Miguel Garcia-Diaz, Department of Pharmacological Sciences and Robert Rizzo, Department of Applied Mathematics and Statistics

Pharmacological inhibition of SARS-CoV-2 replication

Antivirals targeting replication are extremely successful. Most are nucleoside analogs that act as chain terminators. The conservation of polymerase active sites reduces resistance, but leads to significant toxicity due to similarities between viral and human polymerases. Recently, there has been considerable interest in using protein-protein interfaces (PPIs) as drug targets. These drugs are exquisitely selective for a particular PPI (reducing side effects) while targeting a highly conserved pocket (reducing resistance). This led to the development of pritelivir, in Phase III clinical trials for the treatment of HSV. The SARS-CoV-2 replicase, nsp12, needs to interact with nsp7 and nsp8 to successfully replicate the genome. We will develop small molecules capable of precluding these essential interactions. The proposal has two aims: (i) identification of an initial set of small molecule candidate compounds through structure-based computational screening; (ii) development of high-throughput assays and validation of initial hits.

The proposal capitalizes on our expertise in large scale virtual screening and the targeting of PPIs (Rizzo), the analysis of viral RNA polymerases and the characterization of protein-protein interactions and drug receptor complexes (Garcia-Diaz). It will lead to the identification of initial hits and the development of high-throughput assays that will support a joint R01 application.