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The Thomä lab uses X-ray crystallography and recently cryo-electron microscopy to study large protein assemblies implicated in human disease states. Our initial focus was on rare DNA repair disorders (Xeroderma pigmentosum) (Scrima et al., Cell 2008; Fischer et al., Cell 2011), where we detailed the molecular machinery that safeguards the genome against potentially mutagenic ultraviolet-light exposure. We recently expanded our focus to ubiquitin E3 ligases and their regulators in DNA repair and beyond. This led to the structure of the Cop9 signalosome, a master-regulator of the cullin-RING type ubiquitin ligases (Lingaraju et al., Nature 2014), and to a molecular understanding of the drug Thalidomide (Fischer et al., Nature 2014). While our targets have so far mostly been in the space of oncology research, we wish to explore a new field. Given recent advances in structure determination by electron-microscopy, it will be possible to use structural biology as a discovery engine to look at protein complexes implicated in diseases for which there is only limited protein-based understanding available. This proposal is aimed to study proteins implicated in autism spectrum disorders. We speculate that intricate allosteric regulatory circuits operate in the postsynapse and that some of these regulatory functions are impaired in autism spectrum patients (see also work of

Schmitges et al., Mol Cell 2010). By solving the structure of these protein complexes implicated in disease and characterizing them in vitro (at the FMI) and in cell culture (in the Chemical Biology & Therapeutics department), we wish to contribute to our understanding of how these assemblies operate in health and disease.

Selected Publications

Structure of the DDB1-CRBN E3 ubiquitin ligase in complex with thalidomide. [2]
Fischer ES, Boehm K, Lydeard JR, Yang H, Stadler MB, Cavadini S, Nagel J, Acker V, Lingaraju GM, Tichkule RB, Forrester WC, Schirle M, Hassiepen U, Ottl J, Hild M, Beckwith REJ, Harper JW, Jenkins JL, Thomä NH.
Nature 2014; Aug 7;512(7512):49-53.

Crystal structure of the human COP9 signalosome. [3]
Lingaraju GM, Bunker RD, Cavadini S, Hess D, Hassiepen U, Renatus M, Fischer ES, Thomä NH.
Nature 2014 Aug 7;512(7512):49-53.

Rif1 and Rif2 shape telomere function and architecture through multivalent Rap1 interactions. [4]
Shi T, Bunker RD, Mattarocci S, Ribeyre C, Faty M, Gut H, Scrima A, Rass U, Rubin SM, Shore D, Thomä NH.
Cell. 2013 153(6):1340-53.

Click here [5] for additional publications.

Links
[1] https://www.novartis.com/our-science/postdoc-program/research-themes/structural-biology/nicolas-thoma-phd
[2] http://www.ncbi.nlm.nih.gov/pubmed/25043012
[3] http://www.ncbi.nlm.nih.gov/pubmed/25043011
[4] http://www.ncbi.nlm.nih.gov/pubmed/23746845
[5] http://www.ncbi.nlm.nih.gov/pubmed/?term=Thoma_NH