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 3: Build and Instrumentalize Vascularized Organoids

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Relevant diseases and unmet clinical needs:

The research field of vascular biomedicine urgently needs novel human model systems to understand vascular biology in health and disease and identify possible targets for novel therapeutic approaches. The focus of the projects in this focus group is to develop such models and to provide/apply them together with the other two focus groups to address specific questions. The clinical need will co-evolve with capabilities (e.g., organ regeneration *in vivo*, organ survival after transplantation, revascularization). The activities of the group are not limited to specific types of organoids and will work on organoids derived from primary cells, adult and pluripotent stem cells as well as tumors. (This will include organoids from brain, liver, lung, kidney, pancreas and gut as well as tumor organoids.)

Goals:

Current stem cell-derived 3D organoid culture models are able to retain some cellular complexity and functionality of the human organs and can therefore bridge the gap between *in vitro* and *in vivo* research. Despite the potential of organoids to probe human biology and disease, it remains challenging to obtain fully developed and functional tissue due to the lack of vasculature in any of the current organoid models. The focus of the group is the improvement of organoid models by developing strategies and methods to add a vascular compartment. This will, for example, significantly reduce the necrotic core present in many types of organoids and improve organoid maturation.

There are several technological challenges to be addressed:

- A major challenge is to design a media which is favorable for the development of blood vessel-like structures and does not impair the development of the tissue-specific organoids.
- In view of the inter- and intra-organ heterogeneity of the endothelium, it is further of importance to identify and recognize suitable types of endothelial cells relevant for organoids of the different organs, e.g., by making use of single cell approaches. Upon identification of the

relevant endothelial cells, either protocols for their derivation form pluripotent or adult stem cells have to be developed (tissue-specific endothelial cells).

- To promote the growth of endothelial-like structures, the development of suitable culture conditions including biochemical conditions (e.g., culture medium that promotes vessel formation while not impairing organoid maturation and specific functionality) and mechanical/physical conditions (e.g., perfusion technology) is of great importance.

The challenge of creating vascularized organoids needs the application of a broad variety of technologies including organ-on-a-chip, micro-perfusion, bioprinting, biomaterials, imaging, *in silico* modeling and stem cell technology. Therefore these challenges have to be addressed in interdisciplinary teams including biologists, engineers, computational scientists and industry partners.

Goals:

Short-term goals:

- Formation of an interdisciplinary expert network to address the above mentioned challenges
- Development/optimization of protocols that promote the growth of organoids with an endothelial-like structure (identify the right endothelial cell type and a way to connect it to the perfusion system)
- Tissue-specific vascularization (assessment of the relevance of tissue-specific differences)
- Generation of specific endothelial cell types from stem cells
- Development/establishment of technology for perfused culture, generation of 3D scaffolds promoting vessel formation by, e.g., bioprinting and/or application of biomaterials
- Methods for organoid analysis of live and fixed specimens by, e.g., quantitative imaging, life cell/tissue imaging, spatial genomics, electrophysiology
- Improvement of data reproducibility (integration of all data, definition of parameters for quantification/assessment of heterogeneity)

Long-term goals:

- Gain understanding of micro-vascularization
- Gain understanding of spatial orientation and interaction within organs
- Implementation of a computational modeling platform
- Application of vascularized organoids as disease models to gain mechanistic insight, identify potential targets for treatments
- Automation of organoid generation, cultures systems and analysis to increase and enable screening approaches