Attachment C-1

Covid-19 Grant Project Status Report

Before it will be possible to make any disbursement, you are required to provide to the Agency the status towards the specific purpose as stated in the grant contract (Attachment A-1). This report is to be completed by the grant recipient and each subrecipient. The grant recipient is to ensure all subrecipients' reports are to be included with cost reimbursement requests. RECIPIENT COMPLETION INFORMATION:

Upload forms using the following link: https://ncosbm.sharefile.com/r-rc7f2ca49d574af2a

1. Organization

Organization Name	North Carolina Policy Collaboratory at the University of North Carolina at Chapel Hill (GSPH/Epidemiology/Baric H5L09)
Contract Agreement Number	23-01
Date	February 15, 2021

2. Financial Summary

Total Funding Authorized	Total Funding Received to Date	Balance
702,095	689,625.84	$12,468.16

Collaboratory Covid-19 Research Summaries

Rapidly Emerging Antiviral Drug Discovery Initiative (READDI CCP).
Ralph S. Baric, PI

Introductory Text: The goal of the Rapidly Emerging Antiviral Drug Discovery Initiative (READDI) is to develop antiviral drugs for epidemic and pandemic viruses. In the current environment, READDI is focused exclusively on identifying and developing antiviral drugs to treat and/or prevent COVID-19 infections. 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. We will test hit and lead compounds, identified in collaboration with commercial groups for antiviral activity against SARS2 using in vitro and in vivo assays at Biosafety level 3 (BSL3). We will also develop enhanced models of COVID-19 disease for use on testing antiviral drug efficacy.

Start of Block: Contact Information

Q1 Name
Ralph S. Baric
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Q2 Email Address
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End of Block: Contact Information

Start of Block: Research Project Information: Rapidly Emerging Antiviral Drug Discovery Initiative (READDI CCP). R. Baric, PI

Q6 Succinctly state your research question in 2-3 sentences (character limit 100).
The goal of the Rapidly Emerging Antiviral Drug Discovery Initiative (READDI) is to develop antiviral drugs for epidemic and pandemic viruses. In the current environment, READDI is focused exclusively on identifying and developing antiviral drugs to treat and/or prevent COVID-19 infections.

Q7 Describe your research methods and activities in a short paragraph. Please use plain language and avoid technical terms unless necessary. (character limit 1,000).
READDI is focused exclusively on identifying and developing antiviral drugs to treat and/or prevent COVID-19 infections. 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. We will test hit and lead compounds, identified in collaboration with commercial groups for antiviral activity against SARS2 using in vitro and in vivo assays at Biosafety level 3 (BSL3). We will also develop enhanced models of COVID-19 disease for use on testing antiviral drug efficacy. The large numbers of drug candidates that need to be tested. These efforts will be coordinated with the Heise lab to provide maximum testing capability while avoiding duplication of efforts. All experiments performed in human airway epithelial cells (HAEs) as well as continuous human airway epithelial cells. Work is geared towards development of therapeutics, which include small molecule inhibitors or immunotherapeutics that block virus replication in vitro or in vivo.

To accomplish the goals described above, deliverables generally include the development of:
a) small animal models of human disease,
b) identifying novel high-risk zoonotic coronaviruses that are poised for cross specie movement and vulnerable to lead compounds,
c) testing novel drugs from commercial and local sources
d) identifying lead compounds for in testing in primary human airway epithelial cells and then small animal models of human disease.

Q8 Describe your research findings and conclusions in a short paragraph. Please use plain language and avoid technical terms unless necessary. (character limit 1,000).

We have purchased all equipment and supplies . We have identified many lead compounds and validated over 15 using high throughput screens and nLUC encoding SARS-CoV2 and MERS-CoV recombinant viruses. Two of these leads, Osimertinib and Afatinib failed to block SARS-CoV2 replication and pathogenesis in vivo. We have developed new mouse models of human disease and used these to identify one drug, which is currently in phase IIII human trials, called pegylated interferon lambda. We have identified new high risk emerging coronaviruses, designated SADS-CoV, which is a threat to human health and the pork industry. The most recent publication (Linsky et al., Science) describes a SARS-CoV2 human angiotensin-converting enzyme 2 (hACE2) decoy molecule that binds and neutralizea severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The best monovalent decoy, CTC-445.2 was very potent and high specificity to the receptor-binding domain (RBD) of the SARS-CoV2 spike protein. A bivalent decoy, CTC-445.2d, showed ~10-fold improvement in binding. CTC-445.2d potently neutralized SARS-CoV-2 infection of cells in vitro, and a single intranasal prophylactic dose of decoy protected Syrian hamsters from a subsequent lethal SARS-CoV-2 challenge.

Q9 From your perspective as a researcher, explain any implications or policy recommendations resulting from your research (character limit 1,000).

The program demonstrates the critical importance of public, academic, and commercial collaborations to bring forward key reagents and models for rapidly identifying and moving products toward human use. Our data suggests that the new SADS-CoV is likely a critical One health pathogen that threatens human health and the swine industry, arguing that vaccines should be developed. Our data also argue that this virus should only be worked on in high containment BSL3 facilities. We were pleased to see the Chinese government restrict all research on this live virus to BSL3 facilities in China.

End of Block: Research Project Information

Start of Block: By the Numbers

Q11 How many members were a part of your research team? Include faculty, staff, postdoctoral researchers, graduate, and undergraduate students. If a type does not apply, please indicate with a numeric zero (0).

- O Faculty (3) Baric, Sheahan, and Graham
- O Staff, permanent (6) Lindesmith, Yount, Schaefer, West, Brown, and Parrish
- O Staff, temporary (0) _____
- O Postdoctoral researchers (2) Leist and Hou
- O Graduate students (0) _____
- O Undergraduate students (0)_____

* Q12 How many community members or participants did you engage in your research project? If not applicable, please indicate with a numeric zero (0).
five, Gralinski, Sheahan, Currie, Randell, Moorman

Q20 How many University-external stakeholders or partners did you work with as part of your research project? If not applicable, please indicate with a numeric zero (0).
four, Glenn, Gale, DeSilva, Ekins

Q18 Please detail any other interesting project-specific metrics (e.g. number of samples) that are relevant to your project below.

A mouse-adapted model of SARS-CoV-2 to test COVID-19 countermeasures.
Dinnon KH 3rd, Leist SR, Schäfer A, Edwards CE, Martinez DR, Montgomery SA, West A, Yount BL Jr, Hou YJ, Adams LE, Gully KL, Brown AJ, Huang E, Bryant MD, Choong IC, Glenn JS, Gralinski LE, Sheahan TP, Baric RS. Nature. 2020 Oct;586(7830):560-566. doi: 10.1038/s41586-020-2708-8. Epub 2020 Aug 27. PMID: 32854108.

Linsky TW, Vergara R, Codina N, Nelson JW, Walker MJ, Su W, Barnes CO, Hsiang TY, Esser-Nobis K, Yu K, Reneer ZB, Hou YJ, Priya T, Mitsumoto M, Pong A, Lau UY, Mason ML, Chen J, Chen A, Berrocal T, Peng H, Clairmont NS, Castellanos J, Lin YR, Josephson-Day A, Baric RS, Fuller DH, Walkey CD, Ross TM, Swanson R, Bjorkman PJ, Gale M Jr, Blancas-Mejia LM, Yen HL, Silva DA. De novo design of potent and resilient hACE2 decoys to neutralize SARS-CoV-2. Science. 2020 Dec 4;370(6521):1208-1214. doi: 10.1126/science.abe0075. Epub 2020 Nov 5. PMID: 33154107.

Edwards CE, Yount BL, Graham RL, Leist SR, Hou YJ, Dinnon III KH, Sims AC, Swanstrom J, Gully K, Scobey TD, Cooley MR, Currie CG, Randell SH, and Baric RS. Swine Acute Diarrhea Syndrome Coronavirus Replication in Primary Lung and Intestinal Cells Reveals Potential Human Susceptibility to Infection. Proc Natl Acad Sci U S A. 2020 Oct 27;117(43):26915-26925.

Puhl AC, Fritch EJ, Lane TR, Sacramento CQ, Tavella TA, Costa FTM, Frieman M, Premkumar L, Pearce KH, Hurst B, Schult DC, Cherry S, Andrade CH, Scholle F, Moreno T, Souza L, Moorman NJ, Baric RS, Madrid P and Ekins S. Repurposing The Ebola and Marburg Virus Inhibitors Tilorone, Quinacrine and Pyronaridine: In vitro Activity Against SARS-CoV-2. Under review, Virus Research

o X Yes (1)

Display This Question:

If Were you able to leverage additional funding to continue the research funded by the NC General As... Yes

See Below

Q15 Please detail the amount of leveraged funding and the funding agency or agencies below. If you received funding from more than 5 sources, please email Hope Thomson at thomson1@email.unc.edu .

NIH AID. U19AI116484-05S1 Calvin Kuo (PI), Baric R Co-Investigator $155,500
Sept 2020 to June 2021
Human lung and intestinal organoid models of SARS-CoV-2 infection. Given our use of primary cells to identify broad based drugs and other antivirals against the SARS-CoV2. We leveraged primary airway culture data and mouse models to develop a collaboration with researchers at Stanford University (Calvin Kuo) request for supplement to develop primary organoid cultures for evaluating drugs in vitro.

Pfizer Baric, RS (PI) $323,614
June 2020-July 2020
To evaluate the potency of a panel of drugs against SARS-CoV2 replication in vitro and in vivo.

Takeda Baric, RS (PI) $413,919
June 2020-April 2021
To evaluate the potency of a panel of drugs against SARS-CoV2 replication in vitro and in vivo.

Gates Baric, RS (PI) $280,501
June 2020-July 2021
To investiage the potency of drugs against the SARS-CoV2 replication in vitro and in vivo.

Q16 Do you have a grant in progress or plan to apply for additional funds to continue your work as funded by the Collaboratory? If so, please detail the grant amounts and funding agencies below to the best of your knowledge.

No

Q17 Please include below any links to news coverage, press releases, or other public-facing documentation of your Collaboratory-funded work:

None

End of Block: By the Numbers