

## SARS-CoV-2 Methyltransferase ligand screening and peptide inhibitors

Non-structural protein 10 (nsp10) and nsp16 are part of the SARS-CoV-2 viral RNA replication complex. Nsp16 exhibits methyltransferase activity needed for mRNA capping and is active in heterodimeric complexes with the enzymatic inert nsp10. The inactivation of this complex interferes severely with viral replication, making it a promising drug target against COVID-19. As only limited information on ligands binding to nsp10-nsp16 is available, we screened small compound libraries (~ 200 compounds) containing potential methyltransferase-binders that were soaked into protein crystals and the structures solved by X-ray crystallography. This has only recently become possible due to a dramatically shortened measuring time for single crystals at synchrotrons. We obtained 36 data sets of the nsp10-16 complex with purine derivatives bound to the substrate binding sites. Promising compounds are being tested in binding, activity, and viral inhibition assays.

In parallel, we are testing small nsp10-derived peptides that potentially disrupt the complex formation of nsp10-16. We see significant reduction of enzyme activity with several peptides and indications of complex disruption in small-angle-X-ray scattering (SAXS) data. Virus inhibition is currently being tested. Our results can be used for structure-based drug design to fight COVID-19 and may contain potent inhibitors of SARS-CoV-2 methyltransferases.

**Primary authors:** Dr SPRENGER, Janina (Deutsches Elektronen Synchrotron); Dr KREMLING, Viviane (DESY)

**Co-authors:** Dr OBERTHUER, Dominik (Deutsches Elektronen Synchrotron); Dr GALCHENKOVA, Marina (Deutsches Elektronen Synchrotron); Dr MIDDENDORF, Philipp (Deutsches Elektronen Synchrotron); Dr GELISIO, Luca (Deutsches Elektronen Synchrotron); Dr CARNIS, Jerome (Deutsches Elektronen Synchrotron); Dr EHRT, Christiane (Universitaet Hamburg); Mrs KIENE, Antonia (Deutsches Elektronen Synchrotron); Prof. CHAPMAN, Henry; Mr KLOPPROGGE, Bjarne (Deutsches Elektronen Synchrotron); Dr YEFANOV, Oleksandr (Deutsches Elektronen Synchrotron)

**Presenter:** Dr SPRENGER, Janina (Deutsches Elektronen Synchrotron)