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Pulmonary and extrapulmonary vascular injury in respiratory infections

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Short summary:

Pneumonia is a leading cause of morbidity and mortality world-wide. In the lung, severe pneumonia can trigger an acute respiratory distress syndrome (ARDS), a potentially fatal lung disease characterized by hyperinflammation and endothelial barrier failure. In the systemic circulation, pneumonia can drive chronic vascular disease as suggested by epidemiological studies. In our work, we aim to identify mechanism of pulmonary and extrapulmonary vascular injury in pneumonia, and to identify potential therapeutic targets for novel treatment strategies.

In a series of recent studies, we have identified dysregulation of endothelial ion channels as a driver of vascular barrier failure and permeability-type lung edema in

response to respiratory pathogens. Specifically, we identified cystic fibrosis transmembrane conductance regulator (CFTR) as an important regulator of endothelial barrier function and homeostasis that is, however, rapidly lost from lung endothelial cells in pneumonia. The resulting increase in endothelial chloride concentration inhibits the Cl- sensitive with-no-lysine kinase 1 (WNK1) which acts as a natural inhibitor of the central endothelial barrier regulating cation channel transient receptor potential vanilloid 4 (TRPV4). The resulting disinhibition of TRPV4 in turn drives lung edema formation as well as pneumonia-associated morbidity and mortality. As such, pharmacological approaches targeting TRPV4 or CFTR present promising strategies to alleviate lung injury in respiratory infections.

In parallel, pneumonia induces distinct changes in systemic vessel structure and function which extend and progress far beyond the duration of initial respiratory infection. Following infection with Streptococcus pneumoniae, atheroprone ApoE-/- mice develop characterized distinct, time-dependent changes in vascular reactivity, vessel wall morphology, and atherosclerotic plaque burden that predispose for cardiovascular events. Respective analyses of underlying mechanisms are ongoing.

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Biosketch:

Current position: Director and Full Professor, Institute of Physiology, Charité – Universitätsmedizin Berlin, Germany (since 2016)

Previous positions

1994-1997 Residency, Institute for Surgical Research and Deptartment of Surgery, University of Munich, Germany

1997-1999 DFG Research Fellow, Lung Vascular Biology Lab, Columbia University, New York, NY

2000-2002 Postdoctoral Research Fellow, Institute for Surgical Research, University of Munich, Germany

2002-2008 Associate Professor for Physiology and Pathophysiology, Charité Universitätsmedizin Berlin, endowed by the German Heart Institute Berlin, Germany

since 2008 Staff Scientist, St. Michael´s Hospital, Toronto, Canada

since 2015 Associate Full Professor, Departments of Surgery & Physiology, University of Toronto, Canada

2014-2016 Founding Director; Critical Care and Injury Research Centre, Toronto

Training

1987-1994 Medical School, University of Munich, Germany

1993-1994 Internships at Royal Devon & Exeter Hospital, University of Bristol, UK
Brigham and Women´s Hospital, Harvard Medical School, Boston, MA.

Relevant publications:

1. M.M. Kucherenko, P. Sang, J. Yao, T. Gransar, S. Dhital, J. Grune, S. Simmons, L. Michalick, D. Wulsten, M. Thiele, O. Shomroni, F. Hennig, R. Yeter, N. Solowjowa, G. Salinas, G.N. Duda, V. Falk, N. Vyavahare, W.M. Kuebler*, C. Knosalla*: Elastin stabilization restores pulmonary arterial biomechanics and prevents pulmonary hypertension in left heart disease. *Nat Commun* 14: 4416, 2023 (IF 16.6). *shared senior authorship.,

2. Y. Fan, A.M. Zhang, X.L. Wu, Z.S. Huang, K. Kontogianni, K. Sun, W.L. Fu, N. Wu, W.M. Kuebler, F.J.F. Herth: Transbronchial needle aspiration combined with cryobiopsy in the diagnosis of mediastinal diseases: a multicentre, open-label, randomised trial. *Lancet Respir Med* 11: 256-264, 2023 (IF 76.2).

3. L. Erfinanda, L. Zou, B. Gutbier, L. Kneller, S. Weidenfeld, L. Michalick, D. Lei, K. Reppe, L.G. Teixeira Alves, B. Schneider, Q. Zhang, C. Li, D. Fatykhova, P. Schneider, W. Liedtke, E. Sohara, T.J. Mitchell, A. Grube, A. Hocke, S. Hippenstiel, N. Suttorp, A. Oleschewski, M.A. Mall, M. Witzenrath, W.M. Kuebler: Loss of endothelial CFTR drives barrier failure and edema formation in lung infection and can be targeted by CFTR potentiation. *Sci Transl Med* 14: eabg8577, 2022 (IF 17.1).

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6. M.J. McVey, M. Maishan, A. Foley, R. Turki, E.J. Roach, R. Deschler, S. Weidenfeld, N.M. Goldenberg, C.M. Khursigara, W.M. Kuebler: Pseudomonas aeruginosa membrane vesicles cause endothelial barrier failure and lung injury. *Eur Respir J* 59: 2101500, 2022 (IF 24.3).

7. P. Georg, R. Astaburuaga-García, L. Bonaguro, S. Brumhard, L. Michalick, L.J. Lippert, T. Kostevc, C. Gäbel, M. Schneider, M. Streitz, V. Demichev, I. Gemünd, M. Barone, P. Tober-Lau, E.T. Helbig, D. Hillus, L. Petrov, J. Stein, H.P. Dey, D. Paclik, C. Iwert, M. Mülleder, S.K. Aulakh, S. Djudjaj, R.D. Bülow, H.E. Mei, A.R. Schulz, A. Thiel, S. Hippenstiel, A.E. Saliba, R. Eils, I. Lehmann, M.A. Mall, S. Stricker, J. Röhmel, V.M. Corman, D. Beule, E. Wyler, M. Landthaler, B. Obermayer, S. von Stillfried, P. Boor, M. Demir, H. Wesselmann, N. Suttorp, A. Uhrig, H. Müller-Redetzky, J. Nattermann, W.M. Kuebler, C. Meisel, M. Ralser, J.L. Schultze, A.C. Aschenbrenner, C. Thibeault, F. Kurth, L.E. Sander, N. Blüthgen, B. Sawitzki; PA-COVID-19 Study Group: Complement activation induces excessive T cell cytotoxicity in severe COVID-19. *Cell* 185: 493-512, 2022 (IF 64.5).

8. M.J. McVey, M. Maishan, C. Spring, M. Kim, A. Tabuchi, V. Srbely, A. Takabe-French, C. Arenz, J.W. Semple, W.M. Kuebler: Platelet-derived extracellular vesicles mediate transfusion-related acute lung injury by imbalancing the bioactive sphingolipid rheostat. *Blood* 137: 690-701, 2021 (IF 25.5).

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10. Y. Fan, X. Gu, B. Ghanim, W. Klepetko, P. Solymosi, G. Kwapiszewska, W.M. Kuebler: Inhibition of TWIST1 attenuates smooth muscle cell proliferation and lung vascular remodeling in pulmonary hypertension. *Am J Respir Crit Care Med* 202: 1283-1296, 2020 (IF 21.4).