UNC SCHOOL OF MEDICINE

COVID-19 NC Collaboratory Projects

Final Narrative
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Rapidly Emerging Antiviral Drug Discovery Initiative (READDI)

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The goal of this Rapidly Emerging Antiviral Drug Discovery Initiative (READDI) project is to develop antiviral drugs to treat COVID-19. Developing these new drugs requires a multidisciplinary effort, with expertise in virology, medicinal chemistry, biochemistry, and viral pathogenesis. The READDI drug discovery pipeline leverages UNC-CH expertise in each of these areas into an integrated workflow with well-defined roles for each team member. The program uses an existing, validated antiviral drug discovery pipeline that has been active since late 2018. Using this pipeline, the Moorman and Baric labs have already identified targets for COVID-19 antivirals. Some of these targets have been validated for SARS2 antiviral activity using hit compounds from the Pearce and Willson labs, which have already begun to optimize these compounds. Approved inhibitors exist for a subset of these validated targets, and the Heise and Baric labs are testing these lead compounds for antiviral activity in vivo using highly advanced small animal models of COVID-19 replication and pathogenesis developed in the Baric lab.

The funds received were used to as described in the submitted proposal. In addition to the consumables used for these studies, the funds supported the purchase of critical equipment for these studies, including a luminometer capable of handling the throughput needed for this work. Specifically, the Moorman lab, in collaboration with the Baric lab, has generated a murine hepatitis virus reporter virus expressing nanoluciferase (MHV-NLuc), Due to its close relation to SARS-CoV2, and the ability to grow the MHV-NLuc virus under lower biosafety precautions that SARS-CoV2, the MHV-NLuc virus has been used to rapidly screen compounds for antiviral activity. Efficacious compounds were then tested for antiviral activity against SARS2-CoV in collaboration with the Baric and Heise labs.

After creating virus stocks, we determined the optimal parameters of the MHV-NLuc assay (amount of virus and time after infection), andused the MHV-NLuc assay to test compounds for antiviral activity. We completed screening of the entire Kinase Chemogenomic Set (KCGS), a set of 188 highly specific and potent kinase inhibitors, for antiviral activity using the MHV-NLuc assay. From this data weidentified approx. 12 kinase targets whose inhibition decreased MHV replication by >50%. We also completed testing of an additional kinase inhibitor set, the Major Kinase Set, provided by Dr. Ken Pearce's lab in the Center for Integrative Chemical Biology and Drug Discovery (from the CICBDD) as a complementary approach. We also tested a collection of >80 clinical candidates and drugs (provided by the SGC) that were predicted to have antiviral activity against SARS-CoV2. We tested a series of NSD2 inhibitors developed by Dr. Lindsay James (UNC). We continue to work with Dr. Tim Willson's group to develop new SARS-CoV2 inhibitors targeting cellular kinases.

This funding allowed us to screening of the SGC Chemical Probes library, the SGC Epigenetic Probe library, and a collection of selected compounds pulled from the libraries of various pharma companies. Promising compounds (>50% inhibition at a concentration of 1μM) underwent secondary testing to accurately define the 50% inhibitory concentration (IC50). We identified more than ten compounds that inhibited MHV replication at 1μM or less and were not toxic to uninfected cells at concentrations that inhibited virus replication. These data identified additional potential kinase and non-kinase targets. We are currently testing additional inhibitors to validate that these proteins may be useful targets for antiviral drug development campaigns. Dr. Mark Heise is testing the most promising compounds for SARS-CoV2 antiviral activity in the BSL-3 facility. In summary, over the course of the funding period we screened >400 compounds for antiviral activity and cellular toxicity. This work led directly to identification and validation of multiple novel targets for new SARS-CoV-2 antiviral compounds. This work has also play an essential role in the ongoing development of a new antiviral compound targeting a cellular kinase, which is progressing forward through a medicinal chemistry campaign.

In collaboration with the Heise lab, we also analyzed several anti-inflammatory drugs for their utility in treating SARS-CoV 2 and other CoV infections. These results indicate that targeting Jak family kinases can improve SARS-CoV2 disease outcomes in mice, however there are important differences between different classes of JAK inhibitors. An inhibitor that targets JAK1/JAK3 results in improved clinical outcome, while an inhibitor that targets JAK1/2 results in enhanced disease pathogenesis. We also tested the ability of these inhibitors to affect SARS-CoV2 replication through modulation of host antiviral activity, and demonstrated that combining JAK inhibitors with direct acting antivirals can protect from SARS-CoV2-induced disease, or result in enhancement disease by JAK1/2 inhibitors. These results, which are consistent with human studies reported by others, suggest the combining JAK inhibitors with direct acting antivirals may have therapeutic benefit for treating SARS-CoV2-induced disease.

Together with the work of our collaborators, these studies led directly to identification and validation of multiple novel targets for new SARS-CoV-2 antiviral compounds. This work has also play an essential role in the ongoing development of a new antiviral compound targeting a cellular kinase, which is progressing forward through a medicinal chemistry campaign. Importantly, the Collaboratory funding has supported our ability to pursue new funding opportunities, including a R01 application that was co-submitted on Feb. 5th with the Heise lab. As noted above, the equipment that was purchased has also allowed us to expand our drug testing capacity and capabilities, making us more competitive for both federal and industry funding to support our SARS-CoV2 drug testing efforts. Lastly, we are in the process of preparing a manuscript describing our results evaluating the efficacy and safety of JAK inhibitors for treating SARS-CoV2 disease, and this work was in large part supported by Collaboratory funds.

This subproject led by PI Nat Moorman is part of the coordinated READDI pipeline with collaborators Ralph Baric and Mark Heise. Personnel funded by the subproject include a Research Associate, Research Technician, and a Graduate Student.