COVID-19 SEED GRANT PROGRAM

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Title: Targeted degradation of the SARS-CoV-2 M^{pro} protease as a novel therapy for treating COVID-19 infection

Summary

Novel therapies are urgently needed to combat the COVID-19 pandemic. To address this need, we will synthesize proteolysis targeting chimeras (PROTACs) to degrade the SARS-CoV-2 main protease M^{pro}, a protein that is essential for viral replication. PROTACs are heterobifunctional small molecules that recruit an E3 ligase to the protein of interest leading to ubiquitination and hence selective degradation of the target protein. Although PROTACs are a highly promising therapeutic strategy which is being adopted by most of the major pharmaceutical and biotechnology companies, one of the main hurdles in deploying this technology is the design of the PROTAC. Significantly, one of us (Kozakov) has developed a novel computational approach to predict the structure of the complex formed between E3 ligase and the target protein. In the current proposal we will predict the structure of the E3 ligase:M^{pro} complex, and design heterobifunctional PROTACs that will bind to this complex. The PROTACs will be synthesized and their ability to degrade M^{pro} will be evaluated in cell lines expressing this protein. Subsequently the antiviral activity will be evaluated in cells infected with SARS-COV-2. Collectively, the outcome of these studies will serve as preliminary data for a NIH proposal to NIAID.