Designing Novel Disruptors of SARS-CoV-2 Viral Spike Protein Function by Targeting the Substrate Binding Domain of Chaperone Protein GRP78

Team 16: **Jonathan R. Hutton, Maria Lazou**
Technical Advisors: **Diane Joseph-McCarthy, Arijit Chakravarty (Fractal Tx)**

SARS-CoV-2, the virus that causes COVID-19, had led to an ongoing health emergency across the globe, claiming the lives of millions and impacting billions of others to a profound extent. Despite the increasing availability of vaccines, the virus continues to spread and mutate into new variants. Because most vaccines tend to target the spike protein of the SARS-CoV-2 virus, there exists the threat of viral escape by evolution from vaccine effectiveness. As such, there is an urgent need for antiviral treatments that target a different mechanism of viral entry to increase the evolutionary selection pressure placed on the virus, potentially extending the duration of effectiveness of vaccines across viral variants and directly reducing viral transmission and infection. The protein GRP78 provides one possible novel target for antiviral treatments. GRP78 is known to act as a host auxiliary factor for the binding of [JDM1] the SARS-CoV-2 viral spike protein to the human cellular ACE2, the primary pathway of cell infection. Here, we first modeled the binding of GRP78 to the spike protein ACE2 structure. We then used that model of the GRP78-Spike-ACE2 complex to propose a set of molecules determined through structure-based virtual screening of known drug databases that can be computationally demonstrated to disrupt the SARS-CoV-2 viral spike protein from binding to the GRP78 substrate binding domain (SBD), effectively preventing viral entry to the cell. A subset of the lead compounds has been selected to be suitable for intranasal administration to prevent viral propagation beyond the nasal mucosa, offering the potential for an early exposure intranasal treatment for COVID-19 following further clinical development.