Contribution ID: **62** Type: **Oral contribution**

Massive X-ray screening against SARS-CoV-2 main protease

Tuesday 16 March 2021 10:35 (20 minutes)

Contributed on behalf of the Hamburg SARS-CoV-2 X-ray screening initiative

As a response to the current SARS-CoV-2 pandemic we have set up a large consortium of more than one hundred scientist centered around DESY in Hamburg. In contrast to common screening techniques such as biochemical activity-based assays or X-ray fragment screening, here we employed massive X-ray crystallographic screening of two drug-repurposing libraries against SARS-CoV-2 main protease (MPro) of SARS-CoV-2 as initial target. Already in March 2020 co-crystallization experiments of 5953 individual drugs with MPro were setup. In April data from more than 8000 of these crystals were collected at the PETRA III MX beamlines. In the following weeks a data analysis pipeline for fully automatic data processing and subsequent structure refinement followed by ligand identification by pan-dataset density analysis (PanDDA) was established. Our screening effort resulted in the identification of 37 compounds binding to MPro. Secondary screening of these hits in a cell-based virus-infection assay revealed antiviral activity in combination with low cytotoxicity for six compounds which have not yet been reported as inhibitors of SARS-CoV-2. While four of these inhibitors bind to the catalytic site of the enzyme, the remaining two bind to an allosteric site within the dimerization domain(1).
To our knowledge, this is the first time X-ray crystallography has been used as a primary screen for drug discovery while using drug-like molecules rather than smaller fragments. The platform developed for this project is currently being further extended and optimized and will be available for future drug discovery efforts.

Reference
(1) S. Günther, P. Y. A. Reinke, et al. , bioRxiv, in press, doi:10.1101/2020.11.12.378422.

Figure: SARS-CoV-2 MPro dimer with hits derived from X-ray screening of drug repurposing libraries. Drug binding (stick representation) is observed across the complete MPro dimer. One MPro monomer with bound drugs is shown in white surface representation. The other monomer is shown as mixed cartoon/surface representation.

Primary author: GUENTHER, Sebastian (FS-BMX (FS-CFEL-1 Fachgruppe BMX))

Co-authors: Dr REINKE, Patrick (DESY); MEENTS, Alke (DESY)

Presenter: GUENTHER, Sebastian (FS-BMX (FS-CFEL-1 Fachgruppe BMX))

Session Classification: Bio-crystallography

Track Classification: Bio-crystallography