CSC-RUB PhD Project Proposal

Title: Identification of new molecular targets in lung injury

Sector of research: Dr.rer.nat. (PhD)

Degree awarded: Biosciences

Keywords: lung physiology, respiration, lung function, lung injury, ARDS, ventilator-induced lung injury, inflammation, cytokines, airway regulation, airway resistance, airway compliance, G protein signaling, animal research, experimental research, medicine and health, population and health, human health and disease, major new drug discovery, GPCR, qPCR, Western Blotting, ELISA, severe hypoxemia, critical care medicine, mechanical ventilation, diffuse alveolar damage, endothelial lung injury, epithelial lung injury, pharmacological therapies, respiratory failure, respiratory mechanics, volutrauma, positive-pressure ventilation, LPS-induced lung injury, flexivent, spirometry

Supervisor of PhD project:
Prof. Dr. med. Daniela Wenzel, Department of Systems Physiology, Faculty of Medicine, Ruhr University Bochum, e-mail: daniela.wenzel@ruhr-uni-bochum.de

Research focus of supervisor:
Our lab focuses on lung and cardiovascular physiology. Hereby, we are interested to identify signaling molecules in common diseases with the long-term goal to develop new therapeutic approaches. We are applying various standard methods from cell culture techniques to molecular biology, immunostaining and microscopy. In addition, we use a variety of ex vivo and in vivo approaches for the investigation of mouse tissues such as isometric force measurements of vessels and airways, precision-cut lung slices, the isolated perfused lung model, whole body plethysmography, flexivent spirometry and pressure-volume catheter measurements. These techniques are also applied in mouse disease models for lung injury, asthma bronchiale, pulmonary hypertension, COPD, heart hypertrophy, atherosclerosis and aortic aneurysm. Thus, we cover a wide spectrum of experimental methods to investigate the mechanisms of lung and cardiovascular diseases that are major health problems worldwide.

Publications:
53 publications (original research articles in peer-reviewed international journals), H index 26

1x Nature, 1x Circulation, 1x Cell Stem Cell, 1 x Cell Metab, 1 x Circulation Research, 2x Neuron, 1x Mol Cell, 1x ACS Nano, 1x Nat Commun, 2x PNAS, 2x Hypertension

Second Supervisor of PhD project:
Prof. Dr. Andreas Reiner, Cellular Neurobiology, Faculty of Biology and Biotechnology, Ruhr University Bochum

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<th>Summary of research plan</th>
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| **Background:** Lung injury as a result of extensive long-lasting mechanical ventilation and/or during acute respiratory distress syndrome (ARDS) are common but often under-recognized problems with high mortality rate in intensive care units. Pathophysiological changes in the lung are characterized by compromised lung function, enhanced vascular permeability and inflammation. In order to improve survival new molecular targets have to be identified that enable the development of innovative treatment options.  

**Study objective:** In an experimental approach using different transgenic mouse lines (constitutive, conditional knockouts) related to G protein-coupled receptors (GPCRs)/G protein signaling new molecular targets for the treatment of lung injury will be identified. Hereby, a variety of innovative in vitro, ex and in vivo approaches will be applied. Students will be trained in experimental techniques, they will learn to interpret the results in the context of lung (patho)physiology, they will generate high-quality scientific presentations and they are introduced to scientific writing.  

**Expected Results:** We hypothesize that molecular targets of the G protein-related signaling pathways contribute to lung injury by mechanical ventilation or ARDS. We will identify the contribution of single molecules to the pathophysiology of these diseases and this should result in new pharmacologic treatment options. The experimental results will be published in high-ranking international peer-reviewed scientific journals.  

**Methods:**  
Ventilator-induced lung injury will be induced in mice by established protocols for the flexivent ventilator. In order to mimic ARDS in mouse the well-characterized LPS-induced lung injury mouse model will be used. Airway responsiveness (pressure-volume loops, airway resistance, compliance) will be analyzed by the gold-standard flexivent method in vivo. Infiltration of immune cells will be investigated in broncho-alveolar lavage and lung histology. Cytokines will be quantified using qPCR, Western Blotting and ELISA. Furthermore, pulmonary permeability will be determined by analysis of the lung weight and dextran perfusion.  

**Candidate Requirements:** The successful candidate is highly motivated and able to work independently. She/he needs to hold an MSc degree related to life sciences. Very good English language skills and the willingness to work with mice are prerequisites. Experience with animal experiments is welcome.  

**Motivation for CSC application:** Students will be trained in experimental techniques, they will learn to interpret the results in the context of lung (patho)physiology, they will generate high-quality scientific presentations and they are introduced to scientific writing. The successful candidate will be enrolled in the International Graduate School of Biosciences at the Ruhr-University Bochum to expand his/her interdisciplinary experience.