Translation Hub - Organoids and Cell Engineering

The BIH Translation Hub "Organoids and Cell Engineering" is specifically devised to use **human cell based disruptive technologies**, to enable and facilitate the discovery, development and application of new diagnostic and therapeutic approaches for precision medicine. To achieve its mission, it is therefore based on two central areas of research:

1) The development and application of **advanced preclinical human model systems.** These model systems include human induced pluripotent stem cells (hiPSCs), adult/somatic stem cells, primary human cells and tissues as well as stem cell-derived cells applied in 2D, 3D and organoid culture models. Development of these cutting edge models will be supported by the utilization of disruptive technologies for their generation such as genome engineering, organoid culture, organ-on-a-chip technology and bioprinting, as well as for their analysis for instance via advanced microscopy and single cell sequencing. Especially in these advanced preclinical human model systems, cells as well as their gene-edited forms can be analyzed in a near-physiological environment considering a variety of additional aspects such as their vascularization or functional characteristics. Therefore, these model systems represent a crucial bridge between traditional 2D and *in vivo* model systems and are thus prime candidates for translational research.

2) The development and application of **cellular engineering techniques**, including both **genome and base engineering** as well as **cell engineering techniques**. **Genome and base engineering techniques** such as CRISPR/Cas9, TALENs or ZFNs will be used and further developed to genetically engineer human somatic cells and human primary or induced pluripotent stem cells, thus allowing the analysis of differentiation processes as well as patient- and disease-specific pathomechanisms. **Cell engineering techniques** for cell-based therapies comprise the genetic engineering of human immune cells to generate CAR T cells for cancer immunotherapy or the gene editing of mutations in patient cells (primary cells or adult stem cells), which can in turn be used as a basis to improve and develop a variety of personalized adoptive cell therapies and Advanced Therapy Medicinal Products (ATMPs) in general. The Hub will unite researchers who are investigating human stem cell and immune cell engineering, including all aspects that bear on the induction, isolation, expansion, genetic modification, transplantation, and functional monitoring of therapeutic cells as well as cell delivery, transfer and regulation of genes in human cells, or gene repair. This will strengthen the continuum between biological, translational, and clinical aspects of cell engineering and cell therapies.

In addition to the two main research topics, the Hub will also support the following activities:

- Microscopy using various imaging modalities (e.g. light sheet microscopy, high- and super-resolution microscopy, high-content and high-throughput microscopy and quantitative (3D) microscopy data analysis) is an enabling technology to study phenotypic alterations in organoid models quantitatively. Therefore, **development of a well-organized imaging community is a strategic priority.** Quantitative imaging (microscopy) of organoids / micro-tissues is currently vastly underrepresented in the BIH community. Therefore, development of organoid imaging and appropriate data analysis is a goal for the Translation Hub.

- In order to make primary tissues and cells available for model generation and as reference materials for model validation, it is of utmost importance for the BIH and translational research per se to establish a robust **pipeline for the acquisition and provision of fresh primary cells and tissue** from diseased and healthy donors. The Hub will support the establishment of this pipeline to become a permanent infrastructure for the BIH.

- Regarding single cell analysis, which is one of the state of the art methods for analysis of 3D cellular models next to imaging, the Hub will closely interact with the Omics Hub and the Focus area Single Cell Technologies.

- Another, yet unresolved limitation in 3D organoid models is the lack of a functional vasculature. Here the Hub will join forces with the Vascular Biomedicine Focus area to establish an interdisciplinary research environment, bringing together experts ranging from cell biologists to bio-engineers to enable discovery of a game changing solution. The developments within the Hub will also accelerate the implementation of the 3R principles to replace and reduce animal model systems in the translational pipeline.

Focusing on the development of the technologies mentioned above, the Translation Hub Organoids and Cell Engineering will enable and accelerate precision medicine approaches across medical disciplines.