The Laboratory of Biomolecular Research (LBR[1])

Division of Biology and Chemistry, Paul Scherrer Institute (PSI)

The goal of the research at the LBR is to provide an *atomic level understanding* on how the structure and dynamics of proteins and their complexes control essential biological processes. Our mission aligns with one of PSI's main research focuses: The investigation of fundamental molecular mechanisms that determine human health and disease and exploring possible treatment methods.

In line with the mandate of the Division of Biology and Chemistry (BIO), we perform curiosity-driven, basic molecular biology research in the areas of cell division and signaling. Furthermore, we actively seek for possibilities to get engaged in applied research activities like, for example, drug discovery. Our research focusses on the structural analysis of challenging soluble and membrane-bound protein samples by using state-of-the-art X-ray crystallography techniques at the Swiss Light Source and SwissFEL, in combination with biophysical and modern electron microscopy methods.

Role of the LBR

The LBR provides high-impact biological projects and important structural biology expertise for the further development of the Swiss Light Source and the SwissFEL crystallography beamlines. For this, we implement novel technologies in sample preparation, handling and delivery, as well as in the acquisition and analysis of synchrotron and XFEL X-ray diffraction data. Our samples also foster collaborations with both the Laboratory of Nanoscale Biology and the Center for Radiopharmaceutical Research of the BIO division. When technology developed at the LBR becomes mature for commercial exploitation, we have a proven track record of spinning out such technology in start-up commercial enterprises.

We maintain an extensive network of both academic and industrial collaborations around the globe. These collaborations are important for ensuring that the PSI continues to operate at the forefront of biomolecular research and for showcasing the possibilities of its large-scale facilities for cutting edge structural biology research. Furthermore, we are well integrated within the university landscape of Switzerland through associations with the ETH Zürich and the University of Basel.

The LBR also contributes to the infrastructure and organization of the PSI. It hosts the Vocational Training and Chemical Management group, and runs PSI's Crystallization Facility together with the MX group of the Photon Science Division. Furthermore, several researchers of the LBR are active members of internal committees, including the PSI Scientific Advisory Board (FoKo), the PSI Equal Opportunity Committee and the PSI Personnel Committee.

Research areas of the LBR

Our primary focus of understanding the structure-function relationship of fundamental biological processes implies that we run a well-equipped research lab with strengths in molecular biology, biochemistry, biophysics and crystallography. To this end, we focus our projects on two challenging types of biological samples involved in cell division and signaling: Membrane proteins and biomolecular complexes. Currently, the LBR contains five research groups:

- The "Biomolecular Complexes" group of Prof. M. Steinmetz investigates how proteins and anticancer drugs regulate the microtubule cytoskeleton. Microtubules are dynamic protein filaments that play essential roles in cell division and cell polarity.

[1] Laboratorium für Biomolekulare Forschung; Laboratoire de Biologie Moléculaire

- The “Structural Biology of Membrane Proteins” group of Prof. G. Schertler (head of the Biology and Chemistry division) investigates G-protein coupled receptors (GPCRs) and their signaling complexes. GPCRs represent the largest family of membrane proteins, are essential modulators of external signals for a large variety of cellular processes and are very important drug targets.
- The “Applied Molecular Biology” group of Dr. R. Kammerer collaborates with industrial and academic partners on applied research projects by providing expertise in recombinant protein production and characterization. In addition, the group is interested in structural studies of proteins, with a focus on membrane proteins.
- The “Time-Resolved Crystallography” group of Dr. J. Standfuss investigates the dynamics of soluble and membrane proteins using serial crystallography and employing XFEL and synchrotron X-ray radiation.
- The “Mechanisms of Signal Transduction” group of Prof. V. Korkhov investigates the structure-function relationship of membrane proteins involved in transmembrane and intracellular signaling.

Research strategy 2018-2023

Our biological topics, cell division and signaling, will remain of major scientific and pharmaceutical importance in the foreseeable future. We will therefore continue developing our research program within these two research areas. In order to maintain and further advance our scientific excellence, it is paramount that we capitalize on our strengths in structural biology. Looking at the current developments, it is clear that several technologies are currently dramatically reshaping the field: time-resolved serial crystallography using XFEL X-ray radiation and cryo-electron microscopy.

Accordingly, an important focus of the LBR will be time-resolved structural analyses of proteins upon light activation as the laboratory is already a leading center in this area of structural biology research in Switzerland and beyond. In the future, we will implement new technologies like, for example, temperature jump and small molecule mixing experiments to trigger protein activation. This will allow accessing physiologically relevant but previously intractable conformational states of proteins using the technologies available at the SwissFEL. To further strengthen and increase the visibility of our activities in the area of XFEL, the LBR will continue operating and further develop the Biolab that provides support for sample delivery to users of SwissFEL.

Besides using XFEL technology, we will continue and further expand our efforts in X-ray crystallography at the Swiss Light Source. We will have a particular focus on the structural analysis of protein-ligand interactions, which typically relies on the availability of high resolution (i.e., <2.5 Å) data. We anticipate that such activities will foster new collaborations in particular with the private sector. Since computational modeling is essential in several stages of data analysis and interpretation, we will also strengthen our collaborations with computational modeling groups.

Notably, our protein systems are constantly increasing in complexity and flexibility, and at the same time are decreasing in abundancy and stability. Samples consisting of dynamic protein complexes are often beyond the capabilities of X-ray crystallography, but well suited for structural analysis by cryo-electron microscopy. We already acquired the necessary knowhow to perform cryo-electron microscopy experiments in the LBR. We are already closely collaborating with the Laboratory of Nanoscale Biology to further develop and use such technologies in our research programs. Together with our XFEL and X-ray crystallography efforts, these activities will allow the LBR to remain at the forefront and a center for modern structural biology research over the next decade.

M.O. Steinmetz, 18.6.2018