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Cryo-EM and X-ray-free Electron Laser-enabled Structure Based on Drug Discovery - New Insights in Molecular Interactions

Due to their central importance in many physiological processes, membrane proteins are drug targets for around 60% of all approved drugs. Structure based drug discovery on soluble proteins is managed well within the project timelines and portfolio changes in pharmaceutical industry, but transmembrane proteins remain a significant challenge because of their difficulty to be expressed, purified and made them work for biophysical methods and structural investigation. Consequently, membrane proteins need yet to be fully exploited for structure based drug design and high resolution three dimensional structure of complexes with potential drug molecules will significantly facilitate the drug discovery process.

Based on the preferred access to the SLS/SwissFEL at the Paul Scherrer Institute and the cryo-EM facility of the University of Basel (C-CINA), leadXpro is able to screen, optimize and structurally characterize small molecule and biotherapeutics in complex with protein drug targets timely to impact the drug discovery of novel therapeutics.

Showcase examples will include the structure determination of the chemokine receptor CCR2, an emerging target for inflammation, arthritis and oncology by serial crystallography. Here we explore structural details of ligand binding at the orthosteric and allosteric binding sites to address challenges on drug efficacy and specificity.

Furthermore, examples of high resolution cryo-EM structures of a human TRPV with bound small molecule agonist as well as an antibiotics transporter target.

In August 2018, the SwissFEL facility was used for the very first biostructure experiments. This new facility enables more physiologically relevant room temperature structures giving essential data on protein flexibility at the ligand binding site and new insights for computational chemistry. Furthermore, femtosecond X-ray pulses enable monitoring and capturing of dynamic processes of ligand binding and associated conformational changes with great impact to the design of candidate drug compounds.