Platform Framework Multiscale Omics

Preamble

The Research Platform Multiscale Omics investigates the genetic causes of diseases as well as the role of genes, gene variations and mutations and the microbiome in the development of progressive diseases. The characterization of gene variants in the DNA sequence of individuals and their association with phenotypic features is also highly relevant for translational research at BIH. This applies equally to the characterization of regulatory processes in biological models for a better understanding of pathogenetic mechanisms. These approaches are complemented by state-of-the-art proteomics and metabolomics to create a molecular picture of the disease.

Goals and expected benefits from the Platform Multiscale Omics

The BIH Platform Multiscale Omics develops and provides state-of-the art omics technologies at BIH.

To generate sustained added value, the platform should support the current demand of the local scientific community and enable new research questions within the mission of BIH such as risk factors or therapy responses in chronic diseases. A central approach to initiate specific projects will involve well characterized patient cohorts with (ideally longitudinal) collections of clinical phenotypes and biomaterials, and a data warehouse for joint data analysis.

To explore the full potential of such cohorts and to make the best use of the technologies and resources available, project proposals will be discussed and designed by an expert panel that joins representatives from all omics technologies as well as bioinformatics, biostatistics and clinicians. The coordinated and interdisciplinary approach that links omics technologies with cohorts and specific research questions will put BIH in a position to make substantial contributions to translational research and systems medicine.

The implementation of the aims outlined below should be defined in a five-year plan developed by representatives of all relevant platform stakeholders.

Proposed areas of activity

1. Expand service and infrastructure

The BIH Platform Multiscale Omics recognizes and supports the needs of the individual facilities and researchers to grow and develop in their own fields such that all members have the opportunity to become world-leading and to recruit and retain the best staff. Elements are:

- Establish an inventory of existing infrastructure and services including contacts of persons that have expertise in relevant fields.
- Implement standards for data harmonization (in cooperation with the Platform Digital Medicine), Omics analysis
- Standards for data sharing which will be developed in cooperation with the Platform Digital Medicine or Clinical-Translational Sciences.
- Develop and validate a standardized sample processing pipeline with the following components:
    - standardized asservation and dissection of tissue under frozen-section control (surgery and pathology)
    - processing for direct extraction of DNA, RNA, proteins and/or
    - tissue culture with perturbation experiments

    - useful multi-omics data sets for ‘standard’ analyses, (e.g. common diseases, rare diseases, cancer).
    - bioinformatics analysis and computational modeling
    - identification of functional alterations in tumors
    - integration of omics results with clinical and histopathological data
    - clinical interpretation (molecular tumor board)
    - impact on therapy and clinical follow-up documentation

- Support cooperative, targeted research by developing interfaces between individual units, a central portal for data upload and tools for joint data analysis of different omics data to discover general principles or to develop and train software.
- Identification of internal and external mechanisms of funding for joint staff that connect either two technology platforms or a platform and a research lab for tailored new method development and proof of concept studies that are useful for the entire BIH community.

2. Identify Research Areas

Establishing the infrastructures described above requires biomedical pilot projects that make use of multi-omics data generation and bioinformatics analysis. These research areas should be addressable by similar experimental modalities and offer novel synergistic potential. The following areas represent excellent disease-overarching topics for multiscale omics research:

- **Method development** should drive the platform competence towards emerging technologies and analysis techniques such as the diverse single cell techniques, labeling techniques for sequencing, 3D genomics, pooled (single-cell) screening, small input methods, imaging combined with omics, computational analysis of more complex data. Some of these methods are not readily applicable to translational research, but will be important in near future and ensure that this platform will become and remain cutting edge.

- **Inflammation** is an essential pathogenetic or disease-modifying principle in a wide range of multiple human diseases as well as in human aging. Large patient cohorts or healthy individuals accessible through the Charité clinical departments as well as the BIH-CRUs will be ideal to perform research projects on the plasticity of inflammatory responses to uniform stimuli, the exact contribution of individual cell types to tissue inflammation and the adaptation of the inflammatory host response to current and experimental treatment approaches.

- **Deranged genomics** due to mutational events is a hallmark of cancer and hereditary diseases, but also in diseases not caused by mutational events. What is insufficiently understood and crucial to advances in medicine are the multilevel functional consequences or deranged genomics on protein and metabolic level. More importantly, however, the adaptation of functional consequences during the career of a disease and under pressure of specific targeted treatments has not been sufficiently investigated in homogenous longitudinal patient cohorts. In cancer this would encompass longitudinal analysis of primary tumors, relapses after standard treatment and disease progression under experimental treatments. In hereditary diseases of high penetrance, crucial questions include organ site specific pathogenesis and mechanisms of disease chronification.

- **Rare genetic diseases** as models of common complex diseases. Many organ manifestations characteristic of severe chronic diseases are also observed in monogenic diseases. Despite their cause by mutations in a single gene, genetic diseases often present with highly variable disease severity. To a large extent, this variability is determined by modifier genes in the patient’s genetic background. The study of patient cohorts with well-defined rare genetic

diseases therefore provides a unique opportunity to identify modifier genes that may be implicated in the pathogenesis and serve as biomarker or novel therapeutic target of common complex diseases.

- **Patient-derived tumor tissue models** for genetic and functional analyses. In addition to aspects proposed for deranged genomics, models of patient-derived tissue cultures can be used with perturbation experiments with small molecule inhibitors and analyzed with subsequent phosphoproteomics to identify early (signaling-level) and later (expression-level) responses of pathologically altered networks to better understand and therapeutically exploit oncogenic mechanisms. These functional proteomic data can be related with genomic information to improve the predictive value of molecular profiling through omics-integrative bioinformatics and computational modeling.

- **defined patient cohort(s) with longitudinal clinical** data which evolve from the pilot projects and other initiatives.

3. Develop structures for collaboration and exchange

An efficient exchange of specialized knowledge and expertise will be critical for the successful development and use of the Platform Multiscale Omics. This exchange will be facilitated by a forum that joins local expertise from different fields to provide specialized knowledge and technical expertise necessary to guide project design and analysis of cohort studies. Potential areas of activity for this forum will be:

- Individual project-specific consultation and advice on the planning and conduct of the study including pre-analytical sample collection and preparation, and data analysis and storage in cooperation with the Clinical Study Center.
- Interdisciplinary discussion and assessment of more comprehensive projects, such as the application of multiple omics technologies in patient cohorts. The panel will meet on a regular basis (at least biannually) to jointly discuss the design and feasibility of proposed projects and provide feedback and advice to the lead investigators.
- Determine future requirements (research needs, infrastructure, staff and budget) to match demand for such a service based on focused group discussions with important stakeholders including Platform Heads, PIs and Clinicians.
- Assist the BIH Board of Directors in selecting proposed projects for funding.

The interdisciplinary expert panel will thus play an important role in exploring the full potential of the BIH Platform Multiscale Omics and putting the BIH in a position to make cutting-edge contributions to translational research and systems medicine.

4. Gain additional members

Identify additional members within Charité and MDC, also considering external recruits for BIH junior group position and partnerships with other omics platforms.