Contribution ID: **257** Type: **Oral**

Watching the release of a photopharmacological drug from its target using SLS and SwissFEL

Wednesday, 17 May 2023 19:45 (30 minutes)

Photopharmacology offers a powerful approach to alter ligand affinity and biological activity of small molecule drugs using light as a trigger. However, understanding the molecular mechanisms underlying this process has been challenging due to the inability of conventional structural biology to resolve the relevant transitions. In this presentation, I will outline how we employed time-resolved serial crystallography at the Swiss Light Source (SLS) and the Swiss X-ray Free Electron Laser (SwissFEL) to capture the release of azo-combretastatin A4, an anti-cancer compound, and the resulting conformational changes in tubulin. We obtained a series of structural snapshots logarithmically spaced in time from 100 fs to 100 ms, which, along with computer simulations and time-resolved spectroscopy, provide direct molecular insight into how the cis-to-trans isomerization of the azobenzene bond leads to a switch in ligand affinity, opening of an exit channel, and collapse of the binding pocket upon ligand release. The resulting global backbone rearrangements are related to the action mechanism of microtubule-destabilizing drugs.

References
[1] M. Wranik et al., Watching the release of a photopharmacological drug from tubulin using time-resolved serial crystallography. Nat Commun 14, 903 (2023).

Select Topic 1

Drug Discovery

Select Topic 2

Primary author: STANDFUSS, Jörg (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland)

Co-authors: CAVALLI, Andrea (Computational and Chemical Biology, Instituto Italiano die Tecnologia, 16163 Genova, Italy); FURRER, Antonia (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland); BACELLAR, Camila (Photon Science Division, Paul Scherrer Institut, 5232 Villigen, Switzerland); SLAVOV, Chavdar (Institute of Physical and Theoretical Chemistry, Goethe University, Frankfurt am Main, Germany); MILNE, Chris (Photon Science Division, Paul Scherrer Institut, 5232 Villigen, Switzerland); CIRELLI, Claudio (Photon Science Division, Paul Scherrer Institut, 5232 Villigen, Switzerland); JAMES, Daniel (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland); GASHI, Dardan (Photon Science Division, Paul Scherrer Institut, 5232 Villigen, Switzerland); GIOIA, Dario (Computational and Chemical Biology, Instituto Italiano die Tecnologia, 16163 Genova, Italy); KEKILLI, Demet (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland); OZEROV, Dmitry (Scientific Computing, Theory and Data, Paul Scherrer Institut, 5232 Villigen, Switzerland); DWORKOWSKI, Florian (Photon Science Division, Paul Scherrer Institut, 5232 Villigen,

Switzerland); GLOVER, Hannah (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland); BEALE, John (Photon Science Division, Paul Scherrer Institut, 5232 Villigen, Switzerland); WACHTVEITL, Josef (Institute of Physical and Theoretical Chemistry, Goethe University, Frankfurt am Main, Germany); NASS, Karol (Photon Science Division, Paul Scherrer Institut, 5232 Villigen, Switzerland); FERRAROTTI, Marco (Computational and Chemical Biology, Instituto Italiano die Tecnologia, 16163 Genova, Italy); BRAUN, Markus (Institute of Physical and Theoretical Chemistry, Goethe University, Frankfurt am Main, Germany); WRANIK, Maximilian (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland); WANG, Meitian (Photon Science Division, Paul Scherrer Institut, 5232 Villigen, Switzerland); CARRILLO, Melissa (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland); STEINMETZ, Michel (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland); GAILLARD, Natacha (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland); SKOPINTSEV, Petr (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland); JOHNSON, Philip J.M. (Photon Science Division, Paul Scherrer Institut, 5232 Villigen, Switzerland); STIPP, Robin (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland); BRÜNLE, Steffen (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland); MASINI, Tiziana (Computational and Chemical Biology, Instituto Italiano die Tecnologia, 16163 Genova, Italy); MÜHLETHALER, Tobias (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland); WEINERT, Tobias (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland)

Presenter: STANDFUSS, Jörg (Division of Biology and Chemistry, Paul Scherrer Institut, 5232 Villigen, Switzerland)

Session Classification: Drug Discovery