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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This program supported the development and testing of several host targeted antiviral strategies. This includes analysis of a new class of candidate SARS-CoV2 inhibitors developed by our READDI collaborator, Dr. Tim Willson. As part of this effort, we identified several chemical compounds targeting host cell kinases that exhibit antiviral activity against SARS-CoV2. These candidates are now moving toward more advanced testing to assess their ability to inhibit SARS-CoV2 replication, and to develop new formulations with increased potency. We also analyzed several anti-inflammatory drugs for their utility in treating SARS-CoV2-induced disease. Our results indicate that targeting specific members of a family of kinases called Janus Kinases (JAK), can improve SARS-CoV2 disease outcomes in mice. However, there are important differences in efficacy and safety between different classes of JAK inhibitors, and studies are underway to define specific host pathways that are modulated by these drugs during SARS-CoV2 infection. As part of this analysis, we identified specific cytokines that are differentially affected by these different classes of inhibitors and these results have set the stage for additional studies designed to specifically test whether these cytokines play a direct role in affecting SARS-CoV2 disease outcome. We also demonstrated that combining JAK inhibitors with direct acting antivirals can also protect from SARS-CoV2-induced disease. These results, which are consistent with human studies reported by others, suggest that combining JAK inhibitors with direct acting antivirals may have therapeutic benefit for treating SARS-CoV2-induced disease.

We have used the Collaboratory Funds to cover the costs of personnel salary, supplies, and equipment costs associated with the project, which was focused on identifying new antiviral drugs against SARS-CoV2. The personnel associated with this project were responsible for screening nCoV2 antiviral drugs for their ability to inhibit nCoV2 replication. These assays require a significant amount of reagents, including cell culture supplies, plastic-ware, luciferase detection reagens, and media needed to analyze antiviral activity of candidate nCoV2 drugs and Collaboratory funds were used to cover their purchase. This work also required personal protective gear needed to perform nCoV2 studies under BSL3 conditions, and we have used Collaboratory Funds to cover the costs of these purchases. As detailed above, we made significant progress in identifying and testing new classes of drugs for the treatment of COVID-19, as well as testing anti-inflammatory therapies for safety and efficacy in treating SARS-CoV2-induced disease. This work will set the stage additional studies designed to further develop antiviral treatments for COVID.

Enabling equipment:
The Collaboratory funds were also used to purchase several pieces of equipment for our BSL3 facility that are essential for testing SARS-CoV2 antiviral drugs. These include a Luminex system for measuring host cytokines, a Buxco Unrestrained Plethysmography system and a SP02 System for measuring virus-induced effects on respiratory function, a Vetscan for evaluating virus and drug-induced effects on blood cell counts, and incubators, centrifuges, and small equipment needed for growing SARS- CoV2 infected cells, measuring viral replication in cell culture and from virally infected animals, and testing the antiviral activity of candidate drugs against SARS-CoV2.

Funding Opportunities and Publications:
Importantly, the Collaboratory funding has supported are ability to pursue new funding opportunities, including a R01 application that was submitted on Feb. 5th , 2021 that was supported by preliminary data on the efficacy of JAK inhibitors that was generated through Collaboratory support. As noted above, the equipment that was purchased has also allowed us to expand our drug testing capacity and capabilities, and these capabilities will make 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.

Personnel Supported by the Project:
This subproject led by PI Mark Heise is part of the coordinated READDI pipeline with collaborators Ralph Baric and Nat Moorman. Personnel funded by the subproject include a Research Associate and a Research Specialist.