



EXECUTIVE SUMMARY

Responding to the Coronavirus Threat through Investments in Fundamental Biomedical Research.

From the Public Affairs Committee of the Biophysical Society

The battle against the Coronavirus COVID-19 pandemic is being waged by health care workers and politicians who are implementing the tools of medicine and public policy in an attempt to track the spread of infection, limit its transmission, and treat the sickest individuals. However, effectively containing and limiting the spread of COVID-19, as well as responding to future pandemics by emerging, as yet unknown, infectious diseases, will require substantial increases in our knowledge of how this virus and other pathogens infect humans, how the human immune system responds to infection, and how to leverage this understanding to develop new vaccines and drugs. These needs can only be addressed by substantial increased funding for fundamental biomedical research, as supported through congressional appropriations to federal agencies such as the NIH, NSF and DOE. These funding increases need to be immediate in order to effectively respond to COVID-19, such as to support test and vaccine development. Additionally, any funding increases must be sustained in order to better understand not only this virus but other infectious diseases that could spark the next global pandemic, such as to support the technological infrastructure needed to study these infectious agents and the underlying biology of how pathogens infect humans and how the human immune system responds. Substantially increasing funding in fundamental biomedical research is not only our best weapon in eradicating COVID-19 entirely, but also in preventing future pandemics from killing millions more and ravaging our economies and societies.

Responding to the Coronavirus Threat through Investments in Fundamental Biomedical Research.

From the Public Affairs Committee of the Biophysical Society

The Coronavirus COVID-19 outbreak is putting enormous strains on our hospitals, health care providers and public health system. ***The immediate response to the pandemic*** is focused, necessarily, on tracking the progression of infection, limiting its spread through social distancing and other behavioral modifications, and treating the sickest infected individuals who are unable to recover on their own in self-quarantine. However, effectively containing and limiting the spread of COVID-19 also depend heavily on fundamental biomedical research being conducted right now, in large part because we know so little about this virus, the way in which it infects individuals, how the human immune system responds to it, and how it spreads from person to person. ***The future response to the pandemic*** needed to stop COVID-19 from returning seasonally and to eradicate it from the human population, as well as to responding to other, as yet unknown, emerging infectious diseases, depends almost entirely on the results of fundamental biomedical research yet to be conducted. These current and future research programs are not funded through Medicare, Medicaid or any health insurance provider. Rather, they depend on appropriations to federal agencies, such as the National Institutes of Health (NIH), the National Science Foundation (NSF) and the Department of Energy (DOE). COVID-19, as well as the next coronavirus or other infectious disease that could spark a global pandemic that kills millions and destroys economies worldwide, require ***substantial immediate and sustained increases in appropriations*** to NIH, NSF, DOE and other federal agencies that fund fundamental biomedical research.

The U.S. Congress just passed a \$2 trillion stimulus package with major new investments in the economy and healthcare. To a much lesser extent, funding for fundamental biomedical research was also provided in this bill. Indeed, approximately \$950 million was dedicated to supporting research efforts at the NIH. While this seems like a large amount of funding, it represents less than 0.05% of the stimulus package and only a 2.2% increase in the overall FY20 operating budget of the NIH; substantially less even than recent annual NIH budget increases. A significantly larger immediate and sustained increase in fundamental research funding will be needed to combat COVID-19 and to protect us from the inevitable next pandemic.

The 48-page [NIH-Wide Strategic Plan](#) 2016-2020 summary provides an excellent overview of budgetary needs required to address this crisis, and should be widely read. The [Strategic Plan](#) on vaccine adjuvants for the National Institute of Allergy and Infectious Disease (NIAID) is particularly important. Yet many critical research components for the coronavirus response are led by the roughly 35,000 NIH-funded Principal Investigators, working primarily at research universities and institutes across the nation, whose research is supported by other NIH Institutes and Centers. Supplemental funding to existing NIH grants through mechanisms recently instituted by some NIH institutes, such as NIDA and NIGMS, is one way in which to address these problems quickly and effectively. We recommend that similar steps be taken by the other NIH institutes and US research funding agencies. However, more needs to be done.

In terms of necessary fundamental and applied research, the budgetary response to the outbreak will require focused proposals identifying immediate increased investments, as well as longer term outlays to support a sustained response to this and future pandemics. Identified below are several critical areas of both fundamental and translational research, informed by the collective experience of Biophysical Society members, which require Congressional support for immediate and sustained increased funding in order

to address the challenges posed by the current coronavirus pandemic, as well as to position our nation to respond quickly and effectively to the inevitable next pandemic outbreak.

Immediate fundamental biomedical research funding needs

Outlined below are areas of research and development that require substantial immediate increases in funding for fundamental biomedical research to effectively respond to COVID-19.

Test Development:

Sensitive and accurate tests exist for viral sequences and proteins that unambiguously indicate infection. However, increasing the speed of the tests and ensuring a robust supply line are key to their utilization, as demonstrated by the challenges faced in the February roll out of COVID-19 testing in the US.

- Initiatives to increase the speed of current polymerase chain reaction (PCR)-based testing methods through NIH, NSF and DOE should be established and explicitly funded.
- Programs to support the rapid development of novel tests that leverage non-PCR technologies that could have higher throughput and/or accuracy than current tests, such as serological tests currently under development.
- A new supply chain analysis unit should be established in the Centers for Disease Control and Prevention (CDC) in order to ensure that the biotechnology and pharmaceutical industries produce reagents for millions of testing kits.

Vaccine Development:

Vaccines represent the best long-term response to infectious diseases, including COVID-19, as well as other coronaviruses and emerging pathogens. Vaccines protect healthy individuals from getting sick, stop the spread of disease and, in certain cases such as smallpox, can completely eradicate a particular virus from the world.

- The most effective vaccines currently in use are based on either purified but inactivated virus particles or purified subunits of the virus, for example the influenza hemagglutinin protein. Producing these proteins in the very high amounts needed to manufacture millions of doses requires understanding the mechanisms of production that the virus uses to make copies of its proteins such that it can generate new viruses and spread infection. Congress should appropriate funds adequate to expand substantially the existing NIAID-supported activities in this area.
- Development of vaccines requires testing with the actual infectious agents. This requires enhanced containment facilities for labs and animal facilities. Congress should appropriate funds to ensure institutions are in a position to carry out such testing and development, and can put in place the required containment facilities. NIAID should be provided with a dedicated fund to finance trials of new vaccine candidates.

Sustained fundamental biomedical research funding needs

Outlined below are areas of research and development that require substantial future sustained increases in funding for fundamental biomedical research to effectively respond to COVID-19 and other emerging infectious diseases. These needs can be broadly categorized into: (1) building the infrastructure required to apply the most advanced experimental techniques to understanding coronaviruses and other infectious diseases; and (2) biological studies to understand how viruses and other pathogens infect and replicate in humans and how the human immune system responds, or sometimes fails to respond, to these infectious agents.

Building Infrastructure for Fundamental Biomedical Research

Structural Biology:

In order to understand the possible targets for antibodies and anti-viral drugs, as well as to understand the steps involved in viral attachment to host cells, knowledge of the precise structures of all of the components of the virus are needed. This information is critical for the development of new vaccines and therapeutics to protect and treat individuals. The determination of the high-resolution three-dimensional structures of the viral particles, proteins, nucleic acids and membrane requires sophisticated instrumentation and facilities, including those for cryo-electron microscopy (cryo-EM), nuclear magnetic resonance (NMR), and X-ray diffraction. The purchase costs of these instruments are in the millions of dollars per instrument, and the annual budgets needed to keep each of these instruments working are often in the hundreds of thousands of dollars.

- Congress should substantially increase funding of existing facilities NMR, cryo-EM and X-ray diffraction facilities across the nation.
- In addition, the NIH and DOE budgets should be supplemented for dedicated increases in the X-ray diffraction beamlines at synchrotron facilities, such as at Argonne and Brookhaven National Laboratories.
- To provide the trained personnel needed to use these instruments, budgets for NIH Training Grants to support the next-generation of structural biologists in these areas should be increased.

Computational Biology:

Massive computational resources should also be harnessed in the fight against coronavirus and emerging infectious diseases. Computational biology is a key component of any research effort aimed at understanding and eventually mitigating disease. Funding initiatives to increase access to computational facilities at NIH, NSF and DOE, and to support computational research should be established and explicitly funded, including:

- Computational structural biology, which provides structural models of viral proteins and capsids that can be used in solving experimental structures and virtual screening of potential drugs. These methods can also characterize the dynamic properties of viral proteins and how these may be affected by the mutations which are sure to occur.
- Large, multi-scale simulations help to understand cellular processes and responses to changing conditions such as viral entry, reproduction and budding.
- Epidemiological simulations can track and predict viral spread, integrating real-time human travel data, epidemiological data and viral sequencing data to forecast the impact of potential public-health interventions and better project potential outbreak trajectories in the U.S. and across its borders.

Understanding Infection and Immunity

Biochemistry of Viral Replication:

Current effective targets of anti-viral drugs include the enzymes used by the virus to replicate their RNA and the proteases used by the virus to generate the nucleocapsid and other viral structural proteins – both of which are needed for the generation of new virus particles in the human body. NIH budgets for research on these enzymes and methods by which to inhibit their functions should be supplemented to support substantial expansion of research programs targeting this area.

The Immune Response:

The various types of white blood cells of the human immune system have evolved extremely sophisticated and effective mechanisms for detecting and counterattacking invaders, be they viruses, bacteria, fungi, parasites or toxins. However, many people infected with COVID-19 and other pathogens are unable to mount a sufficient immune response to fight off the virus. The extraordinary variation needed in the nature of the antibodies produced, and the generation of killer white cells that can recognize infected cells, leaves a great deal to be learned. Research in this area represents a key element of developing drugs and vaccines against COVID-19. The immune system protects us from all manner of pathogens, not just coronaviruses. We need to accelerate our understanding of all aspects of the immune system, both because of the importance in the design of vaccines, and in the body's response to infection in the absence of prior vaccination. Congress should greatly increase funding for research focused on the immune system.

Call to Action

Today, we are witnessing how a single infectious disease can spread like wildfire through the world's population, with utter disregard for its victims' stations in life or countries of residence. This global pandemic is not only killing thousands but also changing the very norms of human interaction and shuttering economies around the world. Even when this coronavirus infection is tamed, its societal and economic impacts will be devastating and long-lasting. As certain as we can say that this generation has never experienced anything remotely like this, it is, unfortunately, entirely possible that we could relive this nightmare over and over again. As ill-prepared as we were for this pandemic, we remain equally undefended against the inevitable next emerging infectious disease that will rip through the human population. This situation is not inevitable. We can fight off this coronavirus, perhaps even vanquish it from humankind forever, and generate the knowledge and tools required to stop the next pandemic before it gains hold. This will take an investment in science, the likes of which we have not seen since the Sputnik era, if ever. Fundamental biomedical research is the only way to generate the knowledge of how pathogens with pandemic potential infect humans, how the human immune system responds to these infections, and how to leverage this understanding to develop new vaccines and drugs. It is not only our best weapon in eventually ending this pandemic, but also in preventing future pandemics from killing millions more and ravaging our economies and societies. We call upon our policymakers to implement transformative legislation for massive biomedical research funding now.