The Laboratory of Biomolecular Research[1]

Division of Biology and Chemistry, Paul Scherrer Institute

The Laboratory of Biomolecular Research (LBR) investigates fundamental molecular mechanisms that determine human health and disease, and explores resulting therapeutic opportunities. Specifically, the LBR aims to provide an atomic level understanding of how the structure and dynamics of proteins and their complexes control essential physiological processes. We perform curiosity-driven, basic molecular biology research in the areas of cell division, signaling, host-pathogen interactions, and membrane biology. Furthermore, we actively pursue possibilities to engage in applied and translational research. Our science focuses primarily on the structural analysis of challenging soluble and membrane-bound protein samples by using state-of-the-art X-ray crystallography and cryo-electron microscopy (cryo-EM) techniques in combination with biochemical and biophysical methods.

Role of the LBR

The LBR develops high-impact molecular biology research programs in structural biology, which capitalize on the unique infrastructures at PSI like the Swiss Light Source (SLS) and the Swiss X-ray Free Electron Laser (SwissFEL). We use or implement novel technologies in sample preparation, handling, and delivery, as well as in the acquisition and analysis of synchrotron, X-ray laser, and cryo-EM data. In this context, we have a proven track record of valorization and commercialization of internally developed technologies through start-up enterprises. Within the BIO division, our projects enable collaborations with both the Laboratory of Nanoscale Biology and the Center for Radiopharmaceutical Sciences.

We maintain a worldwide network of both academic and industrial collaborations to ensure PSI's leading position at the forefront of structural biology research. Furthermore, we are well integrated within the Swiss academic landscape through affiliations with the ETH Zürich and the Universities of Zürich and Basel. Several courses for bachelor and master students at these academic institutions or at the PSI are either organized or contributed by members of the LBR. Through these courses and the supervision of semester, master, and doctoral students, the LBR contributes to PSI's teaching program.

The LBR also contributes to the education, infrastructure, and organization of PSI. It hosts the Vocational Training and Chemical Management group, and operates PSI's Crystallization Facility together with the Photon Science Division. Furthermore, several researchers of the LBR are active members of internal PSI committees, including the Equal Opportunity Committee, the Confidential Advisor Committee, the Personnel Committee, and the Research Committee.

Research areas of the LBR

We focus our projects on four broad biological topics: cell division, signaling, host-pathogen interactions, and membrane biology. Accordingly, we work on two challenging types of biological samples, soluble and membrane-bound protein 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.
- The "Time-Resolved Structural Biology" group of Dr. J. Standfuss investigates the structural dynamics of biological macromolecules. The goal is to understand how structural changes occurring from femtoseconds to seconds after protein activation are related to function.
- The "Pathogen-Host Interactions" group of Dr. R. Kammerer investigates the mechanisms by which pathogens interact with their hosts. Currently, the group focuses on botulinum neurotoxins and the styrene degradation pathway.

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

- The “Mechanisms of Signal Transduction” group of Prof. V. Korkhov investigates the structure-function relationship of membrane proteins involved in cellular signaling. Currently, the group investigates the cAMP and Hedgehog pathways, and signaling at the cellular junctions.
- The associated “Structural Biology of Membrane Proteins” group of Prof. G. Schertler (head of BIO) 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.

Research strategy of the LBR for 2022-2026

Our biological topics will remain of major scientific and pharmaceutical importance in the near future. We will therefore continue developing our research program in these fields. To maintain and further advance our scientific excellence, it is paramount that we capitalize on our strengths in high-resolution structural biology. Several technologies are currently dramatically reshaping the field: (i) time-resolved serial crystallography using next-generation synchrotron and X-ray laser radiation, (ii) cryo-EM-based methods for structure determination, and (iii) computational-based structural biology methods.

An important focus of the LBR will remain time-resolved structural biology analyses of proteins upon light activation. The laboratory has established itself as a leading center in this area of research area, both in Switzerland and beyond, and we aim to maintain our excellent track record of publications in leading scientific journals. In the future, we will implement new technologies like temperature jump and small molecule mixing experiments to trigger protein activation. This will allows to accessing physiologically relevant but previously unresolvable conformational states of proteins using technologies available at the SwissFEL.

Besides using X-ray laser technologies, we will further expand our efforts in X-ray crystallography at the SLS to prepare for its upgrade to a diffraction-limited source in 2025. We will have a particular focus on the structural analysis of protein-ligand interactions that rely on the availability of high-resolution data. The LBR possesses a proven, strong track record in this area and contributed to the setup of a crystallographic fragment-screening pipeline at the SLS. We anticipate that such activities will foster new collaborations, particularly with the private sector.

Notably, the protein systems we study are constantly increasing in complexity and flexibility, and at the same time decreasing in abundance and stability. Samples consisting of dynamic protein complexes are often beyond the capabilities of crystallography, but are well-suited for static and time-resolved structural analyses by cryo-EM. We have already implemented single-particle cryo-EM technologies in our research programs, which has allowed us to publish structure-function studies in leading journals. In the coming years, we will continue to pursue challenging projects using cryo-EM as an enabling technology for single-particle and *in situ* structural biology studies. We plan these studies in partnerships with PSI’s Electron Microscopy Facility and the High Performance Computing and Emerging technologies group at PSI, as well as with the ETH Zurich and the University of Basel.

Recent developments in computational structural biology methods are currently having major scientific impact. We apply molecular dynamics simulations and structural modeling in our research projects as essential computational technologies for data analysis and interpretation. To stay competitive in this area, we will further strengthen our collaborations with computational modeling groups, including the newly founded Scientific Computing, Theory and Data Division at PSI. Together with our XFEL, X-ray crystallography, and cryo-EM efforts, these activities will allow the LBR to remain at the forefront of academic research and advance its position as a leading center for modern structural biology research over the next decade.

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