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Keynote 6: Structure-based drug discovery in biotech and pharma

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Advances in structure determination and computational methods facilitate the discovery and optimization of pharmaceutical active compounds in the majority of all projects. Still, integral membrane proteins are drug targets for more than 60% of all approved drugs, but are 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 technologies and their application to relevant drug targets such as the cryo-EM structure of the human TRPV4 ion-channel with bound small molecule agonist. The agonist binding activates the channel opening with a significant structural change enabling direct observation of agonist pharmacology by high resolution cryo-EM analysis. Next example is LPTDE, a clinically validated antibiotics drug target. Due to limited size of 120 kDa and the monomeric ⍁-sheet transmembrane architecture, the leadXpro proprietary tool of Pro-Macrobodies was essential for the successful EM structure at 2.9 A resolution. The cryo-EM structure of the ion-channel Kv3.1 at 2.6 Å resolution using full length wild type protein apo and with the small molecule positive modulator Lu AG00563 reveals a novel ligand binding site for the Kv class of ion channels located between the voltage sensory domain and the channel pore. Recently, leadXpro disclosed the first structure of a proton sensing GPCR. Structure-based optimization of GPR65 activity modulators will open novel therapeutic options for life-threatening diseases such as inflammatory bowel disease and cancer.
Construct engineering, application of in meso in situ serial X-ray crystallography (IMISX) is exemplified with the GPCR structure of CCR2 in complex with an antagonist ligand. This is combined with detailed binding characterization using grating-coupled interferometry (GCI, Creoptix) to facilitate drug design with binding kinetic, affinity.
The outlook at future perspectives includes further advances in cryo-EM and the application of serial X-ray crystallography at synchrotron and femtosecond pulsed Free Electron Lasers (FEL). Here, determination of room temperature structures and observation of structural dynamic of ligand binding and associated conformational changes. All new developments in structural biology will further enhance the impact to the design of candidate drug compounds.

Selected references:
Botte M. et al. Apo and ligand-bound high resolution Cryo-EM structures of the human Kv3.1 channel reveal a novel binding site for positive modulators PNAS Nexus, (2022), 1, 1-8
Botte M. et al. Cryo-EM structural studies of the agonist complexed human TRPV4 ion-channel reveals novel structural rearrangements resulting in an open-conformation (2020), https://doi.org/10.1101/2020.10.13.334797
Nass, K., et al. Advances in long-wavelength native phasing at X-ray free-electron lasers. IUCrJ, 2020 https://doi.org/10.1107/S2052252520011379
Cheng, R.K.Y., Towards an optimal sample delivery method for serial crystallography at XFEL, Crystals, 2020, 10, 215;
Apel, A-C., Crystal structure of CC chemokine receptor 2A in complex with an orthosteric antagonist provides insights for the design of selective antagonists, Structure 27, (2019)

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