Call for PhD students 2016

The international PhD Program “Endothelium in Health and Disease” of the Medical Faculty Carl Gustav Carus, TU Dresden, Germany, in collaboration with the German Academic Exchange Service (DAAD) opens a call for 2 PhD positions in cutting-edge research on the regulatory functions of the vascular endothelium in health and disease. We are looking for highly motivated and talented students with a passion for science. Candidates must demonstrate an excellent performance in their previous academic education. Candidates from developing countries are encouraged to apply.

Requirements:
- MSc, MD or equivalent degree in Physiology, Biochemistry, Biomedicine, Biology or related sciences
- Excellent English language skills and the ambition to work in a dynamic international environment

Required application materials:
- Motivation letter describing the applicant’s work experience and research goals; please indicate your favorite research project (A or B), the project’s description is below
- Resume/CV showing the applicant’s background, professional skills, a list of publications and oral and poster presentations as well as additional achievements (scholarships, awards etc.)
- Transcripts including all undergraduate level certificates and university degrees. All documents, which are not in German, must be accompanied by a legally certified English translation.
- Addresses of at least two potential referees

We offer a top-level research environment, a comprehensive educational and mentoring program, courses in cutting-edge methods and soft skills.

Application deadline for the next term: December 15, 2015

Please send your application as one pdf-file via e-mail to:

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Description of PhD projects

Project A:

“Effects of bioactive peptides on vascular system and tissue”

Hypertension affects more than 50% of the population above an age of 50 years in nearly all countries worldwide and is a major threat to health (Rogers 2002). High blood pressure leads to a number of complications e.g. vessel stiffening, arterial remodeling, peripheral arterial occlusive disease, coronary heart disease, cardiac infarction, cardiac hypertrophy, heart failure and stroke (European Society of Cardiology Guidelines 2003). The renin angiotensin system (RAS) is a key factor for long term blood pressure regulation in man (Johnston et al. 1992). Thus, pharmaceutical angiotensin converting enzyme (ACE) –inhibitors are often used in the treatment of hypertension.

Our group has addressed new aspects related to improved understanding of factors controlling blood vessel remodeling in response to angiotensin (Kopaliani et al., 2014; Otto et al., 2015) and started to investigate the potential role of bioactive natural peptides in modulation of the renin angiotensin system (Martin et al., 2015, Kaiser et al., 2015). Our previous work shows that tryptophan-containing dipeptides, originating from enzymatic hydrolysates of α-lactalbumin, e.g. Ile-Trp (IW) and Trp-Leu (WL) show good ACE inhibition in vitro with an IC50 of 0.7 µM and 10 µM, respectively (Martin et al., 2008). Furthermore, antihypertensive and cardio-protective effects of IW and whey protein hydrolysates enriched with IW were documented in spontaneously hypertensive rats after oral intake (Martin et al., 2015). Most recently, we also provided evidence for the ACE-inhibiting effect of IW in humans after oral intake (Kaiser et al., 2015) and documented that tryptophan containing dipeptides undergo plasma hydrolysis in humans with pronounced inter-individual heterogeneity (Khedr et al., 2015).

The aim of this project is to critically assess the biodistribution of tryptophan containing dipeptides and tissue/organ related remodeling effects. The project will use human plasma samples and, in addition, plasma and tissue samples obtained in mice models. The goals are to assess the kinetics of hydrolysis of tryptophan containing dipeptides in various tissues and organs, and to assess their effects on the pattern of 1) angiotensinogen-derived peptides, 2) further compounds of the renin-angiotensin-aldosterone system, and 3) kallikrein-derived peptides. As a reference for the effects of tryptophan-containing dipeptides pharmacological ACE inhibitors are studied. Samples will be generated in different mouse models with a normal and an activated renin-angiotensin-aldosterone axis, respectively. In addition, plasma and urine samples of human volunteers will be studied. The project will use comprehensive and technically advanced
analytical tools (HPLC/UPLC) and mass spec analysis. For an improved and comprehensive data analysis mathematical modeling will be used. The effects of ACE inhibition will be assessed using biochemical methods (e.g. ACE activity, downstream signaling pathways), physiological methods (e.g. blood pressure, pulse wave velocity, kidney function) and structure analysis (e.g. histology, extracellular matrix proteins, immuno-histochemistry).

The project will be divided in three work packages reflecting a total of 3 research years. In the first, analytical techniques will be optimized for comprehensive analysis of human and mouse samples. Furthermore, a comprehensive set of human plasma samples after oral application of tryptophan containing dipeptides will be generated and analyzed. The second package includes all experimentation with mouse models and the complex analysis of plasma and tissue samples generated in these models. This package is largely allocated to the second year but will extend into year 3. Work on mathematical model analysis will start during year 2 and become the focus in year 3.

References:
S. Khedr, M. Martin, A. Deussen. Inhibitory Efficacy and Biological Variability of Tryptophan Containing Dipeptides on Human Plasma Angiotensin Converting Enzyme Activity. J Hypertension 2015; 4:2 (open access)
Otto S, Deussen A, Zatschler B, Müller B, Barth K, Kasper M, Morawietz H, Kopaliani I. A Novel role of endothelium in activation of latent pro-membrane type 1 matrix metalloproteinase (Pro-MT1MMP) and pro-matrix metalloproteinase-2 (Pro-MMP2) in rat aorta. (Submitted for publication)
Peng X, Xiong YL, Kong B. Antioxidant activity of peptide fractions from whey protein hydrolysates as measured by electron spin resonance. Food Chemistry 2009; 113: 196-201

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Project B:

Nox4, endothelial function and atherosclerosis

Atherosclerosis is an inflammatory disease of the vessel wall which can lead to heart attack and stroke. The role of reactive oxygen species in the pathogenesis of atherosclerosis is not well-understood (Müller & Morawietz 2009). Initial studies supported a proatherosclerotic role of the superoxide anion producing NADPH oxidase (Nox) 2 complex (Rueckschloss et al. 2001). The role of other Nox isoforms in atherosclerosis is less clear (Drummond & Sobey 2014). We could show that Nox4 is the major Nox isoform in endothelial cells and regulated by laminar shear stress (Goettsch et al. 2011). This isoform mainly produces H2O2 and might mediate protective mechanism in the vessel wall. The impact of Nox4 on atherosclerosis is currently not known. Therefore, we want to study the impact of Nox4 knockout on atherosclerosis in a mouse model with high-fat diet. In addition, we want to analyze the impact of obesity and coronary artery disease on structure and function of arterial vessels of patients undergoing coronary artery bypass grafting.

Our lab is interested in the regulation of Nox isoforms Nox2 and Nox4 in endothelial cells for many years (Rueckschloss et al. 2001, Müller & Morawietz 2009). Fine particulate matter and high-fat diet regulated oxidative stress and endothelial function in mouse models (Kampfrath et al. 2011). Furthermore, we could show a downregulation of Nox2 by therapy with statins and AT1 receptor blockers in arterial vessels of patients with coronary artery disease (Rueckschloss et al. 2001, Müller & Morawietz 2009). Recently, we started working with Nox4 knockout mice. In the last months we have generated a novel model with genetic deletion of Nox4 in a proatherogenic LDL receptor knockout background and started to analyze the impact of high-fat diet on endothelial function and atherosclerosis.

This project will be divided in 3 parts. In the first part of the proposal, we want to use the novel model to study the impact of Nox4 on atherosclerosis. C57BL/6 (wild-type), LDL receptor (LDLR) knockout, Nox4 knockout and Nox4/LDLR double knockout mice will be fed a high-fat diet (60 % kcal from fat) of 20 weeks. In these mice, we will analyze the formation of atherosclerotic plaques in serial sections of the aortic arch. In the second part, we will analyze in these mice the arterial expression of pro- and anti-atherosclerotic and -inflammatory genes and the impact on endothelial function. In this way, we want to analyze the impact of Nox4 and high-fat diet on endothelial function and atherosclerosis. In the third part, we want to study the impact of obesity and coronary artery disease on endothelial function in internal mammary arteries of patients undergoing coronary artery bypass grafting surgery. The specimens are kindly provided by the Department of Cardiac Surgery, University Heart Center Dresden (Prof. Matschke).
The vascular function in human vessels will be assessed in the lab of Andreas Deussen using a Mulvany myograph. In addition, we would like to analyze the expression of Nox2, Nox4, pro- and anti-atherosclerotic and inflammatory genes and to perform histological examinations of human arteries. Changes in gene expression, vascular function and structure are likely to occur in vessels from patients with severe coronary artery disease. These data will supplement experimental data from project part 1 and 2 and should lead to additional publications.

In summary, we aim to get in this project a better understanding of the role of Nox4 in atherosclerosis.

References:
Drummond GR, Sobey CG. Endothelial NADPH oxidases: which NOX to target in vascular disease? Trends Endocrinol Metab. 2014;25(9):452-63.