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Sandia National Laboratories

Bioscience COVID Rapid Response Report

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ABSTRACT

The COVID-19 disease outbreak and its impact on global health and economies have highlighted the national security threat posed by pathogens with pandemic potential and the need for rapid development of effective diagnostics and medical countermeasures. The Bioscience IA selected for funding rapid COVID LDRD project proposals that addressed critical R&D gaps in pandemic response that could be accomplished in 1-3 months with the requested funding. In total, the Bioscience IA funded nine rapid projects that addressed 1) rapid and accurate methods for SARS-CoV-2 RNA detection, 2) modeling tools to help prioritize populations for diagnostic testing, 3) bioinformatic tools to track SARS-CoV-2 genomic sequence changes over time, 4) molecular inhibitors of SARS-CoV-2 cellular infection, and 5) method for rapid staging of COVID19 disease to enable administration of more effective treatments. In addition, LDRD funded one larger project to be completed in FY21 that leverages Sandia capabilities to address the need for platform diagnostics and therapeutics that can be rapidly tailored against emerging pathogen targets.

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EXECUTIVE SUMMARY

The Bioscience IA established a review committee for bioscience COVID rapid response proposals including the following members: Dave Chandler, Sandia fellow (8300; committee lead), Cathy Branda, Bioscience IA Deputy, Sr. Manager, Applied Biosciences & Engineering (8620), Victoria (Tori) VanderNoot, Manager, Biotechnology & Bioengineering (8621), and Tom Kulp, Sr. Scientist (8600).The committee reviewed project proposals and selected for funding those that 1) identified R&D gaps in pandemic response, had a strong experimental approach, and were feasible to complete project within the proposed time frame and budget.

The Bioscience IA funded 10 COVID LDRD in all:

1. **COVID-19 infection prevention through natural product molecules (UUR) PI: Cody Corbin**

Abstract: The COVID-19 pandemic requires urgent countermeasures, and naturally occurring product molecules are attractive for therapeutic or prophylactic usage A fairly recent preprint article (H. Chen; Q. Du. "Potential natural compounds for preventing 2019-nCoV infection", 01/20/2020, not yet peer-reviewed) focuses on the modeling of five different natural product molecules for blocking the ACE2 protein active site in human airways, the select site where COVID-19 enters cells and replicates. Putative binding poses were generated using the AutoDock Vina software package with the default scoring function (Trott O, Olson AJ, 2010). Their modeling shows that all five compounds could potentially have inhibition effects, but no actual experimental work had been performed. This high-risk project sought to investigate the utility of four of these compounds (scutellarin, glycyrrhizin, baicalin, hesperetin) through three experimental assays: 1) Determine the *in vitro* toxicity of these compounds in several SARS-CoV-2 permissive tissue culture lines; 2) Determine the inhibitory ability of these compounds in an ACE2::SARS-CoV-2 spike protein ELISA assay; and 3) Determine the effectiveness of these compounds at stopping SARS-CoV-2 infection *in vitro* cell experiments. Overall, compounds exhibited no toxicity until extreme dosages and times were reached. However, neither the ELISA assay nor cell assay using pseudotyped SARS-CoV-2 showed any inhibition of infection.

2. **Testing a novel peptide drug towards a goal of reducing mortality in critically ill COVID19 patients (UUR) PI: Raga Krishnakumar**

Abstract: We have shown that NP64A can reverse the effects of TNFa on lung epithelial cells both at the cellular phenotypic level as well as the molecular level. These results suggest that NP6A4 is a promising therapy for diseases such as COVID19 that are a systemic multi-organ problem, affecting the delicate balance of the immune system to fight infection by not become overactive (as is the case in a cytokine storm). In addition, immunomodulatory drugs such as NP6A4 can have broad applications across many infectious diseases, as well as other conditions relevant to public health such as autoimmune disease and cancer, which makes this therapeutic of broad interest to the scientific and clinical community. We will explore this therapeutic further by publishing our results in a peer-reviewed journal and applying for follow-on funding.

3. **RSVP – Flu like illness and respiratory syndromes (UUR) PI: Susan Caskey**

Abstract: Individuals infected with SARS-CoV-2, the virus that causes COVID-19, may be infectious between 1-3 days prior to symptom onset. People may delay seeking medical care after symptom development due to multiple determinants of health seeking behavior like availability of testing, accessibility of providers, and ability to pay. Therefore, understanding symptoms in the general public is important to better predict and inform resource management plans and engage in reopening. As the influenza season looms, the ability to differentiate between clinical presentation of COVID-19 and seasonal influenza will also be important to health providers and public health response efforts. This project has developed an algorithm that when used with captured syndromic trends can help provide both differentiation to various influenza-like illnesses (ILI) as well as provide public health decision makers a better understanding regarding spatial and temporal trends. This effort has also developed a web-based tool to allow for the capturing of generalized syndromic trends and provide both spatial and temporal outputs on these trends. **SAND2020-9353**

4. Betacoronavirus sequence server (UUR) PI: Kelly Porter Williams

As a viral outbreak progresses, sequence variations in the viral genome accrue that can 1) be used to track chains of transmission, 2) warn us when our diagnostics, vaccines or therapeutics may begin to fail, 3) signal turning points in an outbreak such as attenuation of virulence, and 4) inform us on the origins of the outbreak. A coronavirus sequence server (CSS) has been developed for monitoring the SARS-CoV-2 (SARS2) agent of the COVID-19 outbreak, and facilitating comparison to other coronavirus groups. Automated update of CSS and analysis of sequence variation provides information to Sandia and other National Laboratory colleagues to assist their COVID-19 research on development of diagnostics, protein function, and viral origins. Specific recommendations are suggested from this work for Sandia research directions: 1) Continue to monitor and functionally annotate SARS2 sequences, especially a) sequence involved in molecular interactions with host proteins/RNAs or virus-virus protein contacts; b) contacts with therapeutic antibodies and drugs as they are developed; c) diagnostic oligonucleotide binding sites; 2) Extend to other Coronaviridae, tracking key motifs (furin cleavage sites, host protein interaction sites, recombination events) and the unconserved proteins; 3) Extend to other viral groups, such as the filoviruses and henipaviruses that have known protein receptors; and 4) Support zoonotic virus surveillance as perhaps best done through deep sequencing, developing capabilities for discovering truly novel viruses. **SAND2020-7658**

5. Handheld biosensor for COVID-19 screening (UUR) PI: Darren Waltz Branch

Abstract: We have made significant progress toward the development of an integrated nucleic acid amplification system for Autonomous Medical Devices Incorporated (AMDI's) Optikus handheld diagnostic device. In this effort, we developed a set of loop-mediated isothermal amplification (LAMP) primers for SARS-CoV-2 and then demonstrate amplification directly on a surface acoustic wave (SAW) sensor. We built associated hardware and developed a C-code to control the amplification process. The goal of this project was to develop a nucleic amplification assay that is compatible with SAW sensors to enable both nucleic and serological testing in a single handheld diagnostic device. Toward this goal, AMDI is collaborating Sandia National Laboratories to develop a rapid, portable diagnostic screening device that utilizes Sandia's unique surface acoustic wave biosensor (SAW) for COVID-19 detection. Previously, the SANDIA- AMDI SAW sensor has successfully detected multiple high-

profile bacteria viruses, including Ebola, HIV, Sin Nombre, and Anthrax. Over the last two years, AMDI and SANDIA have significantly improved the sensitivity and detection capability of the SAW biosensor and have also developed a modular hand-held, portable platform called the Optikus, which uses CD microfluidics and handheld instrumentation to automate all sample preparation, reagent introduction, sample delivery, and measurement for a number of different assay targets. We propose to use this platform for the development of a rapid (<30 minutes), point-of-care diagnostic test for detection of COVID-19 from nasal swab samples.

6. **Development of novel medical countermeasures against COVID-19 (UUR) PI: Brooke Harmon;** SAND report to be submitted in FY21

7. COVID-19 biomarkers based on respiratory microbiome content PI: Steven Branda

Abstract: We carried out a meta-analysis of the dataset as a first step in evaluating the potential for profiling of respiratory microbiome dynamics as a means of accurately assessing COVID-19 disease state. The results from this meta-analysis clearly indicate that the respiratory microbiome of COVID-19 patients is radically different from those of healthy subjects and CAP patients. We identified the 12 bacterial families that best illustrate this difference. For 5 of these bacterial families, measurement of their relative abundance in BALF should enable recognition of COVID-19; and for the remaining 7 bacterial families, detection of them at all should be sufficient for recognition of COVID-19. It is important to keep in mind that while the BALF RNA-Seq dataset used as the basis for this study served as an excellent starting point, analysis of additional studies will be required to determine whether the observed differences in respiratory microbiome content are resilient to study-to-study variability. However, our results strongly suggest that classifiers based on the 12 bacterial families of greatest interest (or, ideally, small subsets of them) should enable diagnosis of COVID-19 through BALF analysis (eg, using qPCR or microarrays, which are faster than RNA-Seq). Moreover, these classifiers, or variations on them, may also enable accurate assessment of COVID-19 severity and stage, a hypothesis that should be tested in future work. Successful verification of the observed trends and proposed classifiers in future prospective studies should lead to commercial licensing for assay implementation and rapid translation to clinical use, potentially improving patient management in the ongoing and/or future COVID-19 outbreaks. **SAND2020-1207941**

8. Computational modeling to adapt neutralizing antibody PI: Michael S Kent

Abstract: We performed computational modeling of the SARS-CoV-neutralizing antibody S230 to predict mutations needed to adapt this antibody to SARS-CoV2. The computational modeling involved a combination of Monte Carlo-based mutational analysis and molecular dynamics simulations. These two approaches are used because Monte Carlo-based mutational analysis is able to search the enormous sequence space and MD is the best approach for establishing structural fidelity. Two iterations of mutational analysis followed by MD simulation were performed. Two methods were used to assess the best mutations after the second iteration: DDG values from the mutational analysis, and an analysis of the contacts during the second MD simulation. After selecting the best mutations and inserting them into the structure, a docking analysis was performed to compare with the docking

results of the as-built structure. Based on the modeling results, 7 antibodies were purchased and testing for binding to SARS-CoV and SARS-CoV-2. The results show that 2 of the S230 variants bind to SARS-CoV-2. However, they did not compete with soluble human ACE2. Most likely the binding to SARS-CoV-2 is too weak to compete with ACE2, but it is also possible that the variants bind in a location that does not compete with ACE2. Using computational modeling we successfully adapted SARS-CoV-neutralizing antibody S230 to bind to SARS-CoV-2 but the binding level is insufficient for a therapeutic-caliber antibody. Further affinity maturation is needed to improve binding to SARS-CoV-2.

9. Pre-symptomatic COVID screening (UUR) PI: Ronen Polsky

Abstract: Temperature checks for fever are extensively used for preliminary COVID screenings but are ineffective during the incubation stage of infection when a person is asymptotic. Researchers at the European Centre for Disease Prevention and Control concluded that approximately 75% of passengers infected with COVID-19 and traveling from affected Chinese cities would not be detected by early screening. Core body temperature is normally kept within a narrow range and has the smallest relative standard deviation of all vital signs. Heat in the body is prioritized around internal organs at the expense of the periphery by controlling blood flow. In fact, blood flow to the skin may vary by a factor of 100 depending on thermal conditions. This adaptation causes rapid temperature fluctuations in different skin regions from changes in cardiac output, metabolism, and likely cytokine diffusion during inflammation that would not be seen in average core body temperature. Current IR and thermal scanners used for temperature checks are not necessarily reflective of core body temperatures and require cautious interpretation as they frequently result in false positive and false negative diagnosis. Hand held thermometers measure average skin temperatures and can get readings that differ from core body temperature by as much as 7°. Rather than focusing on a core body temperature threshold assessment we believe that variability of temperature patterns using a novel wearable transdermal microneedle sensor will be more sensitive to infections in the incubation stage and propose to develop a wearable transdermal temperature sensor using established Sandia microneedle technology for pre symptomatic COVID screening that can additionally be used to monitor disease progression at later stages. **SAND2020-1207931**

10. Efficacy and delivery of novel FAST agents for coronaviruses (UUR) PI: Colleen Courtney

Abstract: We proposed to test and develop advanced delivery for novel agents from our collaborators Facile Accelerated Specific Therapeutics (FAST) platform to reduce coronavirus replication. Sachi Bioworks Inc., Prof. Anushree Chatterjee, and Prof. Prashant Nagpal at the University of Colorado Boulder have developed a bioinformatics and synthesis pipeline to produce sequence specific theranostic agents (agents that can be therapies and/or diagnostics) that are inherently transported into the cytoplasm of mammalian host cells and sequence-specifically interfere in nucleic acid replication. The agent comprises a small nanoparticle (2-5 nm) chosen for ideal cellular transport and/or imaging conjugated to a short, synthetic DNA analog oligomer designed for binding to one or more target viral sequences. The sequence specific binding of the FAST agent to its target prevents nucleic acid replication due to its high affinity binding. While the small nanoparticle facilitates delivery *in vitro*, we plan to package the FAST agents into a larger nanoparticle (80-300 nm) for future *in vivo* delivery applications. Our team at Sandia has

expertise encapsulating biomolecules including protein, DNA, and RNA into solid lipid nanoparticles (LNP) and lipid coated mesoporous silica nanoparticles (LC-MSN) and shown successful delivery in mouse models to multiple tissues. Our team focused on formulation parameters for FAST agents into lipid nanoparticles (LNP) and lipid coated mesoporous silica nanoparticles (LC-MSN) for enhanced delivery and/or efficacy and *in vivo* translation. We used lipid formulas that have been shown in literature to facility *in vitro* and more importantly, *in vivo* delivery. In our work discussed below, we successfully demonstrate loading and release of FAST agents on silica core and stable LC-MSN in a reasonable size range for *in vivo* testing. **SAND2020-10149**

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