Thursday, 15 October 2020, 14:00 hrs
VIA ZOOM: please contact psy-office@cbs.mpg.de for the Zoom details

Guest Lecture

Professor Dr Jens Meiler

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Innovative Computational Methods for Protein Structure Prediction, Drug Discovery, and Therapeutic Design

The Meiler laboratory is recognized for methods developed for the structure determination of proteins, in particular using sparse experimental data. The Meiler laboratory pioneers usage of EPR spectroscopic information (Alexander, N.; et al. "De Novo High-Resolution Protein Structure Determination from Sparse Spin-Labeling EPR Data" Structure 2008, 16, 181) and cryo Electron Microscopy (Lindert, S.; et al. "EM-Fold: De Novo Atomic-Detail Protein Structure Determination from Medium-Resolution Density Maps"; Structure, 2012, 20, 464). These methods enable structure-based drug design for proteins that cannot be analyzed using the traditional structure determination techniques NMR Spectroscopy and X-ray crystallography. Such methods are in particular crucial for determining the structure of membrane proteins which are targets for half of our therapeutics: Weiner, B. E.; et al. "BCL::MP-fold: folding membrane proteins through assembly of transmembrane helices" Structure, 2013, 27, 7. One particular focus in our work is structure, dynamics, and interactions of G-Protein Coupled Receptors (Wu, H.; et al. "Structure of a class C GPCR metabotropic glutamate receptor 1 bound to an allosteric modulator"; Science; 2014; 58 or Alexander, N.; et al. "Energetic analysis of the rhodopsin-G-protein complex links the alpha5 helix to GDP release"; Nat Struct Mol Biol; 2014; 56).

Jens Meiler is a co-creator of the Rosetta program. The Meiler laboratory leads the further development of RosettaLigand (Meiler, J.; Baker, D. "RosettaLigand: Protein-small molecule docking with full side-chain flexibility"; Proteins 2006; 65; 538-548). Through RosettaCommons the Meiler laboratory disseminates additions to the Rosetta program developed and has immediate access to novel Rosetta technologies. Specifically we seek to de novo design proteins to bind small molecule ligands with high selectivity. Further the Meiler laboratory develops a structure-based drug design module for Rosetta and docking protocols particularly suited for docking small molecules into comparative models. The PI of the proposal has also experience in cheminformatics method development for chemical biology and therapeutic development (Mueller, R., et al.; "Discovery of 2-(2-Benzoxazoyl amino)-4-Aryl-5-Cyanopyrimidine as Negative Allosteric Modulators (NAMs) of Metabotropic Glutamate Receptor 5 (mGlu5): From an Artificial Neural Network Virtual Screen to an In Vivo Tool Compound"; ChemMedChem; 2012; 7; 406). The Meiler laboratory develops pharmacophore mapping and virtual screening algorithms and applies those often in conjunction with RosettaLigand to therapeutic development.

The Meiler laboratory develops technologies to engineer protein, for example through assembly of large protein scaffolds from fragments (Fortenberry, C.; et al.; "Exploring symmetry as an avenue to the computational design of large protein domains"; JACS 2011; 133; 18026 & Eisenbeis, S.; et al.; "Potential of Fragment Recombination for Rational Design of Proteins"; JACS 2012; 134; 4019). We currently build on these results developing methods for the computational design of protein-ligand interfaces as a therapeutic strategy. Further, we have a keen interest in developing innovative methods for antibody modeling and design (Willis, J.; et al.; "Human germline antibody gene segments encode polyspecific antibodies"; PLoS Comput Biol; 2013; 9; 100304). We apply these technologies to engineer broadly neutralizing antibodies (Willis, J.; et al.; "Redesigned HIV antibodies exhibit enhanced neutralizing potency and breadth"; J Clin Invest; 2015; 125; 2523) and mine novel antibodies from next generation sequencing data (Willis, J.; et al.; "Long Antibody HCDR3s from HIV-Naïve Donors Mediate HIV Neutralization"; pending).

Current application projects include drug and probe development for neurological diseases including Schizophrenia, Alzheimer's, and Parkinson's, fundamentals of G-protein-coupled receptor signaling, cardiac arrhythmia as caused by the complex interplay of potassium channel regulation and drug interactions, multidrug resistance in cancer and bacterial cells related to multidrug transporter proteins, and f) structural basis of viral infections and antibody activity among others.