FULL NARRATIVE REPORT - KENNETH PEARCE

RAPIDLY EMERGING ANTIVIRAL DRUG DISCOVERY INITIATIVE (READDI)

Research Activities and Findings

The goal of our six month effort was to identify potential COVID-19 therapeutics, particularly via repurposing clinic or near-clinic drugs. Our collaborative team has assembled approximately 70 small molecule compounds, including the CICBDD Major Kinase Set for SARS-CoV-2-related studies. Most molecules in this set were evaluated with numerous assays, biochemically and cellularly, for potential effect as an anti-SARS-CoV2 therapeutic. Importantly, several molecules were shown to bind directly to the SARS-CoV-2 Spike Receptor Binding Domain (RBD) using microscale thermophoresis (MST). Each compound in the Major Kinase Set (FDA approved or near approval) from the CICBDD and about twenty additional molecules was tested for antiviral activity against murine hepatitis virus (MHV), a model of SARS2 replication, in DBT cells. Each compound was tested against MHV in dose response format. The same range of compound concentrations was also tested for cytotoxicity in uninfected cells. Several compounds, such as Entrectinib and Dasatinib, were found to have a significant effect on viral replication without causing general host cell toxicity. Entrectinib re-synthesis was completed at large scale to enable pharmacokinetic and in vivo model studies in the near future. To shed light on the mode of Spike RBD binding, we have produced Spike RBD crystals as apo protein and including Entrectinib and Pemetrexed, for x-ray co-crystallography. Additionally, we have made recent progress with an RDB:ACE2 protein:protein interaction using the Promega Lumit technology and we will test molecules noted above for direct effect on this important activity for anti-viral effect.

Expenses

The funds were used to purchase research materials for protein production, assay development, small molecules, small molecule screening, biophysical characterization, consumables for lab automation, and general lab supplies to support the research. The funds were spent by faculty in the UNC Eshelman School of Pharmacy, UNC Department of Microbiology and Immunology, and senior scientists at Collaborations Pharmaceuticals in Raleigh as part of this collaborative effort. Funds were also used to support two graduate students (in the UNC Eshelman School of Pharmacy) and their activities with phage display and DNA-encoded library screens. Additionally, funds were used to support a fraction of salaries for three research professors (two in the UNC Eshelman School of Pharmacy and one UNC Department of Microbiology and Immunology) and two research associates (in the UNC Eshelman School of Pharmacy and UNC Department of Microbiology and Immunology).

Budget Overview

			NON-PERSONNEL EXPENSES							
ORIGINAL BUDGET	**REVISED BUDGET**	**PERSONNEL EXPENSES** (Payroll and benefits cost for employee that are dedicated to COVID-19)	**Contracted Labor Expenses**	**Other Service Expenses** (e.g. utilities, telephone, data, lease related expenses)	**Subcontract Expenses** (e.g. construction, maintenance)	**Goods Expenses (e.g. supplies, PPE)**	**Equipment Expenses**	**TOTAL NON-PERSONNEL EXPENSES**	**TOTAL EXPENDITURES**	**BALANCE**
$196,039	**$191,039**	**$83,484.61**	0	$13,512.50	0	$83,126.30	0	**$96,638.80**	**$180,123.41**	**10,915.59**

Personnel supported by this award

Personnel	Title	Affiliation
Paul Brian Hardy	Research Professional	UNC
Megan Hopkins	Post-Doc Research Associate	UNC
Ramesh Shambanna Jadi	Research Associate	UNC
Premkumar Lakshmanane	Research Assistant Professor	UNC
Jacob Larson	Graduate Research Assistant	UNC
Kenneth Hugh Pearce, Jr.	Research Professor	UNC
Devan Joe Shell	Graduate Research Assistant	UNC
Xiaodong Wang	Research Associate Professor	UNC
Yubai Zhou	Post-doc Research Associate	UNC

NC Policy Collaboratory Project-related Grants

Additional grant applications are in progress for submission in 2021 using data produced herein in support of these proposals.