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【926】Advanced Instrumentation Enables Structure-based Drug Discovery on Challenging Membrane Protein Targets

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Integral membrane proteins are drug targets for the majority 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 are still underexplored because of their challenges to be expressed, purified and get high resolution structures or enable biophysical methods to investigate target engagement and ligand binding kinetics.
The presentation includes recent advances in the technologies and their application to relevant drug targets with an emphasis on technologies such as the cryo-EM and X-ray structure determination. The talk will show examples how structural dynamics can experimentally be investigated to improve the understanding of ligand recognition and drug action. The Cryo-EM structures of human TRPV4 ion-channel with bound small molecule agonist activating the channel opening with a significant structural change enabling direct observation of agonist pharmacology by high resolution cryo-EM analysis.
Application of serial X-ray crystallography using synchrotron (SLS) and femtosecond pulsed Free Electron Lasers (SwissFEL) for determination of room temperature structures and observation of structural dynamic of ligand binding and associated conformational changes will be the second part of the talk. Using the model system A2A receptor and a photosensitive ligand, the ligand unbinding and the associated structural change (induced fit of the ligand and ligand binding pocket) can directly be observed and analysed. Together with advanced drug design software this opens the opportunity for enhanced impact of structure knowledge to the design of candidate drug compounds resulting in better treatments for patients.

Author: HENNIG, Michael (leadXpro AG)

Presenter: HENNIG, Michael (leadXpro AG)

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