

iNEXT workshop on Integrated methodologies and approaches for structural biology

Name of Speaker: **Michael Sattler**

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Title of Lecture: **Decoding regulatory protein-RNA recognition and dynamics using integrative structural biology**

Abstract:

RNA plays essential roles in virtually all aspects of gene regulation, where single-stranded or folded regulatory RNA motifs are recognized by RNA binding proteins (RBPs). Most eukaryotic RBPs are multi-domain proteins that comprise multiple structural domains connected to mediate protein-RNA or protein-protein interactions. Thus, molecular mechanisms of regulatory protein-RNA complexes often involve dynamic structural ensembles and are controlled by population shifts between inactive and inactive conformations. The domains in these proteins are often connected by flexible linkers or flanked by intrinsically disordered regions, where posttranslational modifications can further modulate the protein-RNA interactions and to regulate the biological activity.

We employ integrative structural biology combining solution techniques such as NMR, small angle scattering (SAXS/SANS) and FRET with X-ray crystallography to unravel the molecular recognition and dynamics for the assembly and molecular function of regulatory RNP (ribonucleoprotein) complexes.

Examples will be presented that highlight the importance of conformational dynamics in the recognition of single- and double-stranded RNA by RBPs in the regulation of pre-mRNA splicing RNAi and miRNA pathways. These data provide unique insight into conformational dynamics underlying the regulation of essential biological processes.

Research Profile:

Our research focuses on understand molecular mechanisms of physiological and disease-linked cellular pathways, using integrative structural biology. We study the role of protein-RNA and protein-protein interactions in RNA based gene regulation, especially linked to alternative splicing regulation. We combine solution techniques (NMR, small angle X-ray and neutron scattering) and crystallography to understand the structure and dynamics of important protein complexes. We also have established infrastructure and activities in exploiting structural biology and NMR for the rational design of small molecules inhibitors for structure-based drug discovery, also within the EU HORIZON2020 innovative training network AEGIS.

Three selected publications:

1. Kooshapur H, Choudhury NR, Simon B, Muhlbauer M, Jussupow A, Fernandez N, Jones AN, Dallmann A, Gabel F, Camilloni C, Michlewski G, Caceres JF, Sattler M *Structural basis for terminal loop recognition and stimulation of pri-miRNA-18a processing by hnRNP A1*. (2018) **Nat Commun** 9, 2479. doi: 10.1038/s41467-018-04871-9
2. Dawidowski M, Emmanouilidis L, Kalel VC, Tripsianes K, Schorpp K, Hadian K, Kaiser M, Maeser P, Kolonko M, Tanghe S, Rodriguez A, Schliebs W, Erdmann R*, Sattler M*, and Popowicz GM* *Inhibitors of PEX14 disrupt protein import into glycosomes and kill Trypanosoma parasites*. (2017) **Science** 355, 1416-1420. doi: 10.1126/science.aal1807
3. Sonntag M, Jagtap PKA, Simon B, Appavou MS, Geerlof A, Stehle R, Gabel F, Hennig J, and Sattler M *Segmental, Domain-Selective perdeuteration and Small-Angle Neutron Scattering for Structural Analysis of Multi-Domain Proteins*. (2017) **Angew Chem Int Ed Engl**. doi: 10.1002/anie.201702904