 2013). To further dissect the mechanisms of neutrophil-dependent monocyte adhesion we employed intravital microscopy of the cremaster muscle. In these experiments we found that cathelicidin is indeed released from activated neutrophils – however, his process occurs only after neutrophils exited the vessel (*Döring et al,* Circ Res 2012). CRAMP is then transported across the endothelium to be presented on endothelial proteoglycans. Classical monocytes rolling along the endothelium sense CRAMP via formyl-peptide receptor 2. Downstream signaling events lead to the activation of phospholipase C and subsequent conformational changes of $\beta 1$- and $\beta 2$- integrins towards a high-affinity conformation. As a result, classical monocytes

adhere on ICAM-1 and VCAM-1 expressed by cytokine-activated endothelium (*Döring et al,* Circ Res 2012).

To further address the role of monocyte subsets in atherosclerosis, we developed a novel approach of cytostatically induced leukocyte depletion and subsequent reconstitution with leukocytes deprived of classical or non-classical monocytes (*Soehnlein et al,* EMBO Mol Med 2013). *Apoe*$^{-/-}$ mice lacking classical but not non-classical monocytes displayed reduced lesion size and macrophage and apoptotic cell content. Conversely, high fat diet induced a selective expansion of classical monocytes in blood and bone marrow. Increased CXCL1 levels accompanied by higher expression of its receptor CXCR2 on classical monocytes and inhibition of monocytosis by CXCL1-neutralization indicated a preferential role for the CXCL1/CXCR2 axis in mobilizing classical monocytes during hypercholesterolemia. Studies correlating circulating and lesional classical monocytes in gene-deficient *Apoe*$^{-/-}$ mice, adoptive transfer of gene-deficient cells and pharmacological modulation during intravital microscopy of the carotid artery revealed a crucial function of CCR1 and CCR5 but not CCR2 or CX3 CR1 in classical monocyte recruitment to atherosclerotic vessels. Collectively, these data establish the impact of classical monocytes on atheroprogression, identify a sequential role of CXCL1 in their mobilization and CCR1/CCR5 in their recruitment (*Soehnlein et al,* EMBO Mol Med 2013).

Taken together, our data indicate an important role for neutrophils and classical monocytes during early stages of atherosclerosis and lend further evidence to the intimate partnership these cells share.

Group members
Prof. Dr. Dr. med. Oliver Söhnlein
Dr. rer. nat. Maik Drechsler
Dr. rer. nat. Sarawuth Wantha
Jean-Erich Alard, PhD
Almudena Ortega-Gomez, PhD
Helene Hartwig, MSc
Carlos Silvestre-Roig, PhD
Nicole Paulin
Maximilian Schiener
Yvonne Jansen, MTA
Patricia Lemnitzer, MTA



Clinical Pathobiochemistry - Lipid Signaling in Cardiovascular Disease

Univ.-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)**.

We recently found that knockout mice with genetic ablation of the endocannabinoid anandamide metabolizing enzyme fatty acid amide hydrolase (FAAH) developed smaller plaques with high neutrophil content and thus more vulnerable phenotype. In an experimental mouse model of balloon-induced carotid injury, FAAH deficiency was associated with enhanced restenosis, which was dependent on CB1 receptor signaling. We are now investigating whether the other major endocannabinoid 2-arachidonoylglycerol as well as related N-acylethanolamines exhibit differential effects in atherosclerosis as compared to anandamide. Remarkably, levels of 2-arachidonoylglycerol are about 10-fold higher than anandamide levels, both in plasma of patients with or without coronary artery disease as well as in aortas of atherosclerosis-prone mice.

Another focus of our group is to investigate the link between endocannabinoid levels and leukocyte recruitment in myocardial infarction healing **(project 2).** Our previous data suggest that enhanced endocannabinoid anandamide tone triggers neutrophil recruitment to inflammatory sites, ate least in hypercholesterolemia-induced chronic inflammation. Neutrophils contribute to tissue damage after acute myocardial ischemia and reperfusion, but their role in infarct healing is less well understood. 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. In a mouse model of permanent coronary ligation, we found that neutrophil depletion did not affect infarct size

Group members
Prof. Dr. rer. nat. Sabine Steffens
PD Dr.rer.nat. Alexander Faussner
Dr. Michael Horckmans
Larisa Ring, Dipl. Biochem.
Jasmin Leschner, Dipl.Biol.
Martina Rami, MSc Biochem.
Caroline Grubenbauer, cand.med.
Cornelia Seidl, MTA
Orsolya Kimbu Wade, technical assistance

nor survival, but inhibited inflammatory cell (i.e. monocyte/macrophage and T lymphocyte) responses after myocardial infarction. Our data indicate that neutrophils could represent a key regulator in adverse remodeling by fine-tuning the balance between inflammation and reparative state. In the next step we aim to clarify the role of elevated endocannabinoid levels as well as CB1 and CB2 in leukocyte recruitment into the infarcted myocardium.

In a **project 3,** we are investigating the molecular pathways of G protein-coupled receptor (GPCR) signaling leading to opposing effects of CB1 and CB2 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 signalling 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, frizzled 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, NFκB, AP-1, TCF/LEF). We can study the role of GRK2-6 in the regulation of a GPCR in detail through stable (but regulated) 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.

Autoimmune and Neuroimmune Responses in Atherosclerosis

Prof. Dr. med. Andreas J.R. Habenicht

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. Moreover, recent studies revealed comprehensive neuroimmune crosstalk between atherosclerosis and the *peripheral nervous system* (PNS) involving both sympathetic *paraaortic ganglia* and sensory *dorsal root ganglia*. Both types of ganglia connect the PNS with the brain through the spinal cord. Mechanisms of atherosclerosis PNS crosstalk included extensive axon neogenesis; TLO neogenesis around paraaortic ganglia; infiltration of paraaortic ganglia and dorsal root ganglia by *mast cells, T lymphocytes,* and *macrophages*; and immune cell aggregates in *peripheral nerves.* PNS constituents involved in such neuroimmune crosstalk are both the *sensory* and the *sympathetic* but not the *parasympathetic* PNS. These data raised the important possibility that hitherto unrecognized atherosclerosis nervous system circuits connect the diseased arterial wall with both the peripheral and central nervous systems. In addition, other results revealed several hitherto unrecognized types of immune injury of the brain including lipid accumulation in distinct *hotspots* of the brain parenchyma, the *choroid plexus*, and the *ependymal cell layer of brain ventricles;* formation of *macrophage/microglia aggregates* in the brain parenchyma; *glial cell activation; T/B/dendritic cell/plasma cell aggregates* in both meninges and the brain parenchyma; activation of the *classical complement pathway* in the choroid plexus; neuronal *axon loss* due to axon phagocytosis by macrophages; and several types of *blood brain barrier breakdown.* Future studies are aimed at the detailed characterization of autoimmune reactions in atherosclerosis and delineation of functional impacts of the neuroimmune interactions between hyperlipidemia, atherosclerosis, and brain injury.

Group members

Prof. Dr. med. Andreas Habenicht
Sarajo Mohanta, Dr. rer.nat.
Changjun Yin, Dr. rer.nat.
Zhe Ma, PhD student

Immune Modulation in Atherosclerosis and Obesity

Prof. Dr. Esther Lutgens / Dr. Norbert Gerdes

Co-stimulatory molecules

Research Interests

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. 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.

Highlights in 2012/2013

Transforming growth factor beta (TGFβ) is an immune regulatory cytokine whose expression is increased in atherosclerotic plaques when CD40L is inhibited (Lutgens et al, PNAS 2001). Here we investigate the role of TGFβ signalling in dendritic cells (DCs) and in DC-mediated T cell proliferation and differentiation in atherosclerosis. For that purpose we used mice that carry a transgene resulting in functional inactivation of TGFβ receptor II (TGFβRII) signalling in $CD11c^+$ cells (Apoe-/-CD11cDNR). $Apoe^{-/-}$CD11cDNR mice exhibited an over two-fold increase in the plaque area compared with $Apoe^{-/-}$ mice. Plaques of $Apoe^{-/-}$CD11cDNR mice showed an increase in $CD45^+$ leucocyte content, and specifically in $CD3^+$, $CD4^+$ and $CD8^+$ cells, whereas macrophage content was not affected. In lymphoid organs, $Apoe^{-/-}$CD11cDNR mice had equal amounts of $CD11c^+$ cells, and $CD11c^+CD8^+$ and $CD11c^+CD8^-$ subsets, but showed a subtle shift in the CD11c+CD8- population towards the more inflammatory $CD11c^+CD8^-CD4^-$ DC subset. In addition, the number of plasmacytoid-DCs decreased. Maturation markers such as MHCII, CD86 and CD40 on CD11chi cells did not change, but the CD11cDNR DCs produced more TNFα and IL-12. $CD11c^+$ cells from CD11cDNR mice strongly induced T-cell proliferation and activation, resulting in increased amounts of effector T cells producing high amounts of Th1 (IFN-γ), Th2 (IL-4, IL-10), Th17 (IL-17), and Treg (IL-10) cytokines. We conclude that loss of TGFβRII signalling in $CD11c^+$ cells induces subtle changes in DC subsets, which provoke uncontrolled T cell activation and maturation. This results in increased atherosclerosis and an inflammatory plaque phenotype during hypercholesterolemia (*Lievens et al,* Eur Heart J 2013).

We also studied the dynamics of macrophage polarization in human atherosclerosis. Developing lesions progressively accumulated both M1 and M2 cells, as was signified by the enhanced expression of associated markers. In line with their pro-inflammatory characteristics, M1 macrophages dominated the rupture-prone shoulder regions of the plaque over M2 polarized cells, while the fibrous caps of lesions showed no significant differences between subsets. In contrast, vascular adventitial tissue displayed a pronounced M2 activation profile. As expected, areas of intraplaque hemorrhage clearly associated with CD163 staining. Rather than being limited to complicated lesions, this M2 marker was also readily detectable in stable plaques. Finally, foamy macrophages displayed an ambiguous repertoire that incorporates individual M1 and M2 markers (*Stoger et al,* Atherosclerosis 2012).

The relevance of the immune system in atherosclerosis was also discussed within the journals Cellular Molecular Life Sciences and Current Opinion in Lipidology. These reviews highlighted the role of the different immune cells and subsets, as well as the role of co-stimulatory molecules in atherosclerosis (*Legein et al,* 2013; *Smeets et al,* 2013).

Group members

Prof. Dr. med. Esther Lutgens
Dr. rer. nat. Norbert Gerdes
Dirk Lievens, PhD
Holger Winkels, Dipl. Biol.
Christina Bürger, Dipl. Biol.
Tobias Badmann, MTA
Angelika Dandl, MTA
Sigrid Reim, MTA
Charlotte Spitz
Veronika Pilz

Adaptive Immunity – T Cell Subpopulations in Atherosclerosis

Research Interests

Atherosclerosis, the principal cause of most cardiovascular disease, is characterized by a chronic inflammatory reaction within the vessel wall provoked by insufficient clearance of lipid particles. Although innate immune cells such as monocytes, mast cells, or granulocytes are considered the main effector cells within the plaque, increasing evidence points to a decisive involvement of the adaptive immunity in the pathological processes underlying atherosclerosis. In particular, understanding T lymphocytes and their intricate mechanisms of regulation may foster the perspective that such pathways could be utilized for future therapeutic purposes.

Highlights in 2012/2013

Regulatory T cells can limit potentially harmful reactions of the conventional effector T-cell population. In atherosclerosis, the role of this T cell subpopulation which is characterized by the expression of the transcription factor forkhead box protein 3 (Foxp3) has not directly been described. Earlier studies indirectly suggested that regulatory T cells (Tregs) ameliorate atherosclerosis, but exactly how they operate remained unclear. Using a genetically modified mouse model for selective depletion of these anti-inflammatory cells we aimed to determine the causality and the mechanism of action of Treg in atherogenesis. To define the role of Foxp3-expressing Tregs in atherosclerosis, we used the DEpletion of REGulatory T cells (DEREG) mouse, which expresses the human diphtheria toxin (DT) receptor and enhanced green fluorescent protein (eGFP) under control of the Treg-specific Foxp3 promoter, allowing for specific depletion and tracking of Foxp3+ Tregs. Indeed, DT-mediated depletion of Tregs led to doubling of atherosclerotic lesion size and a profound increase in circulating cholesterol concentration, mainly in the very low density lipoprotein (VLDL) fraction. We could further demonstrate that expression of a receptor important in the uptake of cholesterol-rich

lipoproteins, sortilin-1, was decreased in the liver and is likely responsible for decreased clearance of pro-atherogenic particles leading to elevated blood cholesterol levels and enhanced atherosclerosis (*Klingenberg & Gerdes et al,* JCI 2013).

In another study were able to clarify the role another specialized T cell population in obesity, a frequent co-morbidity of cardiovascular disease. Obesity promotes a chronic inflammatory condition in adipose tissue (AT) and impairment of insulin sensitivity coincides with infiltration of T cells into AT in early stages of obesity. We examined the role of invariant natural killer T (iNKT) cells, a subtype of T cells activated by lipid antigens, on glucose and lipid metabolism in obesity (*Strodthoff et al,* ATVB 2013). When studying these cells we observed that AT tissue contained much less INKT cells than the liver which is a known reservoir of this cell type. Accordingly, mice specifically lacking iNKT cells did not differ in their kinetics of glucose clearance compared to wild-type controls. Interestingly, although expression of inflammatory markers in AT did not differ between the groups homeostasis iNKT cell-deficient mice was altered evidenced by lower AT weight, smaller adipocytes, accelerated lipogenesis, increased expression of hormone-sensitive lipase, and accelerated basal lipolysis. These data demonstrate that iNKT cells which normally reside in the liver can impact metabolic changes in other organs while their presence in such organs (e.g., AT) is not required.

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. Many synergies are shared with Esther Lutgens, main interest of whom is the role of the classical co-stimulator CD40/CD40L in vascular biology and obesity.

Platelet Chemokines and Atherosclerosis – Clinical Studies

Dr. Philipp von Hundelshausen / PD Dr. Rory Koenen

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).

Group members

Dr. med. Philipp von Hundelshausen
PD Dr. Rory Koenen
Xavier Blanchet, PhD
Dr. rer. nat. Ela Karshovska
Dr. rer. nat. Birgit Kramp
Dr. rer. nat. Marcella Langer
He Li, PhD
Dr. rer. nat. Delia Projahn
Dipl.-Biol. Martin Schmitt
Veit Eckardt, cand. med.

A non-allelic CXCL4 variant termed CXCL4L1 (PF4alt) showed impaired affinity for RANTES and accordingly had no propensity to enhance RANTES-mediated monocyte arrest. In patients with acute coronary syndrome (ACS) both RANTES and PF4 and PF4alt were increased compared to persons without ACS.
Our perspective for the future is to clarify in greater detail the PF4-RANTES interaction and to detect other possible chemokine interactions aiming to establish the chemokine -interactome. As well the secretory mechanisms where and how platelet chemokines are stored will be investigated.

Chemokines and Cell Adhesion - Molecules in Vascular Inflammation
The team's research deals with protein-protein interactions in the context of leukocyte recruitment during vascular inflammation. In special focus are chemokines (e.g. CCL5 and CXCL4) and cell adhesion molecules e.g. Junctional Adhesion Molecule JAM-A. Further areas of interest are the role of platelets and platelet-derived microparticles in vascular disease.

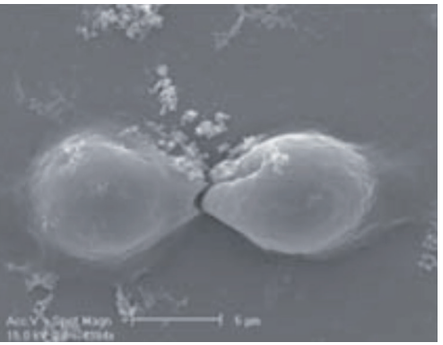


Figure 1: Electron microscopy image of microparticles bound to THP-1 cells

The chemokines CCL5 and CXCL4 are both stored in the secretory α-granules of platelets. During transient rolling interactions, activated platelets and platelet-derived microparticles secrete CCL5 and CXCL4 from these α-granules onto endothelial cells of the inflamed vessel wall. These chemokines subsequently attract monocytes into the vessel wall, a process that might contribute to atherosclerosis. In addition, CCL5 and CXCL4 form a heteromeric complex, which is a potent stimulus for monocytes to adhere to activated endothelial cells. Our previous work has shown that CCL5 and CXCL4 derived from blood cells are indeed involved in atherosclerotic lesion formation in mice. In addition, heteromeric complexes of CCL5 and CXCL4 could be detected in human platelets. The design and subsequent application of a synthetic peptide (termed MKEY) that inhibited the interaction between these chemokines reduced atherosclerotic plaque formation in Apoe$^{-/-}$ mice (*Koenen et al,* Nat Med 2009). Furthermore, in a mouse model of lung injury, the CCL5–CXCL4 heteromers also appeared to play an important role in attracting neutrophils to inflamed lung tissue, leading to increased tissue damage and lung dysfunction. In this setting, administration of MKEY reduced lung damage and decreased the mortality of the treated mice, compared to control mice. These studies highlight the biologic relevance of chemokine heteromerization and identify CCL5–CXCL4 heteromers as novel therapeutic target. Current projects aim to identify novel heterophilic interactions between chemokines with similarly specialized functions that may also serve are potential drug targets.

In addition to chemokines, platelets also release microparticles upon activation. Prolonged storage of platelets leads to the generation of microparticles as well, possibly due to a process that resembles apoptosis. The presence of microparticles in platelet concentrates for transfusion purposes might thus harbor risks for recipient patients. In a recent study, we have assessed the effects of such spontaneously generated microparticles on monocytic cells. The microparticles readily bound to the monocytes (Figure 1), were subsequently internalized and caused phenotypic changes that resembled polarization into professional macrophages (*Vasina et al,* Cell Death Dis 2011; Am J Blood Res 2013). These findings might be relevant for patients at risk for cardiovascular disease, which are designated to receive therapeutic transfusions of platelet concentrates. Current projects aim to further characterize the effects of infused microparticles in animal models.

The cell adhesion molecule JAM-A is expressed in a large variety of cell types, including endothelial cells, leukocytes and platelets. In endothelial cells, JAM-A maintains cell layer permeability and is involved in transendothelial migration of leukocytes. JAM-A is mainly located in the intercellular tight junctions but relocates to the apical side of the endothelial cells during inflammation. In a recent study, we have exploited this feature of JAM-A to monitor the progression of vascular inflammation to an atherosclerotic plaque, as JAM-A–relocation might occur before phenotypic characteristics of a vascular lesion become apparent. Using mouse models of atherosclerosis, we have visualized the localization pattern of JAM-A in the intact vessel wall using 2-photon microscopy and observed notable differences in JAM-A expression between the healthy and diseased vessel wall (Figure 2). This inflammatory redistribution of JAM-A is induced by oxidized lipoproteins or abnormal flow conditions and facilitates the arrest and transmigration of mononuclear cells. We were able to show that treatment with statins could counteract the inflammatory actions of JAM-A, adding another aspect to the mechanism of action of statins. These findings might aid to establish JAM-A as a marker and possible therapeutic target for monitoring the progression and for the treatment of atherosclerosis, respectively (*Schmitt et al,* Circulation 2014; Atherosclerosis 2014).
In an ongoing study, the role of JAM-A in platelets was investigated. Specific deletion of JAM-A led to a hyperreactivity in platelets, characterized by a lower activation threshold. When crossed into an Apoe$^{-/-}$ background, platelet-specific JAM-A–deficiency led to increased formation of early atherosclerotic lesions, possibly due to increased chemokine release and platelet-leukocyte complex formation. These findings emphasize the detrimental role of platelets in early atherosclerosis

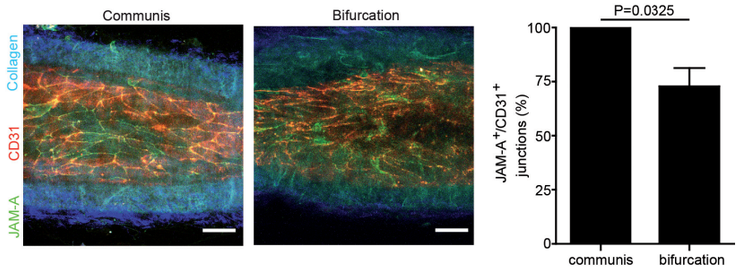
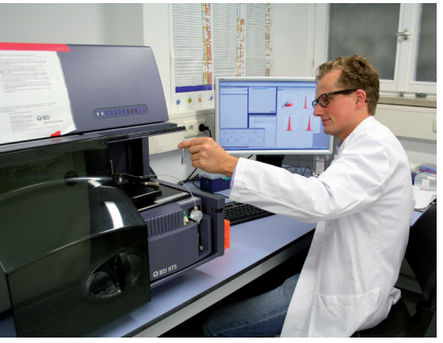


Figure 2: Redistribution of JAM-A under atherogenic conditions.

Flow Cytometry – Circulating Angiogenic Cells in Cardiovascular Pathophysiology

PD Dr. Michael Hristov



The BD FACSCanto II cell analyzer

Our research group intends to elucidate phenotype, trafficking and differentiation of myeloid cell subsets during atherosclerosis and angiogenesis. In terms of clinically related translational research we investigate the prognostic value of CD14/CD16 monocyte subsets in patients with metabolic disease. We previously identified significant correlations of cells-of-interest to cardiovascular risk factors and the extent of coronary artery stenosis. Ongoing clinical trials intend to consider a potential relation of these cells to lipid disorder and lipid lowering therapy as well.

We further investigate the phenotype heterogeneity and subset-specific recruitment of resident monocytes in human bone marrow and aim to compare the gene expression profile of bloodstream monocytes under different disease conditions in experimental animal models as well as in patients.

Our methods are mainly focused on flow cytometry, cell sorting, dynamic cell culture and adhesion in flow. In terms of multicolor, state-of-the art flow cytometric applications, we are interested in developing of advanced technical notes for express quantification of monocyte subsets and endothelial progenitor cells in human blood. These protocols are highly adapted for routine clinical use. Furthermore, by operating on a latest innovation cell sorter device we precisely dissect and sort out leukocyte sub-populations from spleen, peripheral blood, bone marrow or plaque homogenates. Moreover, our cell sorter operates as facility service and we support other research groups in various sorter applications.

Group members
PD Dr. Michael Hristov
Manuela Mandl, MSc
Susanne Schmitz, MTA

Biophysics of Microscopy – Cardiovascular Imaging Technologies

Dr. Remco Megens

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

The IPEK working group on biophysics of microscopy focusses on the application of advanced optical fluorescence techniques such as two-photon laser scanning microscopy (TPLSM) and dual channel intravital microscopy, for (molecular) imaging of atherosclerotic structures and processes directly at sites of occurrence: i.e. the large arteries. In the past years, application of TPLSM in cardiovascular research 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 latter TPLSM methodologies have been successfully applied in various studies that have been conducted by IPEK members and collaborators.

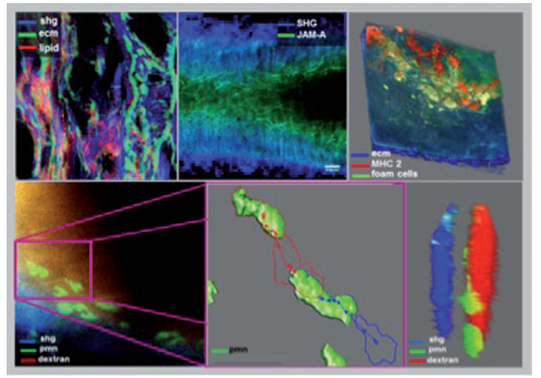


Figure: examples TPLSM in mouse cardiovascular tissue: top left; intrinsic fluorescence signal (autofluorescence, SHG) derived from a plaque section. Top middle: Junctional adhesion molecule-A in endothelial cell junctions of an ex vivo mounted mouse carotid artery (*Schmitt et al*, Circulation 2014). Top right; ex vivo atherosclerotic plaque foam cells (green/red); Lower panel; three dimensional dynamics of neutrophils in in a carotid artery of Apoe$^{-/-}$LysM^{eGFP} 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).

A Leica SP5IIMP TPLSM system is available in the optical imaging facility of IPEK (funded by DFG/LMU) which offers fast image acquisition rates (30Hz) with improved sensitivity. As a result, in vivo imaging of cardiovasculature can be achieved with subcellular spatial resolution and in up to four dimensions. The Megens group will further develop TPLSM applications for imaging in (diseased) cardiovascular targets and apply them for projects studying vessel wall morphology and functionality as well as the dynamics and recruitment of various inflammatory cell subsets in *ex vivo or in vivo* models. Besides TPLSM applications, the PI Megens group aims at expanding the optical imaging facility with novel optical imaging methods with nanoscopic resolution, thereby enabling detailed visualization of subcellular structures and processes involved in cardiovascular disease. Finally, the Megens laboratory functions as an optical imaging core facility for internal and external collaborators.

Group members
Dr. Remco Megens
Dr. rer. nat. Sarawuth Wantha
Jürgen Pyta, MSc

Migration and Differentiation of Mesenchymal Stem Cells – Implications for Atherosclerosis

PD Dr. Christian Ries

Human mesenchymal stem cells (hMSCs) are present in almost all tissues and organs. By asymmetric cell division, hMSCs both replicate and differentiate into various cell types such as osteocytes and muscle cells depending on the presence of environmental stimuli. Another remarkable feature of hMSCs is their ability for secretion of a broad range of chemokines, cytokines and growth factors enabling these cells to exhibit important biological effects including immunomodulation, chemoattraction, anti-fibrosis, anti-apoptosis and support of the growth and differentiation of local progenitor cells.

Plaque formation is a major hallmark in atherosclerosis and is fostered by leukocytes that infiltrate inflamed endothelial lesions. Similar to leukocytes, hMSCs derive from bone marrow and are recruited into sites of inflammation. Unsurprisingly, hMSCs are present in atherosclerotic plaques. However, the role and contribution of hMSCs in atheroprogression is unclear. Our current research is focused on the investigation of molecular mechanisms that control migration and differentiation in vitro as well as recruitment of hMSCs to atherosclerotic plaques in vivo in order to explore the potential atheroprotective roles of hMSCs.

Preliminary data demonstrate an important role of miRNA let-7f in hMSC migration and differentiation. Interestingly, we found that several inflammatory factors present in atherosclerotic plaques such as LL-37 and SDF-1 are potent chemoattractants to hMSCs and simultaneously upregulate let-7f activity in these cells. These findings indicate a key role of let-7f in mechanisms facilitating hMSC recruit¬ment into plaques where these cells might influence plaque stability by immunomodulatory effects and/or by differentiation into mature cell types such as smooth muscle cells (Fig. 1). Another miRNA, miR-126, is predominantly expressed in endothelial cells and known to be atheroprotective. Our recent studies demonstrate that the guide strand miR-126-3p and its passenger strand miR-126-5p exhibit differential subcellular trafficking and localization in endothelial cells in response to cellular stress such as apoptosis and autophagy, indicating differential roles of both strands in the atheroprotective function of miR-126.

Previously we published that hMSCs are capable to transmigrate through barriers of human extracellular matrix by expression of matrix metalloproteinase (MMP)-2, membrane type 1 (MT1)-MMP, and tissue inhibitor of metalloproteinase (TIMP)-2. The chemotactic migration by these cells was greatly stimulated by the inflammatory cytokines/chemokines TGF-β1, IL-1β, TNF-α and SDF-1α which also upregulated the biosynthesis of MMP-2, MT1-MMP and TIMP-2 in these cells, providing a potential mechanism in hMSC recruitment and extravasation into inflamed tissues. Interestingly, pretreatment of hMSCs with TNF-α significantly enhanced expression of the chemokine receptor CXCR4 which facilitated the chemotactic invasiveness of hMSCs toward SDF-1α in vitro, and potentiated the tropism of these cells toward intracranial malignant gliomas in vivo. Our recent studies in hMSCs revealed an novel cytokine factor-like function of TIMP-1 independent of its role as a MMP inhibitor. By use of RNA interference we demonstrated that endogenous TIMP-1 is a repressor of hMSC proliferation and differentiation into bone cell types by affecting the activity of intracellular β-catenin, the key effector of the Wnt/β-catenin pathway. Further studies on TIMP 1's signaling pathways identified CD63 as cell surface receptor used by TIMP-1 and revealed the miRNA let-7f and its target gene axin-2 to be key regulators in the TIMP-1-mediated impact on hMSC differentiation into osteogenic cells.

In collaboration with the Sanitätsamt der Bundeswehr, we examine the role of the hypoxia induced factor (HIF)-1α pathway and miRNA-regulated control of autophagy in the pathophysiology of sulfur mustard-induced skin injuries.

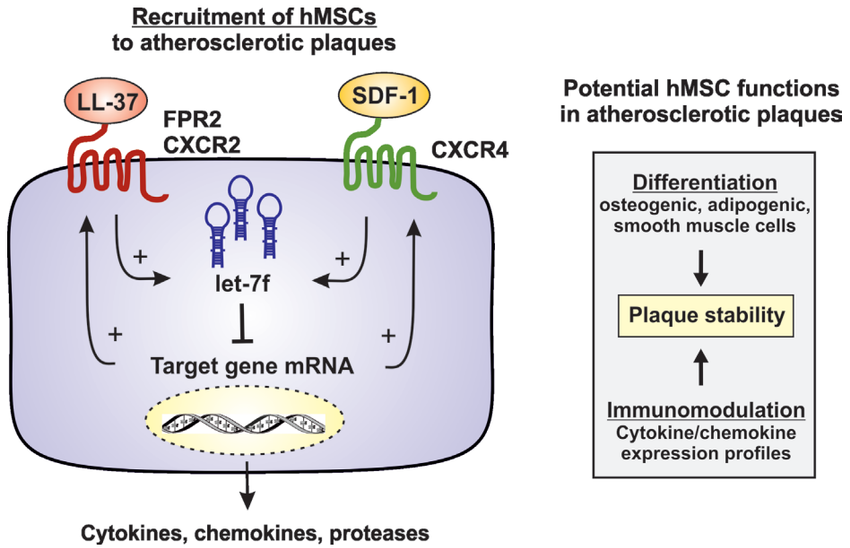


Figure: Schematic illustration of preliminary results and the deduced working hypothesis on mechanisms implicating hMSCs in atherosclerosis

Group members
PD Dr. rer. nat. Christian Ries
Dr. rer. nat. Virginia Egea.
Dr. rer. nat. Tanja Popp
Dr. med. Donato Santovito
Christian Mahl, Dipl. Biol.
Janina Deppe, Dipl. Biol.
Thomas Pitsch, MTA

Head Veterinarian and Animal Welfare Officer

Dr. Annalena Riedasch and Prof. Dr. Frank Richter

Drs. med. vet. Riedasch and 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: Neutrophile in der Atherosklerose
Projektleiter: O. Söhnlein
Förderer: DFG (SO 876/3-1)
Bewilligungszeitraum: 02/2009-09/2012
Kooperationen: L. Lindbom, Karolinska Institut

P 11: Graduiertenkolleg EuCAR Arterial Remodeling
Projektleiter: C. Weber / M. Daemen
Förderer: DFG (GRK1508) über Aachen
Bewilligungszeitraum: 10/2008-09/2013
Kooperationen: diverse

P 12: MIF and CXCR2 in liver fibrosis
Projektleiter: J. Bernhagen / H. Wasmuth / C. Weber
Förderer: DFG (SFBTRR57 / P07)
Bewilligungszeitraum: 07/2009-06/2012

P 13: Differential recruitment of monocyte subsets
Projektleiter: C. Weber / O. Söhnlein
Förderer: DFG (SFB914-B08)
Bewilligungszeitraum: 06/2011-06/2015
Kooperationen: diverse

P 14: Induktion der Entzündungsresolution in der Atherosklerose
Projektleiter: O. Söhnlein
Förderer: DFG (SO 876/6-1)
Bewilligungszeitraum: 02/2013-02/2016

P 15: 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 16: 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 17: Role of LPA in atherosclerosis
Projektleiter: A. Schober
Förderer: DFG (SFB1054/3)
Bewilligungszeitraum: 01/2013-12/2016

P 18: Charakterisierung adaptiver Immunreaktionen in der A-POE-/-Mausaorta durch Multiphotonenmikroskopie
Projektleiter: A. Habenicht
Förderer: DFG (HA 1083/16-1)
Bewilligungszeitraum: 07/2010-09/2013

P 19: 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 20: Neutrophil apoptosis in atherosclerosis
Projektleiter: O. Söhnlein
Förderer: LMUexcellent
Bewilligungszeitraum: 06/2013-06/2014

P 21: Diffraction-unlimited STED nanoscopy
Projektleiter: R. Megens / C. Weber
Förderer: LMUexcellent
Bewilligungszeitraum: 06/2013

P 22: Munich Heart Alliance
Projektleiter: C. Weber
Förderer: BMBF / StMWFK
Bewilligungszeitraum: 01/2011-12/2015

P 23: Vaskuläre Immuntherapie
Projektleiter: C. Weber
Förderer: BMBF DZHK MHA VD1.2
Bewilligungszeitraum: 10/2011-12/2015

P 24: IntenC Research Grant Lipitoxic Stress
Projektleiter: C. Weber / E. Erbay
Förderer: BMBF (TUR10/I13)
Bewilligungszeitraum: 10/2011-09/2014

P 25: Verbund miR-A
Projektleiter: A. Schober
Förderer: BMBF DLR (01KU1213A)
Bewilligungszeitraum: 04/2012-03/2015

P 26: Verbund miR-A
Projektleiter: C. Weber
Förderer: BMBF DLR (01KU1213B)
Bewilligungszeitraum: 04/2012-03/2015

P27: ERC Advanced Investigator Grant Atheroprotect
Projektleiter: C. Weber
Förderer: European Research Council
Bewilligungszeitraum: 01/2011-12/2015
Kooperationen: K. Mayo, University of Minnesota

P 28: 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 29: NWO VICI Grant
Projektleiter: C. Weber
Förderer: NWO
Bewilligungszeitraum: 04/2010-03/2016
Kooperationen: diverse

P 30: Kostimulation via CD40 in der Atherosklerose
Projektleiter: E. Lutgens
Förderer: Humboldt-Stiftung
Bewilligungszeitraum: 12/2008-12/2014

P 31: Identification of chemotactic receptors for human alpha-defensins
Projektleiter: J.-E. Alard
Förderer: Humboldt-Stiftung
Bewilligungszeitraum: 11/2011-11/2013

P 32: Function, recruitment and differentiation of monocyte subsets in atherosclerotic lesion in mice
Projektleiter: O. Söhnlein
Förderer: German-Israeli Foundation
Bewilligungszeitraum: 01/2011-06/2013
Kooperationen: S. Jung, Weizman Institute of Science

P 33: Peptidantagonisten gegen Atherosklerose
Projektleiter: C. Weber / J. Bernhagen
Förderer: Carolus Therapeutics Inc.
Art der Förderung: Sachmittelbeihilfe
Bewilligungszeitraum: 04/2008-07/2012
Kooperationen: J. Bernhagen, Biochemie, RWTH Aachen

P 34: Zellverträglichkeit
Projektleiter: M. Hristov
Förderer: NonWoTECC Medical, Köln
Bewilligungszeitraum: 04/2009-08/2012

P 35: Modulation vaskulärer Kollagendeposition durch regulatorische T Lymphozyten und Plättchen
Projektleiter: D. Lievens
Förderer: Friedrich-Baur Stiftung 43/12
Bewilligungszeitraum: 05/2012-05/2013

P 36: Mechanismen der entzündlichen Rekrutierung von Phagozytensubpopulationen
Projektleiter: O. Söhnlein
Förderer: Friedrich-Baur Stiftung 44/12
Bewilligungszeitraum: 05/2012-05/2013

P 37: Atheroprotektion durch α-Defensine
Projektleiter: O. Söhnlein
Förderer: Else-Kröner-Fresenius Stiftung 2012_A36
Bewilligungszeitraum: 07/2012-02/2015

P 38: Role of serotonin receptors in atherosclerosis
Projektleiter: S. Steffens
Förderer: Friedrich-Baur Stiftung 45/13
Bewilligungszeitraum: 06/2013-06/2014

P 39: Die Rolle des peripheren Serotoninsystems in der Atherosklerose
Projektleiter: S. Steffens
Förderer: Else-Kröner-Fresenius Stiftung 2013_A114
Bewilligungszeitraum: 07/2013-07/2016

P 40: Crossroads of Vascular Inflammation, Obesity, and Autoimmunity in Braun Injury
Projektleiter: A. Habenicht
Förderer: Chinesisch-Deutsches Zentrum für Wissenschaftsförderung
Bewilligungszeitraum: 03/2013

Preise und Auszeichnungen

Jahr : 2011-2012
Preis: VIDI-Preis der Netherlands Organisation for Scientific Research (NWO)
Gewinner: Rory Koenen

Jahr : 2011-2012
Preis: VIDI-Preis the Netherlands Organisation for Scientific Research (NWO)
Gewinner: Oliver Söhnlein

Jahr : 2012
Preis: VIDI-Preis der Netherlands Organisation for Scientific Research (NWO)
Gewinner: Esther Lutgens

Jahr : 2012
Preis: Lehrpreis der LMU
Gewinner: Cornelia Gippner-Steppert

Jahr : 2013
Preis: Denber Pinard Forschungspreis, Medizinische Fakultät der Universität Genf
Gewinner: Sabine Steffens

Jahr : 2013
Preis: Bernd R. Binder Publication Prize
Gewinner: Martin Schmitt

Thrombosis and Haemostasis
International Journal for Vascular Biology and Medicine

Thrombosis & Haemostasis

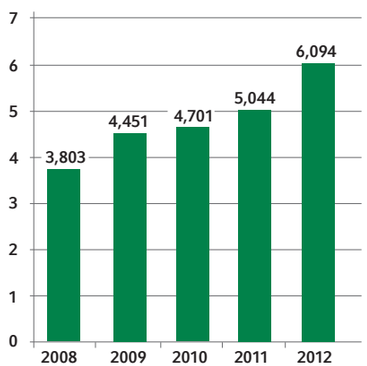
Thrombosis and Haemostasis is a leading journal of the Schattauer Group and publishes reports on basic and clinical research dedicated to novel results and highest quality in any area of thrombosis and haemostasis, vascular biology and medicine, inflammation and infection, platelet and leukocyte biology, from genetic, molecular & cellular studies, diagnostic, therapeutic & preventative studies to high-level translational and clinical research. **Target groups:** Haematologists, clinical pharmacologists, 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 since 2010.

General Information

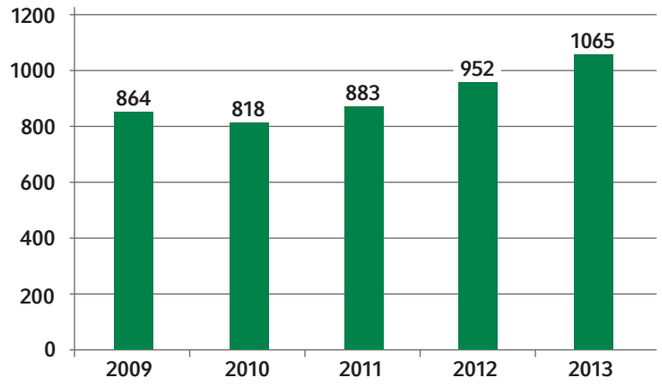
The journal is published monthly in print (ISSN 0340–6245) and online (www.thrombosis-online.com). The journal is covered in the main abstracting and indexing services worldwide. The journal continues serving as a link journal for the European Society of Cardiology Working Groups on Thrombosis and Atherosclerosis & 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 from 2014 for the Australian Vascular Biology Society (AVBS).

Highlights 2012-2013

The main headline news in 2013 is the achievement of a new Impact Factor (2012) yielding 6.094, clearly a steady increase and the highest level ever in the history of the journal!



Two new categories introduced in 2012 - "T&H Insights" - commissioned short succinct Commentaries on basic science articles and "T&H Image" have been very well received in 2013. And from January 2014 one more category is offered in the journal: "Protocol/design papers". Since 2012 the "Best Cover Image of the year" is selected to encourage the authors to provide us with quality illustrations.
The numbers of submissions for the first time significantly exceed millennium mark and in 2013 year reached 1065.



In particular, the flow of submissions from Canada, Germany, China, France, Italy, Spain and Taiwan has significantly increased in the last two years.

At the end of 2013 the Intellectual Property & Science business of Thomson Reuters, the world's leading source of intelligent information for businesses and professionals, had announced in Philadelphia (USA) the winners of the inaugural ScholarOne® Journal Triathlon - an online contest designed to celebrate and recognize the innovative practices of scholarly research journals. **Thrombosis and Haemostasis** was named Journal Triathlon Champion from among 27 total submissions. „We are excited to honour **Thrombosis and Haemostasis** and to help raise awareness of their pioneering publishing methods," said Jasper Simons, vice president of Thomson Reuters Scientific and Scholarly Research business.

Editor-in-Chief

Christian Weber, MD
Institute for Cardiovascular Prevention
Ludwig-Maximilians-Universität (LMU) Munich
Pettenkoferstraße 9
80336 München
Germany
Tel.: +49 (0) 89/5160-4353
Fax: +49 (0) 89/5160-4352
Mail: christian.weber@med.uni-muenchen.de

Editorial Office (Munich)

Irina Moshkova
Phone: +49 (0) 176-63825132
Fax: +49 (0) 89/5160-4352
Mail: thrombosis@med.uni-muenchen.de

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 01.05.1957 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.

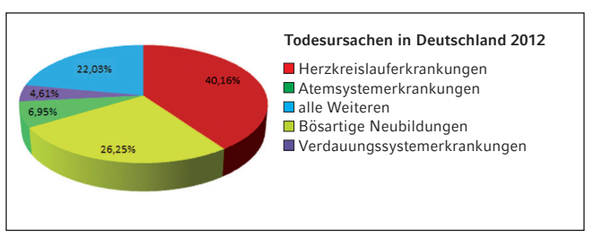
Im Rahmen der August-Lenz-Stiftung kümmert sich das IPEK neben Forschung und Weiterentwicklung von Projekten auch um die Versorgung von Studienpatienten. Wie der Name *Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten* nahe legt, geht es dabei schwerpunktmäßig um Studien im Rahmen von 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, dem in der Praxis durch die Anstellung weiterer Facharztdisziplinen Rechnung getragen wird. So setzt sich das Team aus folgenden Mitarbeitern zusammen: einem Chefarzt mit einem Facharzt für Innere Medizin und Kardiologie, einem Oberarzt ebenfalls mit den Schwerpunkt-bezeichnungen 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 vier technische Assistentinnen unterstützt, sowie zwei Verwaltungsangestellten, die die Terminabsprachen koordinieren.

Hintergrund

Herz-Kreislaufkrankheiten machen mit 40,2% den Hauptanteil der Todesursachen in Deutschland aus (siehe Graphik unten) und liegen damit deutlich vor Krebserkrankungen, die in 26,3% 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.



Statistische Verteilung der Todesursachen im Jahre 2012 in Deutschland

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. Besonders wichtig ist uns, ein vertrauensvolles Verhältnis zu unseren Patienten aufzu¬bauen, da wir davon überzeugt sind, dass eine ganzheitliche Arzt-Patienten-Beziehung die Grund-lage für jede erfolgreiche Behandlung ist. In Abhängigkeit der individuellen Frage¬stellung bieten wir neben der Anamnese und körperlichen Untersuchung folgende Diagnostik an:

- serielle Blutdruckmessung manuell und oszillometrisch
- eine Blutentnahme, u.a. zur Bestimmung der Cholesterin- und Lipidwerte
- eine 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/Exom-Sequenzierung
- Messung von inflammatorischen Zellpopulationen
- Messung inflammatorische Zytokine und Chemokine

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 elektronsicher 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.

Studien

Im Sinne der jahrelangen Tradition beteiligt sich das IPEK auch an der Durchführung von Studien mit klinischer Fragestellung. Dazu wird die Kooperation mit anderen Bereichen des Klinikums der Universität München angestrebt, auch um verschiedene kardiovaskuläre Krankheitsbilder untersuchen zu können. So besteht derzeit eine Kooperation mit der Lipid-Ambulanz unter der Leitung von Frau Dr. Anja Vogt. Der Beginn dieser Anwendungsbeobachtung erfolgte im Dezember 2011. Darüber hinaus wird auch die genetische Komponente des Risikos für auf Atherosklerose basierenden Erkrankungen untersucht. Beispielsweise werden Polymorphismen im Erbgut (SNPs) bestimmt.

Hintergrund

Im Rahmen jahrelanger Forschung einer Arbeitsgruppe des Institutes hat sich die Hypothese herauskristallisiert, dass bei der Entstehung von Atherosklerose, der Grunderkrankung für Herzinfarkte und Schlaganfälle, die Konstellationen bestimmter monozytärer Subgruppen und Vorläuferzellen eine wesentliche Rolle spielen. Mittels FACS-Analyse ist es der Gruppe um PD Dr. Mihail Hristov gelungen tendenzielle Werte an Patienten zu ermitteln, die den Rückschluss auf eine potentielle Risikoeinschätzung bei der Entwicklung einer Atherosklerose am individuellen Patienten zulassen. Dabei hat sich gezeigt, dass die zelluläre Zusammensetzung in Abhängigkeit vom Lipidhaushalt des Individuums steht. Hierzu sind jedoch bislang keine validen Daten rekrutierbar, so dass dies einen Ansatz für die geplante Studie darstellte.

Hypothese

Dyslipidämie führt zu einer reversiblen Erhöhung der absoluten Zahl inflammatorischer Monozyten im Blut, zu einer gesteigerten Aktivität von Thrombozyten und einem Anstieg der Pulswellengeschwindigkeit. Dabei soll gezeigt werden, dass eine Veränderung der Cholesterinwerte zu einer Änderung der oben beschriebenen Messwerte führt.

Methoden

Grundlegend soll diese Studie vor allem einen beobachtenden Charakter haben. So werden Patienten mit Hilfe der Lipid-Ambulanz ausgewählt, bei denen eine Ersteinstellung einer Cholesterin-senkenden Medikation oder die Anpassung einer bereits bestehenden Medikation vorgenommen werden soll. Bei diesen Patienten werden unterschiedliche Parameter vor und nach Behandlung angesehen. So werden die Zellen aus einer ohnehin im Rahmen der regulären Behandlung gewonnenen Blutprobe isoliert, die Plättchenaktivierung kann ebenfalls aus dem Vollblut bestimmt werden und es kommt im Weiteren zu nicht-invasiven Messungen von Blutdruck, Pulswellengeschwindigkeit und Intima-Media-Dicke mittels Ultraschall. Mit den so gewonnen Werten können eine Reihe von Markern bestimmt werden, die zur frühen Diagnostik einer Atherosklerose eingesetzt werden. Im Verlauf sollen diese nun kontrolliert und in Verbindung mit den neuen Parametern aus der Zellzahlbestimmung gebracht werden. Auf diese Weise könnte auf längere Sicht die einfache Differenzierung der Monozytensubpopulationen als Risikomarker bei der Entstehung einer Arterienverkalkung verifiziert und validiert werden.

Ethik

Jeder Proband wird vor der Teilnahme an dieser Studie selbstverständlich nach seinem Einverständnis gefragt. Und nur wenn dieses gegeben ist und auch die medizinischen Parameter mit den Einschlusskriterien des Ethikantrages und des Studienprotokolls übereinstimmen, kann ein Patient an dieser Studie teilnehmen. Zudem werden dem Probanden keine zusätzlichen invasiven Untersuchungen zugemutet. Sein Nachteil ist lediglich ein Zeitaufwand von ca. 10 bis 15 Minuten an den entsprechenden Untersuchungstagen. Als Vorteil ist zudem die besonders intensive Überwachung des Patienten im Rahmen der Studie zu werten.

Dauer

Die Anwendungsbeobachtung soll zunächst auf drei Jahre begrenzt bleiben. Je nach Ergebnislage wird eine Erweiterung im Sinne einer neuen Klinischen Studie angestrebt.

Datenschutz

Selbstverständlich werden alle von einem Patienten gewonnen Daten nach dem regulären Datenschutzgesetz behandelt. Zudem wird jeder Patient pseudonymisiert und bekommt eine ID zugewiesen. Auf diese Weise ist es nur dem Studienleiter und behandelndem Arzt möglich, diese Anonymisierung aufzuheben. Bei Probenmessungen und Auswertungen werden im Anschluss nur die IDs erscheinen. Sollte es nach Abschluss der Studie zu Gutachterkommentaren kommen, die einen Einschluss bislang unberücksichtigter Daten rechtfertigen, so können diese nur vom Studienleiter und behandelnden Arzt durch Entschlüsselung nacherhoben 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 atheroskerotischen 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.

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. Dafür ist der Eintritt in die Phase I der klinischen Prüfung für das Jahr 2014 geplant.

Quelle: www.carolustherapeutics.com

Bauliche Entwicklungen

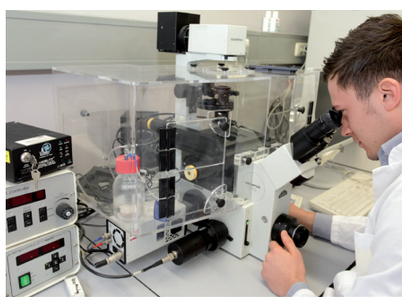
Im historischen Gebäude an der Pettenkoferstr. 9b wurde in den Jahren 2012 und 2013 zahlreiche Umbaumaßnahmen durchgeführt. Insbesondere wurde die EDV Einrichtung komplett erneuert, einschließlich eines neuen Serverraums und einer WLAN Versorgung aller drei Obergeschoße. Zusätzlich wurde auch die Zahl der Steckdosen zur Stromversorgung in allen Labor- und Büroräumen erhöht. Die Labor- und Büroräume wurden neu gestrichen und die Laboreinrichtung erneuert.


Blick entlang der Pettenkoferstraße im Jahr 1906

Sanierungsarbeiten im 1. Obergeschoß

Im Rahmen der W2-Berufung von Prof. Sabine Steffens wurden im Frühjahr und Sommer 2013 die Labore im 1. Stock des Biochemie-Gebäudes unter Leitung des Architekten Heribert Eibicht vom Staatlichen Bauamt saniert.
In den Räumen 1106 und 1108 wurden die Wandanstriche erneuert, neue Arbeitsplatten für Schreibplatz und Laborarbeitsflächen eingebaut und zahlreiche Reparaturarbeiten an Labormöbeln und Spülbecken durchgeführt. Somit wurden ein großes Labor mit mehreren Arbeitsflächen sowie ein Funktionsraum für verschiedene Geräte wie Biacore, Attune II Durchflusszytometer und Light Cycler PCR Maschinen eingerichtet. Zusätzlich wurde der Raum 1109 für die Aufstellung eines mit Klimakammer ausgestatteten Fluoreszenzmikroskops vollständig saniert. Zur Erneuerung des Bodenbelags musste der Estrich erneuert werden. Für die optimale Nutzung des Raumes erhielten die Wände einen dunklen Anstrich. Neue Labormöbel und ein Sicherheits-Gasschrank zur sachgemäßen Lagerung von Gasflaschen für Zellkultur und Mikroskop-Klimakammer wurden aufgestellt. Weiter erfolgt der Einbau einer Klimatisierung in den Räumen 1106 und 1109, um eine Überwärmung bedingt durch die verschiedenen Geräte zu vermeiden.

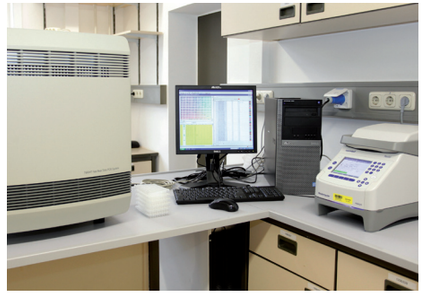

Biacore Gerät in Raum 1106


Arbeit am Fluoreszenzmikroskop in Raum 1109

Sanierungsarbeiten im 2. und 3. Obergeschoß

Im Rahmen der Neuanschaffung eines Laser-Mikrodissektionssystems (LMD7000, Fa. Leica) wurde der beherbergende Raum 1209 vollständig renoviert, einschließlich eines neuen Bodens, neuer Labormöbel, einer Verdunkelung und Klimaanlage.
Zur Aufstellung des PCR Systems 7900 HT (Applied Biosystems) wurde auch der Raum 1206 ebenfalls mit neuen Labormöbeln, einer Verdunkelung und einer Klimaanlage ausgestattet.
Ferner wurde im dritten Obergeschoß der Seminarraum komplett neu gestaltet. Es wurden die Wände gestrichen, ein neuer Teppichboden verlegt, Arbeitsplätze für wissenschaftliche Mitarbeiter und Doktoranden eingerichtet und ein großer Konferenztisch einschließlich eines Beamers und einer Leinwand eingebracht.

Laser-Mikrodissektionssystem LMD7000 in dem neu renovierten Raum 1209



PCR System 7900HT (Applied Biosystems) in dem renovierten Raum 1206 im 2. Obergeschoß

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.

The research group FOR809 is investigating 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 aim of FOR809 is 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)

Translational strategies for prevention and treatment of coronary heart disease

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 (DZHK). 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 Heart Alliance Centre as part of the German Cardiovascular Research Centre (DZHK)

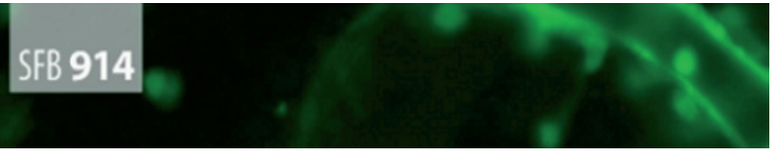
The Munich research area is the ideal site to address these goals, as it combines excellent basic and clinical research on the disease mechanisms and interventions to prevent and treat CHD. In particular, Munich provides the nation's leading cardiovascular framework with regards to the conduct of large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

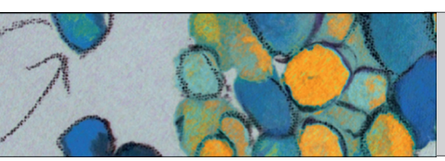
DFG Sonderforschungsbereich 914



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



SFB 1054 Control and Plasticity al Cell-Fate Decisions in the Immune System

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 cell 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 received an Advanced Investigator Grant from the European Research Council (ERC). Weber's ERC project started in 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 Euro, 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.

NWO VICI Grant for Atherosclerosis

Netherlands Organisation for Scientific Research

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."

Geplanter DFG Sonderforschungsbereich 1123

Atherosclerosis - Mechanisms and Networks of Novel Therapeutic Targets

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 31.12.2013	Drittmittelfinanzierung 31.12.2013
Institutsdirektor	1	1	
Professoren	6	6	
Arbeitsgruppenleiter	9	6	3
Post-Doktoranden	18	5	13
Doktoranden	32	1	31
nichtwissenschaftliche Mitarbeiter	26	15	11
Gesamt	**91**	**34**	**58**

Zahlen im Bereich des klinisch tätigen Personals

Berufsbezeichnung	Gesamtzahl	Haushaltsfinanzierung 31.12.2013	Drittmittelfinanzierung 31.12.2013
Chefarzt	1	1	
Oberärzte	2	2	
Assistenzärzte	1	1	
nichtärztliche Mitarbeiter	5	4	1
Gesamt	**9**	**8**	**1**

Aufgrund von überlappenden Aufgabenverteilungen in hauptsächlich wissenschaftlich tätigem oder vornehmlich klinisch arbeitendem Personal, beläuft sich die Gesamtzahl der Mitarbeiter auf **100** Personen. In dieser Zahl enthalten sind ebenfalls Mitarbeiter, die über Stipendien finanziert werden und/oder eine 50-75%-Teilzeitanstellung am IPEK ausüben.

Mitarbeiter

Alard, Jean-Eric, PhD

Badmann, Tobias
Bauer, Andrea
Bidzhekov, Kiril, Dr. rer. hum. biol.
Blanchet, Xavier, PhD
Blay, Richard, M. Phil.
Böhlig, Barbara
Bretzke, Eva
Bürger, Christina
Busygina, Kristina

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

Dandl, Angelika
de Jong, Renske
Deppe, Janina
Döring, Yvonne, Dr. rer. nat.
Drechsler, Maik, Dr. rer. nat.

Egea Alonso,Virginia, Dr. rer. nat.

Faußner, Alexander, PD Dr. rer. nat.
Feische, Gesa
Forstner, Jürgen
Friese, Henrik

Geißler, Claudia
Gerdes, Norbert, Dr. rer. nat.
Gimpfl, Christiane
Grubenbauer, Caroline

Haberbosch, Markus
Hartmann, Heike
Hartmann, Petra, Dipl. Troph.
Hartwig, Helene, Dipl. Biol.
Herrle, Corinna
Heyll, Kathrin
Horckmans, Michael, Dr. biol.
Hristov, Michael, PD Dr. med.
Jamasbi, Janina, Apothekerin
Jansen, Yvonne

Karshovska, Ela, Dr. rer. biol. hum.
Kramp, Birgit, Dipl. Biol.

Langer, Marcella, Dr. rer. nat.
Lemnitzer, Patricia
Leschner, Jasmin, Dipl. Biol.
Li, He, Dr.
Lievens, Dirk, PhD
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
Moshkova, Irina, Dipl.-Ing.
Mus, Mümine

Natarelli, Lucia, MSc
Nazari-Jahantigh, Maliheh, MSc
Neideck, Carlos
Neth, Peter, PD Dr. rer. nat.

Ortega Gomez, Almudena, Dr.

Paulin, Nicole
Pawig, Lukas
Pellicena, Paula
Pilz, Veronika
Pitsch, Thomas
Popp, Tanja, Dr. rer. nat.
Projahn, Delia, Dr. rer. nat.

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

Santovito, Donato, Dr. med.
Saroyan, Lusine
Schaffer, Sabine
Schiener, Maximilian, Dipl. Chem.
Schmitt, Martin, Dipl. Biol.
Schmitz, Susanne
Schober, Andreas, Univ.-Prof. Dr. med.
Seidl, Cornelia
Siess, Wolfgang, Univ.-Prof. Dr. med.
Silvestre-Roig, Carlos, PhD
Simon, Stefan
Söhnlein, Oliver, Univ.-Prof. Dr. Dr. med.
Spitz, Charlotte
Steffens, Sabine, Univ.-Prof. Dr. rer. nat.
Stöger, Brigitte
Streicher, Sabine
Subramanian, Pallavi, Dr. rer. nat.

v. Hundelshausen, Philipp, Dr. med.
v. Oheimb, Kathrin
Vershinina, Ksenia

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

Yin, Changjun, Dr. rer. nat.

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

Publikationen

2012

	n	IF Summe	IF Mittelwert
Gesamt	55	290.5	5.8
Erst-/Seniorautorschaften IPEK	35	200.7	6.3

	n	IF Summe	IF Mittelwert
Originalarbeiten	35	200.7	6.3
Erst-/Seniorautorschaften IPEK	19	122.6	6.8

	n	IF Summe	IF Mittelwert
Übersichtsarbeiten	20	89.8	5.0
Erst-/Seniorautorschaften IPEK	17	78.1	5.6

Original Articles

Bidzhekov K, Gan L, Denecke B, Rostalsky A, Hristov M, Koeppel TA, Zernecke A, Weber C. microRNA expression signatures and parallels between monocyte subsets and atherosclerotic plaque in humans. Thromb Haemost 2012;107:619-25. IF 5.044

Bras G, Bochenska O, Rapala-Kozik M, Guevara-Lora I, Faussner A, Kozik A: Extracellular aspartic protease SAP2 of Candida albicans yeast cleaves human kininogens and releases proinflammatory peptides, Met-Lys-bradykinin and des-Arg9-Met-Lys-bradykinin. Biol Chem 2012;393:829-39. IF 2.965

Brauner R, Johannes C, Ploessl F, Bracher F, Lorenz RL. Phytosterols reduce cholesterol absorption by inhibition of 27-hydroxycholesterol generation, liver X receptor activation, and expression of the basolateral sterol exporter ATP-binding cassette A1 in Caco-2 enterocytes. J Nutr 2012;142:981-9. IF 3.916

Cardilo-Reis L, Gruber S, Schreier SM, Drechsler M, Papac-Milicevic N, Weber C, Wagner O, Stangl H, Soehnlein O, Binder CJ. Interleukin-13 protects from atherosclerosis and modulates plaque composition by skewing the macrophage phenotype. EMBO Mol Med 2012;4:1072-86. IF 10.333

Djafarzadeh R, Sauter M, Notohamiprodjo S, Noessner E, Goyal P, Siess W, Wörnle M, Ribeiro A, Himmelein S, Sitter T, Nelson PJ. Recombinant GPI-anchored TIMP-1 stimulates growth and migration of peritoneal mesothelial cells. PLoS One 2012;7:e33963. IF 4.092

Döring Y, Soehnlein O, Drechsler M, Shagdarsuren E, Chaudhari S, Meiler S, Hartwig H, Hristov M, Koenen RR, Hieronymus T, Zenke M, Weber C, Zernecke A. Hematopoietic interferon regulatory factor 8-deficiency accelerates atherosclerosis in mice. Arterioscler Thromb Vasc Biol 2012;32:1613-23. IF 6.368

Döring Y, Drechsler M, Wantha S, Kemmerich K, Lievens D, Vijayan S, Gallo RL, Weber C, Soehnlein O. Lack of neutrophil-derived CRAMP reduces atherosclerosis in mice. Circ Res 2012;110:1052-6. IF 9.489

Döring Y, Manthey H, Drechsler M, Lievens D, Megens RTA, Soehnlein O, Busch M, Manca M, Koenen RR, Pelisek J, Daemen MJ, Lutgens E, Zenke M, Binder CJ, Weber C, Zernecke A. Auto-antigenic protein-DNA complexes stimulate plasmacytoid dendritic cells to promote atherosclerosis. Circulation 2012;125:1673-83. IF 14.739

Egea V, Zahler S, Rieth N, Neth P, Popp T, Kehe K, Jochum M, Ries C. Tissue inhibitor of metalloproteinase-1 (TIMP-1) regulates mesenchymal stem cells through let-7f microRNA and Wnt/β-catenin signaling. Proc Natl Acad Sci USA 2012;109:e309-16. IF 9.681

Faussner A, Schüssler S, Feierler J, Bermudez M, Pfeifer J, Schnatbaum K, Tradler T, Jochum M, Wolber G, Gibson C.: Binding characteristics of [(3) H]-JSM10292: a new cell membrane-permeant non-peptide bradykinin B(2) receptor antagonist. Br J Pharmacol 2012;167:839-53. IF 0.500

Grismayer B, Sato S, Kopitz C, Ries C, Soelch S, Schmitt M, Baretton G, Krüger A, Luther T, Kotzsch M, Magdolen V. Overexpression of the urokinase receptor splice variant uPAR-del4/5 in breast cancer cells affects cell adhesion and invasion in a dose-dependent manner and modulates transcription of tumor-associated genes. Biol Chem 2012;393:1449–1455. IF 2.965

Grommes J, Alard JE, Drechsler M, Wantha S, Mörgelin M, Kuebler WM, Jacobs M, von Hundelshausen P, Markart P, Wygrecka M, Preissner KT, Hackeng TM, Koenen RR, Weber C, Soehnlein O. Disruption of platelet-derived chemokine heteromers prevents neutrophil extravasation in acute lung injury. Am J Respir Crit Care Med 2012;185:628-36. IF 11.080

Grommes J, Mörgelin M, Soehnlein O. Pioglitazone attenuates endotoxin induced acute lung injury by reducing neutrophil recruitment. Eur Respir J 2012;40:416-423. IF 5.895

Grommes J, Vijayan S, Drechsler M, Hartwig H, Mörgelin M, Dembinski R, Jacobs M, Koeppel TA, Binnebösel M, Weber C, Soehnlein O. Simvastatin reduces endotoxin-induced acute lung injury by decreasing neutrophil recruitment and radical formation. PLoS One 2012;7:e38917. IF 4.092

Hamesch K, Subramanian P, Li X, Dembowsky K, Chevalier E, Weber C, Schober A. The CXCR4 antagonist POL5551 is equally effective as sirolimus in reducing neointima formation without impairing re-endothelialisation. Thromb Haemost 2012;107:356-68. IF 5.044

Hristov M, Schmitz S, Nauwelaers F, Weber C. A flow cytometric protocol for enumeration of endothelial progenitor cells and monocyte subsets in human blood. J Immunol Methods 2012;381:9-13. IF 2.203

Kolben T, Peröbner I, Fernsebner K, Lechner F, Geissler C, Ruiz-Heinrich L, Capovilla S, Jochum M, Neth P. Dissecting the impact of Frizzled receptors in Wnt/β-catenin signaling of human mesenchymal stem cells. Biol Chem 2012;393:1433-47. IF 2.965

Megens RT, Vijayan S, Lievens D, Doering Y, van Zandvoort MA, Grommes J, Weber C, Soehnlein O. Presence of luminal neutrophil extracellular traps in atherosclerosis. Thromb Haemost 2012;107:597-8. IF 5.044

Nazari-Jahantigh M, Wei Y, Noels H, Akhtar S, Zhou Z, Koenen RR, Heyll K, Gremse F, Kiessling F, Grommes J, Weber C, Schober A.J MicroRNA-155 promotes atherosclerosis by repressing Bcl6 in macrophages. J Clin Invest 2012;22:4190-202 IF 13.069

Peröbner I, Karow M, Jochum M, Neth P. LRP6 mediates Wntβ-catenin signaling and regulates adipogenic differentiation in human mesenchymal stem cells. Int J Biochem Cell Biol 2012;44:1970-82. IF 4.634

Postea O, Vasina EM, Cauwenberghs S, Projahn D, Liehn EA, Lievens D, Theelen W, Kramp BK, Dragomir Butoi E, Soehnlein O, Heemskerk JW, Ludwig A, Weber C, Koenen RR. Contribution of platelet CX3CR1 to platelet-monocyte complex formation and vascular recruitment during hyperlipidemia. Arterioscler Thromb Vasc Biol 2012;32:1186-93. IF 6.368

Poti F, Costa S, Bergonzini V, Galletti M, Pignatti E, Weber C, Simoni M, Nofer JR. Effect of sphingosine 1-phosphate (S1P) receptor agonists FTY720 and CYM5442 on atherosclerosis development in LDL receptor deficient (LDL-R(-/-)) mice. Vasc Pharmacol 2012;57:56-64. IF 1.986

Redondo S, González-Rocafort A, Navarro-Dorado J, Ramajo M, Hristov M, Gordillo-Moscoso A, Reguillo F, Carnero M, Martinez-Gonzalez J, Rodríguez E, Weber C, Tejerina T. Decreased pre-surgical CD34+/CD144+ cell number in patients undergoing coronary artery bypass grafting compared to coronary artery disease-free valvular patients. J Cardiothorac Surg 2012;7:2. IF 1.187

Rohwedder I, Montanez E, Beckmann K, Bengtsson E, Dunér P, Nilsson J, Soehnlein O, Fässler R. Plasma fibronectin deficiency impedes atherosclerosis progression and fibrous cap formation. EMBO Mol Med 2012;4:564-76. IF 10.333

Rowinska Z, Zander S, Zernecke A, Jacobs M, Langer S, Weber C, Merx MW, Koeppel TA. Non-invasive in vivo analysis of a murine aortic graft using high reslolution ultrasound microimaging. Eur J Radiol 2012;81:244-49. IF 2.606

Schuh A, Kroh A, Konschalla S, Liehn EA, Sobota RM, Biessen EA, Bot I, Sönmez T, Schober A, Marx N, Weber C, Sasse A. Myocardial regeneration by transplantation of modified endothelial progenitor cells expressing SDF-1 in a rat model. J Cell Mol Med 2012;16:2311-20. IF 4.125

Schuh A, Sasse A, Konschalla S, Kroh A, Merx MW, Weber C, Liehn EA. Repetitive transplantation of different cell types sequentially improves heart function after infarction. J Cell Mol Med 2012;16:1640-1647. IF 4.125

Schwartz V, Krüttgen A, Weis J, Weber C, Ostendorf T, Lue H, Bernhagen J. Role for CD74 and CXCR4 in clathrin-dependent endocytosis. Eur J Cell Biol 2012;91:435-449. IF 2.806

Van de Vijver P, Schmitt M, Suylen D, Scheer L, Thomassen MC, Schurgers LJ, Griffin JH, Koenen RR, Hackeng TM. Incorporation of disulfide containing protein modules into multivalent antigenic conjugates: generation of antibodies against the thrombin-sensitive region of murine protein S. J Am Chem Soc 2012;134:19318-21. IF 9.907

Review articles and Commentaries

Bampalis VG, Annette Brantl S, Siess W. Why and how to eliminate spontaneous platelet aggregation in blood measured by multiple electrode aggregometry. J Thromb Haemost 2012;10:1710-4. IF 5.044

Blanchet X, Langer M, Weber C, Koenen RR, von Hundelshausen P. Touch of chemokines. Front Immunol 2012;3:175. IF 0.500

Döring Y, Noels H, Weber C. The use of high-throughput technologies to investigate vascular inflammation and atherosclerosis.Arterioscler Thromb Vasc Biol 2012;32:182-95. IF 6.368

Döring Y, Zernecke A. Plasmacytoid dendritic cells in atherosclerosis. Front Physiol 2012;3:230. IF 0.500

Egea V, Schober A, Weber C. Circulating miRNAs: messengers on the move in cardiovascular disease. Thromb Haemost 2012;108:590-1 IF 5.044

Kamchybekov U, Figulla HR, Gerdes N, Jung C. Macrophage migration inhibitory factor is elevated in obese adolescents. Arch Physiol Biochem 2012;118:204-9. IF 0.500

Kanzler I, Liehn EA, Koenen RR, Weber C. Anti-inflammatory therapeutic approaches to reduce acute atherosclerotic complications. Curr Pharmaceut Biotechnol 2012;13:37-45. IF 2.805

Karshovska E, Weber C. Atherosclerosis: cell biology and lipoproteins - New mechanistic links in atherosclerosis: chemokines mediating the effects of lipids, platelets and dendritic cells. Curr Opin Lipidol 2012;23:400-1. IF 6.086

Liehn E, Bucur O, Weber C. Role of microparticles as messengers enhancing stem cell activity after genetic engineering. Circ Res 2012;111:265-267. IF 9.489

Lip GY, Weber C. Welcome to a new year in Thrombosis and Haemostasis. Thromb Haemost 2012;107:1-2. IF 5.044

Lutgens E, Leiner T, Weber C. RANK(L)-ing biomarkers as surrogates for coronary calcium score. Thromb Haemost 2012;107:3. 3. IF 5.044

Matusik P, Guzik B, Weber C, Guzik TJ. Do we know enough about the immune pathogenesis of acute coronary syndromes to improve clinical practice? Thromb Haemost 2012;108:443-56. IF 5.044

Nazari-Jahantigh M, Wei Y, Schober A. The role of microRNAs in arterial remodelling. Thromb Haemost 2012;107:611-8. IF 5.044

Projahn D, Koenen RR. Platelets: key players in vascular inflammation. J Leukoc Biol. 2012;92:1167-75. IF 4.992

Raffetseder U, Liehn EA, Weber C, Mertens PR. Role of cold shock Y-box protein-1 in inflammation, atherosclerosis and organ transplant rejection. Eur J Cell Biol 2012;91:567-75. IF 2.806

Schober A, Siess W. Lysophosphatidic acid in atherosclerotic diseases. Br J Pharmacol. Br J Pharmacol 2012;167:465-82. IF 4.409

Soehnlein O. Multiple roles for neutrophils in atherosclerosis. Circ Res 2012;110:875-88. IF 9.489

Stöger JL, Gijbels MJ, van der Velden S, Manca M, van der Loos CM, Biessen EA, Daemen MJ, Lutgens E, de Winther MP :Distribution of macrophage polarization markers in human atherosclerosis. Atherosclerosis 2012;225:461-8. IF 3.794

Weber C, Lip GY. Highlights and hot topics from 2011 in Thrombosis and Haemostasis. Thromb Haemost 2012;107:196-9. IF 5.044

Zernecke A, Weber C. Improving the treatment of atherosclerosis by linking anti-inflammatory and lipid modulating strategies. Heart 2012;98:1600-6. IF 4.223

Book Chapters

Noels H, Bernhagen J, Weber C (2012) MIF in atherosclerosis. In The MIF Handbook, p. 321-346, edited by R. Bucala, World Scientific Publishing. ISBN: 978-981-4335-35-5

Schober A, Zhou Z, Weber C (2012) Smooth muscle progenitor cells: A novel target for the treatment of vascular disease? In Muscle: Fundamental biology and mechanisms of disease. ISBN: 978-012-3815-10-1

2013

	n	IF Summe	IF Mittelwert
Gesamt	56	346.2	7.2
Erst-/Seniorautorschaften IPEK	31	189.6	6.5

	n	IF Summe	IF Mittelwert
Originalarbeiten	36	237.1	7.9
Erst-/Seniorautorschaften IPEK	14	100.7	7.7

	n	IF Summe	IF Mittelwert
Übersichtsarbeiten	20	109.1	6.1
Erst-/Seniorautorschaften IPEK	17	88.9	5.6

Original articles

Akthar S, Gremse F, Kiessling F, Weber C, Schober A. CXCL12 promotes the stabilization of atherosclerotic lesions mediated by smooth muscle progenitor cells in mice. Arterioscler Thromb Vasc Biol 2013;33:679-86. IF 6.338

Asare Y, Shagdarsuren E, Schmid J, Tilstam PV, Grommes J, El Bounkari O, Schütz AK, Weber C, de Winther MP, Noels H, Bernhagen J. Endothelial CSN5 impairs NF-κB activation and monocyte adhesion to endothelial cells and is highly expressed in human atherosclerotic lesions. Thromb Haemost 2013;110:141-52. IF 6.094

Badr Eslam R, Lang IM, Koppensteiner R, Calatzis A, Panzer S, Gremmel T. Residual platelet activation through protease-activated receptors (PAR)-1 and -4 in patients on P2Y12 inhibitors. Int J Cardiol 2013;168:403-6. IF 5.509

Borissoff JI, Otten JJ, Heeneman S, Leenders P, van Oerle R, Soehnlein O, Loubele ST, Hamulyák K, Hackeng TM, Daemen MJ, Degen JL, Weiler H, Esmon CT, van Ryn J, Biessen EA, Spronk HM, ten Cate H. Genetic and pharmacological modifications of thrombin formation in apolipoprotein E-deficient mice determine atherosclerosis severity and atherothrombosis onset in a neutrophil-dependent manner. PLoS One 2013;8:e55784. IF 3.730

Bras G, Bochenska O, Rapala-Kozik M, Guevara-Lora I, Faussner A, Kamysz W, Kozik A. Release of biologically active kinin peptides, Met-Lys-bradykinin and Leu-Met-Lys-bradykinin from human kininogens by two major secreted aspartic proteases of Candida parapsilosis. Peptides 2013;48C:114-123. IF 2.522

Casanova-Acebes M, Pitaval C, Weiss L, Nombela-Arrieta C, Chèvre R, A-González N, Kunisaki Y, Zhang D, van Rooijen N, Silberstein L, Weber C, Nagasawa T, Frenette P, Castrillo A, Hidalgo A. Rhythmic modulation of the hematopoietic niche through neutrophil clearance. Cell 2013;153:1025-1035. IF 31.957

Fujita B, Strodthoff D, Fritzenwanger M, Pfeil A, Ferrari M, Goebel B, Figulla HR, Gerdes N, Jung C. Altered red blood cell distribution width in overweight adolescents and its association with markers of inflammation. Pediatr Obes 2013;8:385-91 IF 0.200

Ghosh M, van den Akker NM, Wijnands KA, Poeze M, Weber C, McQuade LE, Pluth MD, Lippard SJ, Post MJ, Molin DG, van Zandvoort MA. Specific visualization of nitric oxide in the vasculature with two-photon microscopy using a copper based fluorescent probe. PLoS One 2013;8:e75331. IF 3.730

Goyal P, Pandey D, Brünnert D, Hammer E, Zygmunt M, Siess W. Cofilin oligomer formation occurs in vivo and is regulated by cofilin phosphorylation. PLoS One 2013;8:e71769. IF 3.730

Guevara-Lora I, Blonska B, Faussner A, Kozik A. Kinin-generating cellular model obtained from human glioblastoma cell line U-373. Acta Biochim Pol 2013;60:299-305. IF 1.185

Heymans S, Corsten MF, Verhesen W, Carai P, van Leeuwen RE, Custers K, Peters T, Hazebroek M, Stöger L, Wijnands E, Janssen BJ, Creemers EE, Pinto YM, Grimm D, Schürmann N, Vigorito E, Thum T, Stassen F, Yin X, Mayr M, De Windt LJ, Lutgens E, Wouters K, de Winther MP, Zacchigna S, Giacca M, van Bilsen M, Papageorgiou AP, Schroen B. Macrophage microRNA-155 promotes cardiac hypertrophy and failure. Circulation 2013;128:1420-32. IF 15.202

Kanzler I, Tuchscheerer N, Steffens G, Simsekyilmaz S, Konschalla S, Kroh A, Simons D, Asare Y, Schober A, Bucala R, Weber C, Bernhagen J, Liehn EA. Differential roles of angiogenic chemokines in endothelial progenitor cell-induced angiogenesis. Basic Res Cardiol 2013;108:310. IF 5.904

Klingenberg R*, Gerdes N*, Badeau RM, Gisterå A, Strodthoff D, Ketelhuth DF, Lundberg AM, Rudling M, Nilsson SK, Olivecrona G, Zoller S, Lohmann C, Lüscher TF, Jauhiainen M, Sparwasser T, Hansson GK. Depletion of FOXP3+ regulatory T cells promotes hypercholesterolemia and atherosclerosis. J Clin Invest 2013;123:1323-34. IF 12.812

Kramp BK, Megens RT, Sarabi A, Winkler S, Projahn D, Weber C, Koenen RR, von Hundelshausen P. Exchange of extracellular domains of CCR1 and CCR5 reveals confined functions in CCL5-mediated cell recruitment. Thromb Haemost 2013;110:795-806. IF 6.904

Kumar N, Ippel H, Weber C, Hackeng T, Mayo KH. Protein lysine N(zeta) alkylation and O-phosphorylation mediated by DTT-generated reactive oxygen species. Protein Sci 2013;22:327-46. IF 2.735

Lenglet S, Thomas A, Soehnlein O, Montecucco F, Burger F, Pelli G, Galan K, Cravatt B, Staub C, Steffens S. Fatty Acid amide hydrolase deficiency enhances intraplaque neutrophil recruitment in atherosclerotic mice. Arterioscler Thromb Vasc Biol 2013;33:215-23. IF 5.615

Leschner J, Wennerberg G, Feierler J, Bermudez M, Welte B, Kalatskaya I, Wolber G, Faussner A. Interruption of the ionic lock in the bradykinin b2 receptor results in constitutive internalization and turns several antagonists into strong agonists. J Pharmacol Exp Ther 2013;344:85-95. IF 3.891

Liehn EA, Kanzler I, Konschalla S, Kroh A, Simsekyilmaz S, Sönmez TT, Bucala R, Bernhagen J, Weber C. Compartmentalized protective and detrimental effects of endogenous migration-inhibitory factor mediated by CXCR2 in a mouse model of myocardial ischemia/reperfusion. Arterioscler Thromb Vasc Biol 2013;33:2180-6. IF 6.338

Lievens D, Habets KL, Robertson AK, Laouar Y, Winkels H, Rademakers T, Beckers L, Wijnands E, Boon L, Mosaheb M, Ait-Oufella H, Mallat Z, Flavell RA, Rudling M, Binder CJ, Gerdes N, Biessen EA, Weber C, Daemen MJ, Kuiper J, Lutgens E. Abrogated transforming growth factor beta receptor II (TGFβRII) signalling in dendritic cells promotes immune reactivity of T cells resulting in enhanced atherosclerosis. Eur Heart J 2013;34:3717-27. IF 14.097

Lundberg AM, Ketelhuth DF, Johansson ME, Gerdes N, Liu S, Yamamoto M, Akira S, Hansson GK. Toll-like receptor 3 and 4 signalling through the TRIF and TRAM adaptors in hematopoietic cells promotes atherosclerosis. Cardiovasc Res 2013;99:364-73. IF 5.940

Manthey HD, Cochain C, Barnsteiner S, Karshovska E, Pelisek J, Koch M, Chaudhari SM, Busch M, Eckstein HH, Weber C, Koenen RR, Zernecke A. CCR6 selectively promotes monocyte mediated inflammation and atherogenesis in mice. Thromb Haemost 2013;110:1267-77. IF 6.094

Molica F, Burger F, Thomas A, Staub C, Tailleux A, Staels B, Pelli G, Zimmer A, Cravatt B, Matter CM, Pacher P, Steffens S. Endogenous cannabinoid receptor CB1 activation promotes vascular smooth muscle cell proliferation and neointima formation. J Lipid Res 2013;54:1360-8. IF 0.500

Nakahata AM, Mayer B, Neth P, Hansen D, Sampaio MU, Oliva ML. Blocking the proliferation of human tumor cell lines by peptidase inhibitors from bauhinia seeds. Planta Med 2013;79:227-35. IF 2.348

Oral H, Kanzler I, Tuchscheerer N, Curaj A, Simsekyilmaz S, Sönmez TT, Radu E, Postea O, Weber C, Schuh A, Liehn EA.CXC chemokine KC fails to induce neutrophil infiltration and neoangiogenesis in a mouse model of myocardial infarction. J Mol Cell Cardiol 2013;60:1-7. IF 5.148

Petzold T, Ruppert R, Pandey D, Barocke V, Meyer H, Lorenz M, Zhang L, Siess W, Massberg S, Moser M. β1 integrin-mediated signals are required for platelet granule secretion and hemostasis in mouse. Blood 2013;122:2723-31. IF 9.060

Potì F, Gualtieri F, Sacchi S, Weißen-Plenz G, Varga G, Brodde M, Weber C, Simoni M, Nofer JR. KRP-203, sphingosine 1-phosphate receptor type 1 agonist, ameliorates atherosclerosis in LDL-R-/- mice. Arterioscler Thromb Vasc Biol 2013;33:1505-12. IF 6.338

Schaffer S, Tandon R, Zipse H, Siess W, Schmidt A, Jamasbi J, Karshovska E, Steglich W, Lorenz R. Stereo specific platelet inhibition by the natural LXR agonist 22(R)-OH-cholesterol and its fluorescence labelling with preserved bioactivity and chiral handling in macrophages. Biochem Pharmacol 2013;86:279-85. IF 4.576

Soehnlein O, Drechsler M, Döring Y, Vijayan S, Lievens D, Hartwig H, Projahn D, Koenen RR, Hristov M, Lutgens E, Zernecke A, Weber C. Distinct functions of chemokine receptor axes in the atherogenic mobilization and recruitment of classical monocytes. EMBO Mol Med 2013;5:471-81. IF 7.795

Strodthoff D, Lundberg AM, Agardh HE, Ketelhuth DF, Paulsson-Berne G, Arner P, Hansson GK, Gerdes N. Lack of invariant natural killer T cells affects lipid metabolism in adipose tissue of diet-induced obese mice. Arterioscler Thromb Vasc Biol 2013;33:1189-96. IF 6.338

Strüßmann T, Tillmann S, Wirtz T, Bucala R, von Hundelshausen P, Bernhagen J. Platelets are a previously unrecognised source of MIF. Thromb Haemost 2013;10:1004-13. IF 6.094

Vasina EM, Cauwenberghs S, Staudt M, Feijge MA, Weber C, Koenen RR, Heemskerk JW. Aging- and activation-induced platelet microparticles suppress apoptosis in monocytic cells and differentially signal to proinflammatory mediator release. Am J Blood Res 2013;3:107-23. IF 0.200

Wantha S, Alard JE, Megens RT, van der Does AM, Döring Y, Drechsler M, Pham CT, Wang MW, Wang JM, Gallo R, von Hundelshausen P, Lindbom L, Hackeng TM, Weber C, Soehnlein O. Neutrophil-derived cathelicidin promotes adhesion of classical monocytes. Circ Res 2013;112:792-801. IF 11.861

Wei Y, Nazari-Jahantigh M, Chan L, Zhu M, Heyll K, Corbalán-Campos J, Hartmann P, Thiemann A, Weber C, Schober A. The microRNA-342-5p fosters inflammatory macrophage activation through an Akt1- and microRNA-155-dependent pathway during atherosclerosis. Circulation 2013;127:1609-19. IF 15.202

Wu Z, Curaj A, Fokong S, Liehn EA, Weber C, Lammers T, Kiessling F, van Zandvoort M. Rhodamine-loaded ICAM-targeted microbubbles for dual-modality imaging under controlled shear stresses. Circ Cardiovasc Imaging 2013;6:974-81. IF 5.795

Ziegler T, Horstkotte J, Schwab C, Pfetsch V, Weinmann K, Dietzel S, Rohwedder I, Hinkel R, Gross L, Lee S, Hu J, Soehnlein O, Franz WM, Sperandio M, Pohl U, Thomas M, Weber C, Augustin HG, Fässler R, Deutsch U, Kupatt C. Ziegler T, Horstkotte J, Schwab C, Pfetsch V, Weinmann K, Dietzel S, Rohwedder I, Hinkel R, Gross L, Lee S, Hu J, Soehnlein O, Franz WM, Sperandio M, Pohl U, Thomas M, Weber C, Augustin HG, Fässler R, Deutsch U, Kupatt C. Angiopoietin 2 mediates microvascular and hemodynamic alterations in sepsis. J Clin Invest 2013;123:3436–3445. IF 12.812

Zimmermann R, Krueger J, Filipoviá MR, Ivanoviá-Burmazoviá I, Calatzis A, Weiss DR, Eckstein R. A detailed examination of platelet function inhibition by nitric oxide in platelet-rich plasma and whole blood. Clin Lab 2013;59:629-38. IF 0.920

Review articles and Commentaries

Döring Y, Weber C, Soehnlein O. Footprints of neutrophil extracellular traps as predictors of cardiovascular risk. Arterioscler Thromb Vasc Biol. 2013;33:1735-6 IF 6.338

Drechsler M, Soehnlein O. The complexity of arterial classical monocyte recruitment. J Innate Immun. 2013 2013;5:358-66. IF 4.458

Drechsler M, Soehnlein O, Weber C. Nitric oxide-donating statins upgrade the benefits of lipid-lowering in vascular inflammation by desensitizing neutrophil activation. Cardiovasc Drugs Ther 2013;27:183-5. IF 2.673

Gerdes N, Winkels H, Weber C. Atherosclerosis: cell biology and lipoproteins - focus on anti-inflammatory mechanisms as therapeutic options. Curr Opin Lipidol 2013;24:187-188. IF 5.839

Karshovska E, Weber C, von Hundelshausen P. Platelet chemokines in health and disease. Thromb Haemost 2013;110:894-902. IF 6.094

Langer HF, Weber C, Gawaz M. The platelet - thrombosis and beyond. Thromb Haemost 2013;110:857-8. IF 6.094

Legein B, Temmerman L, Biessen EA, Lutgens E. Inflammation and immune system interactions in atherosclerosis. Cell Mol Life Sci 2013;70:3847-69. IF 5.615

Neth P, Nazari-Jahantigh M, Schober A, Weber C. MicroRNAs in flow-dependent vascular remodeling. Cardiovasc Res 2013;99:294-303. IF 5.940

Ortega-Gómez A, Perretti M, Soehnlein O. Resolution of inflammation: an integrated view. EMBO Mol Med 2013;5:661-74. IF 7.795

Preissner KT, Weber C. Go with the flow: the passion for vascular biology research. Thromb Haemost. 2013;109:366-367. IF 6.094

Seijkens T, Kusters P, Engel D, Lutgens E. CD40-CD40L: Linking pancreatic, adipose tissue and vascular inflammation in type 2 diabetes and its complications. Diab Vasc Dis Res 2013;10:115-22. IF 2.594

Soehnlein O. Myeloid cells in traffic. J Innate Immun 2013;5:301-3. IF 4.458

Soehnlein O, Swirski FK. Hypercholesterolemia links hematopoiesis with atherosclerosis. Trends Endocrinol Metab 2013;24:129-36. IF 8.901

von Hundelshausen P, Weber C. Chronic inflammation and atherosclerosis Dtsch Med Wochenschr 2013;138:1839-44 IF 0.500

Weber C, Lip G. Editors' Choice papers in Thrombosis and Haemostasis. Thromb Haemost 2013;109:170-173. IF 6.094

Weber C, Lip G. A Happy New Year 2013 for Thrombosis and Haemostasis… Thromb Haemost 2013;109:1-2. IF 6.094

Weber C. MicroRNAs - from basic mechanisms to clinical application in cardiovascular medicine. Arterioscler Thromb Vasc Biol 2013;33:168-9. IF 6.338

Wei Y, Nazari-Jahantigh M, Neth P, Weber C, Schober A. MicroRNA-126, -145, and -155: A therapeutic triad in atherosclerosis? Arterioscler Thromb Vasc Biol 2013;33:449-54. IF 3.629

Wei Y, Schober A, Weber C. Pathogenic arterial remodeling: the good and bad in microRNAs. Am J Physiol Heart Circ Physiol 2013;304:1050-9. IF 0.500

Ylä-Herttuala S, Bentzon JF, Daemen M, Falk E, Garcia-Garcia HM, Herrmann J, Hoefer I, Jauhiainen S, Jukema JW, Krams R, Kwak BR, Marx N, Naruszewicz M, Newby A, Pasterkamp G, Serruys PW, Waltenberger J, Weber C, Tokgözoglu L; ESC Working Group of Atherosclerosis and Vascular Biology. Stabilization of atherosclerotic plaques: an update. Eur Heart J 2013;34:3251-8. IF 14.097

Book Chapters

Koenen RR, Weber C (2013) Chemokines as therapeutic targets of atherosclerosis. In Atherosclerosis: Treatment and Prevention, edited by C. Weber & O. Söhnlein, Pan Stanford Publishing. ISBN: 978-981-4316-26-2. IF 0.500

Soehnlein O, Weber C (2013) Neutrophils and their granule proteins in the treatment of atherosclerosis. In Atherosclerosis: Treatment and Prevention, edited by C. Weber & O. Söhnlein, Pan Stanford Publishing. ISBN: 978-981-4316-26-2. IF 0.500
2011;106:757-62.

Impressum

Herausgeber:
Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten (IPEK)
August Lenz-Stiftung
Direktor Prof. Dr. Christian Weber
Pettenkoferstraße 8a & 9
80336 München
Web: www.kreislaufinstitut.de

Redaktion und Text:
Arbeitsgruppenleiter
Brigitte Stöger, Irina Moshkova
Prof. Dr. C. Weber

Gestaltung, Satz und Layout:
cachelle grafikdesign
Claudia Müller
Mail: cachelle.grafikdesign@googlemail.com
Web: www.cachelle-grafikdesign.de

Institut für Prophylaxe und Epidemiologie
der Kreislaufkrankheiten (IPEK)

August - Lenz - Stiftung

Experimental Vascular Medicine