Cover Page

PI: Markus A Seeliger (Department of Pharmacological Sciences, Department of Chemistry, Stony Brook University),

Co-PI: David R. Liu (The Broad Institute, Harvard University, and HHMI)

Title: Structure-based Development of Novel Cyclophilin Inhibitors for Studying and Blocking Viral Replication of Human Coronaviruses.

Summary: The human cyclophilins (Cyps) consist of 17 peptidyl-prolyl-isomerases. In addition to helping human proteins fold, they are essential chaperones for viral replication, and cyclophilin inhibitors demonstrated a clinical response in trials against hepatitis C. Similarly, the following coronavirus (CoV) strains require cyclophilin A to various degrees for propagation: SARS-CoV, CoV-NL63 (two human coronaviruses that share a host-cell receptor (ACE2) and symptoms with SARS-CoV-2), MERS-CoV and CoV-229E. Additionally, human CoV-OC43 depends on cyclophilin D. Non-specific cyclophilin inhibitors, like the FDA-approved drug cyclosporine A, are potent immunosuppressants and therefore impractical antivirals. The lack of specific inhibitors has also hampered efforts to elucidate which of the 17 human cyclophilins are required for CoV replication to further advance Cyps as antiviral targets.

Our goals are to (i) develop isoform specific and potent CypA and CypD inhibitors that (ii) lack immunosuppressant activity. Proof of concept exists for both goals: We recently developed selective and potent CypD inhibitors with the Liu group, and cyclosporine A analogs without immunosuppressive activity exist. Both goals require detailed structural characterization of Cyp complexes with inhibitors. Here, we propose to determine co-crystal structures of Cyps with our re-targeted CypD-selective inhibitors to guide selectivity and to prevent immunosuppression.