New chemical entities for modulating SARS-CoV-2 activity

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Even after over two and a half years the SARS-CoV-2 pandemic is still a global threat and while there are effective approved vaccines against the coronavirus, emerging new variants as the Omicron variant are more resistant towards the vaccine[1]. Moreover, there is a general decline in vaccine protection over time which together results in the urgent need to develop drugs against SARS-CoV-2. With enormous effort made, two therapeutics, Molnupiravir and Paxlovid, could recently be approved. However, it is still of great interest to find potent drugs against the virus, foremost to increase efficiency of treatment, which is far from ideal yet, and also to prepare for upcoming variants that could evade established treatments.

The NECESSITY (New chemical entities for modulating SARS-CoV-2 activity) project aims to find inhibitors against the main protease of SARS-CoV-2 (M^{PRO}). M^{PRO} is vital for the viral life circle, has a relatively low mutation rate and was proven to be druggable[2]. The NECESSITY project is a trilateral project between the Innsbruck Medical University, the Palacký University Olomouc and the Helmholtz-Zentrum Berlin. For the project, a library of over 8000 small-molecule compounds and peptide analogous, most of them synthesized as kinase and protease inhibitors will be employed. Focused selections will be screened using high-throughput X-ray crystallography. Initial hits will further be developed into strong binders and analysed with biophysical methods like MST, ITC, NMR, and TSA and virological assays.

Drug-design in academia is usually bound to individual groups and methodologies initiating the process and acquire collaboration partners stepwise once suitable first starting points are identified. This can slow down to the academic drug discovery process considerably. Therefore, the NECESSITY project is designed from the start as a closely interconnected consortium with a shared vision of finding lead structures for new antivirals. The project could be a blueprint for increasing collaboration in academic compound development approaches, and thereby the speed of how fast global health threats can be combated, not only during the current SARS-CoV-2 pandemic but as well in the future for other viral diseases.

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