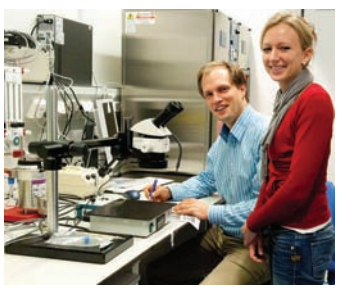
Team 2011: Philip Wenzel, MD, Maike Knorr, MD, and Colleagues, Department of Cardiology and Centre for Thrombosis and Haemostasis, Johannes Gutenberg University, Mainz, Germany



"We Are Building on Professor Thomas Münzel's Comprehensive Experience in Vascular Biology and Oxidative Stress"

Philip Wenzel, MD, junior research group leader and attending physician, and Maike Knorr, MD, clinical cardiology fellow, Department of Cardiology and Centre for Thrombosis and Haemostasis, Johannes Gutenberg University, Mainz, Germany, talk to Mark Nicholls.

Philip Wenzel, MD, junior group leader and attending physician, and Maike Knorr, MD, clinical cardiology fellow, Department of Cardiology and Centre for Thrombosis and Haemostasis, Johannes Gutenberg University, Mainz, Germany, are joint first authors of a recent article in *Circulation* titled "Lysozyme M-positive monocytes mediate angiotensin II-induced arterial hypertension and vascular dysfunction."[1] Dr Wenzel says, "The article tries to cover the full story, from an initial observation to finding a mechanistic insight. Time will tell whether other researchers find our work helpful in broadening the understanding of the causes of vascular inflammation and dysfunction." The article concludes that infiltrating monocytes with a proinflammatory phenotype and macrophages rather than neutrophils appear to be essential for angiotensin II-induced vascular dysfunction and arterial hypertension.

Dr Wenzel says, "We are building on the comprehensive experience in vascular biology and oxidative stress of Thomas Münzel [MD, chair, Department of Cardiology, Johannes Gutenberg University, see http://circ.ahajournals.org/content/117/21/f121.full. pdf+html] and his team. Their work demonstrated the principles of vascular dysfunction in nitrate tolerance,[2,3] hypercholesterolemia,[4,5] diabetes mellitus,[6] and angiotensin II-induced hypertension.[7] In 2006, we identified that redox sensitive aldehyde dehydrogenase 2 is regulated by superoxide and peroxynitrite and by the endogenous antioxidant lipoic acid. These mechanisms have implications for several disease states that involve mitochondrial oxidative stress."[8]

From left to right: Professor Münzel, head of cardiology and acting scientific director of the Centre for Thrombosis and Haemostasis; Dr Oelze, his postdoc; and Professor Daiber, head of the Molecular Cardiology Lab. Photographs courtesy of Dr Wenzel.

"We Have Diverse Scientific Backgrounds Resulting in Different, Stimulating Views on Specific Questions"

The research group working with Drs Wenzel and Knorr comprises several MD and PhD postdocs, 1 PhD student, 1 veterinary student, 3 technicians, and several undergraduates working on their MD theses. Dr Knorr says, "We have diverse scientific backgrounds—biochemistry, biology, medicine, veterinary medicine, and experienced technicians—resulting in different, stimulating views on specific questions. All members are extremely motivated, and working together is effective and also a lot of fun."

Basic scientist Sabine Kossmann, MSc, works on immune cells and their influence on arterial hypertension in different mouse models, whereas basic scientist Matthias Oelze, PhD, investigates streptozotocin-induced diabetes mellitus in a rat model and the influence of different nitrates on endothelial function and dysfunction. Susanne Karbach, MD, studies the role of interleukin-17 in the pathogenesis of arterial hypertension and endothelial function; Eberhard Schulz, MD, and Swenja Schuhmacher, PhD, investigate AMP-activated kinase in vascular dysfunction and oxidative stress; and Christian Becker, PhD, focuses on the role of T cells in immunomodulation, inflammation, and graft versus host disease.

Biochemist Andreas Daiber, PhD, heads the research to identify targeted antioxidant strategies. He has a strong background in redox chemistry, and his special interests include organic nitrates and their function in endothelial function and dysfunction. His methodology and analytical thinking support Drs Knorr and Wenzel and the rest of the team in their research. Dr Wenzel says, "Pharmacological activation of the powerful antiinflammatory and antioxidative enzyme heme oxygenase-1 can protect from nitrate

Coauthors of the 2011 Circulation *article[1] and members of the research team. From left to right: Susanne Karbach, Melanie Schwenk, Nir Yogev, Sabine Kossmann, Tanja Schönfelder, Thomas Münzel, Maike Knorr, Ari Waisman, Anja Conrad, Philip Wenzel, Katharina Perius, Christian Becker, Michael Hausding, Jessica Alber, and Swenja Kröller-Schön (born Schuhmacher). Photograph courtesy of Dr Wenzel.*

tolerance,[9] angiotensin-II induced vascular dysfunction,[10] and diabetes-associated vascular injury.[11] As another example, we were recently able to show that angiotensin-1 receptor blockade by telmisartan can protect from endothelial nitric oxide synthase uncoupling, which is another important source of superoxide formation in vascular dysfunction."[12]

The team collaborates with other clinical and scientific departments, including the Institute for Molecular Medicine in Mainz, headed by Professor Ari Waisman, which has generated a mouse strain that harbours a Cre inducible human diphtheria toxin receptor (iDTR) mouse.[13] Dr Wenzel explains, "When crossed to a cell-specific Cre line, it renders the respective cell type extremely susceptible to diphtheria toxin-mediated cell death, thereby permitting cell type-specific cell ablation in vivo. We have crossed the iDTR mouse to the LysMCre mouse. This mouse model allows the depletion of myelomonocytic cells via intraperitoneal injection of diphtheria toxin."

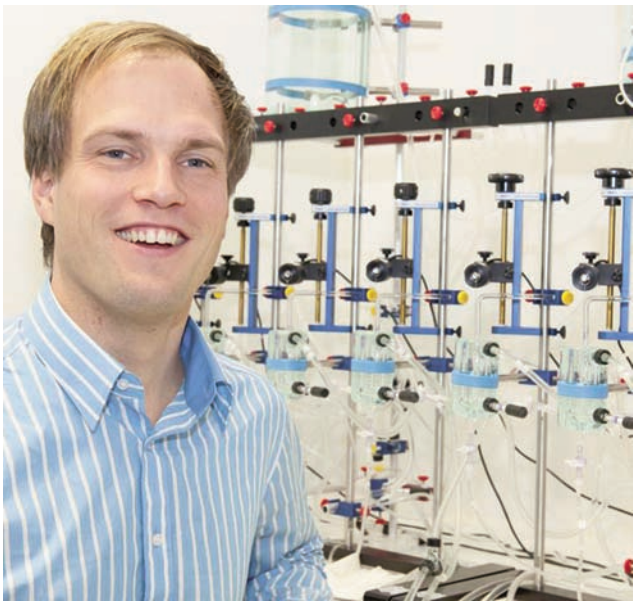
Head of the department, Professor Münzel, MD, leads several experimental and clinical science research groups and mentors the group with "great support and enlightening comments and advice." Dr Wenzel adds, "Professor Münzel knows many of the pioneers in the field of nitric oxide and oxidative stress research from personal collaborations and mentor–mentee relationships. In the past few years, he has established a fruitful scientific environment, and I am grateful to have the opportunity to pursue my research interest here in his department."

The group has recently moved its lab into the Centre for Thrombosis and Haemostasis in Mainz, which supports thrombosis and haemostasis research, treatment, and education (www.cth-mainz.de). It integrates the Departments of Clinical Chemistry, Pharmacology, Haematology, Cardiology/Angiology and Clinical Epidemiology, and it is scientifically headed by Professor Münzel, who will pass on the chair of scientific head to haemostaseologist Ulrich Walter, MD, in January 2012.

The research group is currently analysing the influence of myelomonocytic cells on remodelling after infarction in a left anterior descending coronary artery ligature mouse model. Dr Wenzel explains, "We want to follow up on the role of inflammatory monocytes in other relevant models of human disease, for instance, diabetes mellitus. In addition, we plan to investigate the modes of activation of inflammatory cells and their orchestrated response to angiotensin II in more detail." The work is funded by the German Research Foundation and the German Ministry of Education and Research.

Dr Wenzel studied medicine in Erlangen, Barcelona, Spain, and Hamburg, Germany, where he graduated in 2002, joining Professor Münzel's group in Hamburg in 2003 at the Department of Cardiology headed by Professor Thomas Meinertz, MD. Professor Münzel then took over the Department of Cardiology in Mainz in 2004. Dr Wenzel joined him and lives in Mainz with his wife and 3 young children. He says, "In the clinic I do interventional cardiology and see patients in the emergency room, chest pain unit, and outpatient clinic. At the Centre for Thrombosis and Haemostasis, I pursue my interests in vascular biology and act as a mentor for undergraduate and graduate students and fellows like Maike." In the future, he hopes to broaden knowledge about the interplay among inflammation, coagulation, and oxidative stress in vascular biology.

Dr Knorr studied medicine in Heidelberg, graduating in 2007. At university she developed a passion for cardiology and joined the cardiology research team of Norbert Frey, MD, for her medical doctorate, where she focussed on



Dr Wenzel in the lab. He says, "I try to combine scientific work with patient care. I encourage young fellows to pursue a topic of their own, which ideally is embedded in a larger scientific consortium or group initiative. It is important to take responsibility for grant applications and teaching and supervision of undergraduates early. There should be a thread visible through the scientific workplan and career development. This is the task for a good mentor. Maike demonstrated that sticking to that thread can be a good model of personal and scientific development." Photograph courtesy of Dr Wenzel.

hypertrophic cardiomyopathy before she began practising medicine in Professor Münzel's department in Mainz in 2008 as a cardiology fellow. After establishing her clinical career, she successfully applied for a grant from "Stiftung Mainzer Herz" to investigate the role of myelomonocytic cells in the pathogenesis of angiotensin II-induced arterial hypertension within Dr Wenzel's German Research Foundation-funded project.

Dr Knorr says, "I am interested in the cellular and molecular mechanisms of different clinical features and became more and more aware of the importance of the immune system and its different cell types on vascular function and dysfunction, resulting in vascular diseases such as coronary artery disease. Although these pathologies are clinically so important and preeminent, it constitutes a relatively new area of research and still little is known about the exact underlying molecular mechanisms." She aims to specialise in interventional cardiology, while scientifically investigating the influence of immune cells in the pathogenesis of different cardiac diseases.

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