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OFFICE OF THE VICE PRESIDENT – RESEARCH AND INNOVATION

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December 4, 2020

Dr. Francis S. Collins
Office of the Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

RE: UC Comments in Response to NOT-OD-21-018, "Request for Information (RFI): Inviting Comments and Suggestions on the NIH-Wide Strategic Plan for COVID-19 Research"

Dear Dr. Collins:

I write on behalf of the University of California (UC) system with regard to the Request for Information (RFI) on the NIH-Wide Strategic Plan for COVID-19 Research issued on October 28, 2020.

The UC system is comprised of ten research-intensive campuses, six medical schools, and three affiliated U.S. Department of Energy national laboratories. As a system, UC receives approximately $6 billion annually of extramural awards to support research conducted throughout all UC locations. UC generally receives 5 to 6 percent of the NIH's annual appropriations for research, making UC the largest single recipient of NIH funding for academic research.

The UC system has been quick to respond to the compelling and dire need for COVID-19 research, including diversion of biosafety facilities to study SARS-CoV-2, pivoting research labs to perform tests for surveillance and clinical management of the novel coronavirus on campus and in nearby communities and promptly shifting funds to distribute for research endeavors. While the UC system supports, and will continue to support, robust pathways to accelerate research into the fundamental knowledge, detection, treatment, and prevention of COVID-19, we note several areas of research absent from the NIH-Wide Strategic Plan for COVID-19 Research. In addition, we see a ripe opportunity to bring about a significant shift to future pandemic preparedness. We ask for the help of our federal partners, mainly NIH, to ensure sustained federal funding for fundamental research and development activities beyond COVID-19. Furthermore, we recognize the long-term threat posed by emerging infectious diseases, and ask the NIH to create a plan to incentivize researchers and trainees to remain in this field after this pandemic is over.

Our specific comments on the Strategic Plan as well as future pandemic preparedness are provided below.

Priority 1: Improve Fundamental Knowledge of SARS-CoV-2 and COVID-19

We believe that three additional scientific areas merit attention under Priority 1: modeled simulation studies, investigations into so-called "long haulers," longitudinal studies that include asymptomatic people, and the development of new research technologies to better understand the virus.

First, modeled simulation studies are not mentioned in the NIH-Wide Strategic Plan for COVID-19 Research; however, these types of studies have been used extensively by national governments and the World Health Organization in deciding the best strategies to pursue in mitigating the effects of COVID-19. Principally, these have been epidemiological models aimed at understanding the spread of the disease and the impacts of different interventions. A global pandemic like COVID-19 generates a large number of problems and questions, and each requires a different model to find the best solution. We recommend that the NIH include modeled simulation studies as a way to understand the general knowledge around SARS-CoV-2 and COVID-19.

Second, Priority 4.1 mentions research into the effects of COVID-19 across the lifespan; however, the long-term natural history of the infection also needs to be investigated. Specifically, this includes understanding the basic biology of the virus as well as the epidemiology and genetics of people who have persistent symptoms for months after the virus has stopped replicating. Tens of thousands of people in the United States have such a lingering illness following COVID-19. In the US, the term post-COVID "long haulers" is used to describe this occurrence. Published studies[1] and surveys conducted by patient groups indicate that 50% to 80% of patients continue to have significant symptoms three months after the onset of COVID-19, even after tests no longer detect virus in their body.

Third, data from those who are asymptomatic need to be gathered to better understand COVID-19. Much of the data gathered so far are from those who are symptomatic, but about 40% of people who contract SARS-CoV-2 are asymptomatic. We recommend that the NIH-Wide Strategic Plan for COVID-19 Research include longitudinal studies with both symptomatic and asymptomatic participants and investigations into why some people are asymptomatic.

Last, our fundamental understanding of the virus will benefit from technology development to provide better research tools for studying the viral life cycle and its impact on the host. Examples include:

- *In vitro* models of COVID infection, for example lung tissue, to facilitate basic research outside the clinical setting.
- New microscopies that exploit the power of soft X-rays and Terahertz lasers to image viral dynamics in the context of infected cells.
- Automating workflows through linking robotic unit operations, including sample preparation, manipulation, and observation to speed the time to discovery for new anti-viral medications and treatments for COVID-19.
- Rapidly deployable data sharing tools to enable the broad dissemination of research results to minimize the time taken to characterize the virus and develop therapeutics and vaccines.

[1] Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020

Priority 2. Advance Detection and Diagnosis of COVID-19

The limiting factor with most COVID-19 testing is the time it takes to get results because of the high demand, limited number of certified medical labs to perform the tests, and shortages of the proprietary reagents many of the diagnostic machines use. A long turnaround time for COVID-19 test results decreases the value of the test and can put others risk, which keeps the coronavirus spreading through a community. Therefore, we believe that the NIH-Wide Strategic Plan for COVID-19 Research should focus on strategies and technologies that can return results quickly, ideally within 24 hours or less.

UC is already developing novel ways to address the issue of testing and surveillance at speed and scale, for example:

- CRISPR-based approaches: Multiple UC laboratories have developed novel CRISPR-based tests, with or without associated amplification steps designed for a high-throughput laboratory setting or an individualistic point-of-care approach. These tests can be readily adapted to SARS-CoV-2 variants and new emerging pathogens, in addition to providing immediate test results.
- Non-traditional diagnostic tools: One campus is deploying a high-throughput testing machine repurposed from agricultural genetics to conduct COVID-19 testing. This has allowed the campus to minimize supply-chain shortages and bottlenecks at overburdened medical labs while inexpensively and rapidly returning results; this is helping to minimize risks for students returning to the campus.
- AI-powered adaptive surveillance: By using machine learning, researchers can more efficiently and effectively sift through syndromic, behavioral, environmental, public health, and prior testing data to identify geographic hotspots, target testing, and warn of impending outbreaks.
- Environmental surveillance testing: Effluent wastewater testing and air sample testing for SARS-CoV-2 (including use of mobile air sampling and other innovations in environmental surveillance) may serve as an early warning system for the spread of COVID-19 allowing for timely interventions.

Rapid tests alone are not enough to halt the spread of SARS-CoV-2; rapid tests have to be paired with accessibility. In this case, accessibility comes in two forms: having the ability to deploy testing in the community as well as designing tests in a way to increase the likelihood of people, especially those most vulnerable in the community, to get tested. It is essential that the NIH consider accessibility in the development of diagnostic testing. To speak to the first point, the majority of current testing is based on the polymerase chain reaction (PCR), which requires large, expensive automated machines that do many tests at once. Major hospitals or diagnostic facilities have such equipment, however these machines are hard to deploy in community settings. The NIH-Wide Strategic Plan for COVID-19 Research should include alternative approaches to PCR-based testing that could make it easier and quicker for people in the community to learn whether they have been infected. Some methods may include modifications to the standard PCR test or other methods such as those that sequence the virus directly or use CRISPR. Second, the NIH-Wide Strategic Plan for COVID-19 Research should include research into test design, particularly for those at the highest risk. Said simply, it is not enough to have tests available, but people have to be willing and able to take them. This includes considerations over convenient times and locations for testing as well as low costs for the disadvantaged populations.

Priority 3: Advance the Treatment of COVID-19

At present, there is no known treatment that can be administered before exposure to SARS-CoV-2 to prevent infection. Yet, drawing on lessons from the HIV/AIDS pandemic, pre-exposure prophylaxis (PrEP) with antiviral agents is a viable strategy to prevent infection. Therefore, we recommend that Priority 3.2 mention PrEP for SARS-CoV-2 as an alternative way to prevent COVID-19 or reduce disease severity, for instance, in long-term care facilities or in other closed settings.

Priority 3.2 can also consider the use of existing technologies used in novel ways to treat the virus. For example, exposure to low dose x-rays to find inhaled scintillating nano particles bound to the virus could be a way to treat the virus deep in the lungs. Specifically, upon exposure to low dose x-rays, the scintillating particles could emit UV light that destroys the virus *in situ*. The same technology could also be adapted for gamma imaging and/or magnetization for MRI studies of the infection.

Priority 3.3 should consider the need for innovation in the deployment of solutions described in Priority 3.2. For example, investigations into novel outpatient strategies related to the delivery of care via outpatient infusion of therapy, home care in the setting, and home diagnostics and screening should be furthered.

Priority 4: Improve Prevention of SARS-CoV-2 Infection

Priority 4.2 focuses on preventing SARS-CoV-2 transmission. We suggest inclusion of antimicrobials such as existing antiseptic mouthwashes and antivirals such as the new nanobodies-based AeroNabs developed at UC. Research results in this area could be salient for future pandemics, especially airborne coronaviruses.

Priority 4.3 addresses effective distribution of a vaccine as part of the preventive measures against COVID-19. We recommend that this section include modeling and evaluating approaches for a safe return to school.

Priority 4 in general should also include the development of IT risk procedures that allow for those in an exposure area to be alerted in a way that does not compromise the privacy of others.

Priority 5: Prevent and Redress Poor COVID-19 Outcomes in Health Disparity and Vulnerable Populations

With appreciation for the inclusion of Priority 5, the UC system strongly supports research that includes implementation science to ensure historically excluded populations achieve access to new prevention and treatments.

UC is already working on ways to redress health disparities among historically excluded populations, for example:

- Partnerships with community organizations: Collaborating with established community organizations in African-American, Asian-American, Latino, and Pacific Islander neighborhoods, UC has provided voluntary, free SARS-CoV-2 PCR testing to reach communities with high-COVID risk. These partnerships serve as a firm foundation for future vaccination rollouts.
- Telehealth readiness to promote health equity: Research focusing on preparing patients who have lower educational levels, lower English proficiency, or lower technology readiness skills before their telehealth visit can help prevent gaps in access to care.

Supporting the Research Infrastructure for COVID-19 and the Next Pandemic

If there is any lesson to be learned from the COVID-19 pandemic, it is that the nation should never again be at a loss for basic knowledge into how novel viruses, like COVID-19, operate and without pervasive testing capability for them. The country needs to prepare for the next pandemic *now*. We believe that there are several ways to support research and development activities for long-term pandemic preparedness: 1) greater investments into fundamental basic science; 2) sustained funding for long-term pandemic preparedness research and development activities; 3) investments in data science efforts that address interoperability and programmatic accessibility; and 4) incentives for researchers and trainees to continue understanding how viruses operate once the COVID-19 pandemic is over.

1. <u>Greater Investments into Fundamental Basic Science</u>

The UC system appreciates that the NIH lists as its first priority improving the fundamental knowledge of SARS-CoV-2 and COVID-19. However, before understanding the mechanisms of SARS-CoV-2 infection, we believe that there are advantages to deepening understanding into the fundamental science of viruses, in general, and possible scientific responses to future pandemics.

The federal government has long been the largest funder of U.S. basic research, yet the proportion of funding for fundamental knowledge has declined from 70% in 1980 to about 40% in 2018. We ask that the NIH provide continued support for, and advocate for, greater investments into fundamental basic science across federal funding agencies, including NIH Institutes and Centers. The answers to future challenges are as unpredictable as the challenges themselves.

An example of the importance of fundamental research can be seen in Dr. Jennifer Doudna's work into CRISPR technology, which started as a basic research project in her lab at UC Berkeley. This technology is now being used in the current pandemic. Specifically, scientists are deploying CRISPR-based diagnostics to recognize RNA sequences in SARS-CoV-2 genome to quickly detect presence of the virus. Scientists see the potential of using CRISPR diagnostics, which can be adjusted easily to detect other pathogens for rapid diagnosis during future outbreaks. Likewise, the promising mRNA vaccines were built upon decades of curiosity-driven studies of RNA, fundamental virology, and immunology.

Other ways in which NIH can support the general infrastructure for fundamental science include funding for:

- Cellular and animal Biosafety Level 3 (BSL-3) laboratories, which can expedite modeling of underlying emergence mechanisms and virus progressions.
- IT research and high performance computing resources to assist with the distinctive domains of information pertinent to SARS-CoV-2 illness severity.
- One Health research into the movement of potential pathogens from and to animals.

2. <u>Sustained Funding For Long Term Pandemic Preparedness Research and Development Activities</u>

Over the course of this pandemic, many university researchers have transitioned their academic labs to address COVID-19, sacrificing their work and funding to learn a new field in order to help combat the virus. However, once this pandemic is over, there will be a natural inclination for researchers to return to their previous work, which creates a missed opportunity to harness the talent needed to plan for future emergencies. The UC system strongly recommends that the NIH consider ongoing funding and programmatic support to evolve and extend what the scientific community has already built in response to COVID-19 in order to more efficiently and effectively plan for future pandemics.

3. <u>Investments in Data Science Efforts that Address Interoperability and Programmatic Accessibility</u>

Adoption of clear, open-source standards for data interoperability and a data catalog are important steps to facilitate rapid integration of clinical data across a large number of health care systems. We propose that the NIH adopt interoperation standards (such as OMOP and FHIR), a data catalog (such as GSA's catalog.data.gov), and make available software tools and test beds. The NIH should also encourage *model* sharing and provide a platform where researchers can exchange scientifically proven best-of-breed predictive AI models.

4. <u>Incentives for Researchers and Trainees to Continue Work in Pandemic Preparedness</u>

The UC system believes that there is an opportunity to rewire the current pandemic preparedness system to ensure that the U.S. will have the capacity and know-how to respond to the next major societal health crisis, whether that be a virus, bacterium, parasite, fungus, or some other unknown foe. Beyond sustainable funding, we believe that the NIH can play a pivotal role in this by incentivizing work in pandemic preparedness as a fruitful career. This can be done in a number of ways, such as using the existing PO1 funding system or via other new mechanisms that emphasize innovation, so long as implemented mechanisms attract the best and brightest to collaborate on aspects of pandemic preparedness a manner that satisfies individual needs to have a stable and rewarding career.

Additional Comments

Regulatory relief should be provided to research labs during the Public Health emergency period, by 1) permitting enforcement discretion for research laboratories that perform COVID testing and want to return results to research subjects, 2) encouraging consideration of Emergency Use Authorization applications from unregistered research laboratories, provided that they adhere to applicable requirements and performance standards, and 3) encouraging state public health agencies to follow suit with respect to applicable state laws that, like CLIA, preclude full reporting and utilization of research test results.

Finally, because solutions to problems in a pandemic often involve cross-disciplinary efforts, we strongly recommend that the NIH pursue synergies and funding collaborations with other federal agencies (such as NSF, DOE, WH-OSTP), and encourage similar collaboration at the state and local levels.

Thank you for the opportunity to comment on this important issue and we look forward to continued engagement on this issue.

Sincerely,

Theresa A Maldonado

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