Inhibitor screening and structural characterization of virulence factors from SARS-CoV-2

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Coronavirus induced zoonotic diseases like COVID-19 can cause pandemics with unforeseeable consequences to human health and global economy. Ongoing research on SARS-CoV-2 focuses on the role of the virus surface spike protein, its cognate human receptor, the virus protease, the viral replication and transcription as well as its assembly and release.

Our project aims to screen and develop effective therapeutics against SARS-CoV-2, targeting the replication and transcription complex of the virus. Employing an interdisciplinary research approach, compound libraries of approved drugs are used for the discovery of potent inhibitors for RTC enzymes, followed by the structural determination of the enzyme-inhibitor complexes, to reveal their binding mode. The *in vivo* efficacy of the most promising candidates can be evaluated in a future trial. Our workflow includes the production of proteins involved in the coronavirus replication-transcription complex, the high-throughput inhibitor screening with fluorescence-based assays using drug repurposing libraries and the structure/function analysis of the enzyme-inhibitor complexes. The advantages of this approach is that it is cost efficient, high-throughput compatible, allows the direct identification of potent inhibitors and optimizes beamtime use since the identified inhibitors are usually in the range of few dozens. Such a platform can be successfully used in future viral outbreaks.

In this presentation we will give an overview of this project and the results achieved to date. The main focus will be on one of the target proteins, namely the uridine-specific endoribonuclease nsp15, the results from its inhibitor screening and findings that allowed us to understand the role of important activity determinants of this protein.