BIH & MDC Focus Area Translational Vascular Biomedicine – Focus Groups

Based on the results of the kickoff workshop on December 10, 2019, the Steering Committee has defined three overarching goals for the Focus Area *Translational Vascular Biomedicine* that will be further refined and developed in dedicated focus groups. The focus groups are open to interested scientists and clinicians from BIH/Charité/MDC with a commitment to research in vascular biology. Regular meetings (e.g., monthly) of the focus groups will be established.

Focus Group 1: Define and Treat Endothelial Dysfunction and Inflammation

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Relevant diseases and unmet clinical needs:

Endothelial dysfunction and inflammation are currently best studied in the context of larger vessels, in particular in atherosclerosis and vasculitis. Endothelial dysfunction of the microvasculature, however, is poorly understood, and its nature and pathogenesis are involved in a wide variety of end organ damage, e.g., heart failure and/or coronary microcirculatory dysfunction.

There is an urgent need to define and develop translational approaches for new treatments for these disease entities. Clinical needs arise frequently in patients with hypertension, pulmonary hypertension, vascular dementia, retinopathies, kidney damage, peripheral ischemic diseases, heart failure with preserved ejection fraction, coronary microcirculatory dysfunction (CMD) and several neurological diseases. The spectrum is likely even larger and exemplifies the most urgent clinical need to find diagnostic tools, biomarkers, model systems and deep phenotyping approaches to define and ultimately treat microvascular endothelial dysfunction. Biomarkers will need to be established and tested towards their utility for systemic versus local endothelial dysfunction. Pathways need to be identified that are suitable for target discovery and mechanistic research to ultimately define treatment concepts.

Goals:

One of the most urgent specific goals of this focus group is to establish an agreement on the central definitions of endothelial dysfunction as a common basis for diagnosis and treatment. In a joint approach, experimental studies and clinical phenotyping will need to broaden our understanding of the biomarker and disease space of endothelial dysfunction.

Mid-term goals will need to identify diseases caused by endothelial dysfunction using clinical cohorts and experimental models, and map out exactly where and how translation from model to clinical disease management can be established.

Mid- to long-term goals will need to establish a phenotyping platform, based on the agreed definitions, biomarkers and clinical parameters allowing firm assessment of how drugs affect

phenotype – paving the way towards translational and clinical studies/trials following successful pre-clinical development.

A further goal of particular significance will be to determine endothelial heterogeneity in endothelial dysfunction, not only between organs, but also within a given vascular bed, to assess and understand whether particular cell populations are more prone to dysfunction or provide a particular opportunity for treatment. This includes gaining an understanding of endothelial plasticity in acute and chronic disease progression. For example, if only a subpopulation of endothelial cells adopts dysfunctional phenotypes, does progression include population expansion, derailed repair or endothelial-to-endothelial signaling? What is the role of biomechanics, bioenergetics and immunovascular homeostasis in the development and progression of endothelial dysfunction?

Achieving these goals will benefit from improved 3D-models, including organoids, with interdisciplinary approaches that enable measuring and manipulating biomechanics and bioenergetics. It will benefit from studies into human and experimental animal models of naturally occurring dysfunction, as well as from access to biopsies from many tissues to assess endothelial phenotypes in a clinical setting. Multidimensional imaging, meaning structural and functional imaging to gain knowledge of detailed microvascular bed structure, perfusion, label-free imaging of metabolism, ROS, and inflammatory parameters, will greatly facilitate knowledge gain. Similarly, single cell omics and spatial transcriptomics will need to be developed for microvascular characterization to understand heterogeneity and complexity. All efforts in this area will require quality assessment and data management to assure that clinical and experimental data can be used to adequately define endothelial dysfunction.

Milestones:

- Joint publication of agreed definitions of endothelial dysfunction, the phenotype and disease pathophysiology
- Agreed structure of a phenotyping platform and data management
- Understanding the systemic nature of endothelial dysfunction, i.e., established understanding whether phenotyping the microvasculature in one organ is predictive for the status of the microvasculature in another organ
- 2–3 biomarkers with strong diagnostic value
- First *ex vivo* model for drug development
- Reliable animal model
- Proof of concept for treatment avenue