This scanning electron microscope image shows SARS-CoV-2 (yellow), the virus that causes COVID-19, isolated from a patient in the United States, emerging from the surface of cells (pink) cultured in the lab. Credit: NIAID-RML
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Executive Summary

In response to the unprecedented threat of SARS-CoV-2 and the COVID-19 pandemic, the National Institute of Allergy and Infectious Diseases (NIAID) launched its biomedical research response to safeguard the health of people in the United States and around the world. As delineated in the NIAID Strategic Plan for COVID-19 Research, released in April 2020, the response focused on basic research, diagnostics, natural history studies, and the development of safe and effective therapeutics and vaccines. Working with U.S. government agencies, academia, industry, and community partners, NIAID rapidly mounted a comprehensive effort to characterize the virus and develop effective biomedical tools to prevent SARS-CoV-2 infection and treat COVID-19. NIAID supported the most promising candidates through clinical trial testing, prioritizing the inclusion of high-risk and minority populations to ensure broad testing and validation in the most vulnerable populations.

Building upon the growing knowledge base of SARS-CoV-2 and COVID-19, this update to the NIAID Strategic Plan for COVID-19 Research outlines research priorities critical to better understanding, treating and preventing SARS-CoV-2 and COVID-19 and its post-acute sequelae. The plan is structured on four updated strategic research priorities:

- **Advance basic research on SARS-CoV-2 biology, pathogenesis, and transmission** to further evaluate the biology of SARS-CoV-2 and better understand its transmission, epidemiology, pathogenesis, and immunopathogenesis, including the immunologic and clinical markers associated with disease severity. Pursue research to identify and characterize emerging viral variants to understand their epidemiological or clinical considerations and/or their potential impact on vaccines, therapeutics, and diagnostics.

- **Identify and test promising COVID-19 therapeutics**, including the discovery and development of novel antivirals, including SARS-CoV-2–specific and broad-spectrum antivirals; virus-targeted antibody-based therapies (including monoclonal and polyclonal antibody products); and host-directed strategies to treat COVID-19, such as immunomodulators.

- **Develop and test next-generation COVID-19 and pan-coronavirus vaccine candidates** to provide broad and durable protection against SARS-CoV-2 and other coronaviruses with pandemic potential. These include variant-specific vaccine candidates and novel approaches that are designed to increase the breadth or durability of immunity, be given in one dose, or be rapidly scaled up to address the global need.

- **Characterize, prevent, and treat post-acute sequelae of SARS-CoV-2 infection (PASC)**, including characterizing the pathophysiology and clinical manifestations of disease and developing treatment and prevention approaches.

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To accelerate research, NIAID will continue to leverage current resources and global collaborations, including existing research programs and clinical trials networks. A concerted effort has been made to include at-risk and vulnerable populations in all NIAID-sponsored COVID-19 therapeutic and vaccine clinical trials. With collaboration from agencies within the U.S. government and other key U.S. and global partners, NIAID will continue to rapidly disseminate data from these studies so that the information can be translated into clinical practice and public health interventions to help combat the pandemic.

**COVID-19 Research Plan – 2021 Update**

**Priority 1: Advance basic research on SARS-CoV-2 biology, pathogenesis, and transmission**

*In 2020, a coordinated research response provided critical knowledge about SARS-CoV-2 and COVID-19 that enhanced the ability to diagnose and treat the disease. This response included the rapid identification of the human cellular receptor for SARS-CoV-2 and characterization of the structure of the viral spike protein that is critical for cell entry. Additional studies revealed areas of the virus surface that are essential to virus neutralization, paving the way for the development of candidate vaccines and therapeutics that hold promise for altering the trajectory of the pandemic. Further studies on basic characteristics of SARS-CoV-2 and COVID-19 remain paramount to developing the tools to prevent SARS-CoV-2 infection and treat COVID-19. These include studies that enhance understanding of SARS-CoV-2 biology, transmission, incidence, and prevalence, and of COVID-19 pathology. To support these efforts, NIAID will continue to source and supply virus isolates, clinical specimens, and reagents in public repositories to the scientific community. In addition, NIAID will continue to support the development of small and large animal models and ensure that well-characterized animal models are made available to the scientific community for the evaluation of promising medical countermeasures.*

- **Continue to characterize virus biology and immune responses to infection**
  
  Continuing to build on the foundational studies of SARS-CoV-2 and COVID-19 is paramount to developing new medical countermeasures to protect public health. Early studies delineating the primary host receptor, angiotensin converting enzyme 2 (ACE-2), and the structure of the virus receptor-binding domain were crucial to the development of promising candidate vaccines and therapeutics that are now publicly available. NIAID will continue to foster research on the interaction between the virus and host immune responses, and on other factors that correlate with severe disease that ultimately may lead to the identification of novel targets for intervention. In addition, NIAID will pursue investigations of SARS-CoV-2 biology and tropism that will enhance the ability to detect, prevent, and treat disease.

- **Assess functional consequences of newly emerging SARS-CoV-2 variants**

  As SARS-CoV-2 circulates throughout the world, a significant number of genetic mutations are occurring within the spike protein of the virus. Although many of these changes are unlikely to have a major impact on the virus or the efficacy of medical countermeasures, several SARS-CoV-2 variants of concern have been associated with increased transmissibility and significant antigenic variation. The presence of these variants underscores the need for continued studies to identify and characterize virus genetic diversity and evaluate the circumstances that lead to their emergence. NIAID will support research on the impact of these variants on transmission, disease severity, and their potential to escape immunity elicited by natural infection or vaccination. Comprehensive *in vitro* and *in vivo* studies will be performed to rapidly provide a risk assessment of emerging variants, with an emphasis on potential impacts to medical countermeasures.
• **Assess dynamics of disease transmission and progression through natural history and serosurveillance studies**

Ongoing observational studies conducted and supported by NIAID track COVID-19 disease prevalence, transmission, and pathology. These ongoing studies reveal critical features of how the virus spreads and causes disease. Seroprevalence studies provide crucial data on the prevalence of disease in high-risk populations such as healthcare workers and the elderly. Natural history studies provide insight into the immune response over time, pathogenesis, and biomarkers for severe disease. Identification of early biomarkers or characteristics of infection that lead to severe disease are critical to informing early treatment strategies that may improve clinical outcome. Along with informing our understanding of COVID-19 immunopathogenesis and viral tropisms, data from these longitudinal cohorts may elucidate mechanisms of disease transmission, including the duration of virus shedding during infection and the durability of immune protection after infection or vaccination. Data from these studies will continue to be essential to developing and optimizing prevention and treatment strategies for SARS-CoV-2 infection and COVID-19.

**Priority 2: Identify and test promising COVID-19 therapeutics**

*Since the beginning of the COVID-19 outbreak, NIAID has worked with partners across government agencies, academia, industry, and the community to advance promising therapeutics against COVID-19. This approach involved developing and testing drugs and monoclonal antibodies (mAbs) and has yielded several promising therapeutic interventions. The NIAID Adaptive COVID-19 Treatment Trial (ACTT) demonstrated the safety and efficacy of remdesivir, an RNA polymerase inhibitor developed by Gilead Sciences, for shortening time of COVID-19 recovery. Further studies revealed promising safety and efficacy of additional interventions, including baricitinib, a Janus kinase (JAK) inhibitor, and monoclonal antibodies, including Eli Lilly and Company’s, LY-CoV555 (bamlanivimab) for treating various stages of COVID-19. Promising therapeutic candidates will continue to be identified and tested in clinical studies, including those initiated under the NIH Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership.*

• **Identify and test new drugs for COVID-19**

Despite early advances in promising therapeutics, there continues to be an urgent need to identify safe and effective treatments across the spectrum of COVID-19 disease. NIAID will continue supporting basic and translational research efforts to identify promising viral targets and drug classes and generate novel compounds. Leveraging former successful partnerships (as for HIV drug development) and continuing the collaborative interactions that were established in response to the COVID-19 pandemic, NIAID will engage pharmaceutical companies to share compound libraries, medicinal chemistry, and drug development expertise to accelerate internal efforts and ensure that the most promising therapeutic candidates progress rapidly into the clinic. The immediate priority is to identify new SARS-CoV-2 drug targets and expedite the development of direct acting antivirals against SARS-CoV-2, with emphasis on drugs that can be administered orally.

• **Support the identification and testing of mAbs for treatment or prophylaxis**

SARS-CoV-2 specific mAbs are the only therapeutics currently authorized for emergency use by the U.S. Food and Drug Administration (FDA) for early/mild COVID-19. Additional clinical trials are needed to understand their utility as the pandemic evolves and novel SARS-CoV-2 variants become increasingly prevalent. New treatment strategies involving mAbs capable of neutralizing viral variants in vitro will need to be evaluated in ongoing platform trials to determine clinical efficacy.
Furthermore, clinical trials are needed to understand the impact of mAb treatment on convalescent immune responses and immune responses to subsequent vaccination.

- **Evaluate host-directed strategies for treatment**
  Severe cases of COVID-19 have been linked to dysregulated immune responses. Host-directed treatment strategies, such as those that impact inflammation, have shown promise when used in combination with antiviral drugs to accelerate recovery and improve clinical outcomes of patients hospitalized with COVID-19. Building on these findings, NIAID will continue to support investigations of other host-directed strategies, including corticosteroids, kinase inhibitors, or cytokines, alone or in combination with antivirals, mAbs, or other therapeutics, as potential treatments for COVID-19.

- **Conduct clinical trials to demonstrate the safety and efficacy of lead therapeutic candidates**
  NIAID has developed flexible clinical trial structures to facilitate the evaluation of therapeutic candidates as they emerge, including in special populations, high-risk and minority populations, and pregnant or breastfeeding women. Many potential therapeutic candidates have been identified and are being tested in clinical trials for treating COVID-19. NIAID has developed flexible clinical trial structures to facilitate the evaluation of therapeutic candidates as they emerge, including in special populations, high-risk and minority populations, and pregnant or breastfeeding women. This effort includes the following studies:
  - The ACTT study is testing combinations of therapeutics with remdesivir for improving treatment outcomes of hospitalized patients with COVID-19.
  - The Big Effect Trial (BET), also known as ACTIV5, is conducting smaller studies on putative therapeutics that have existing clinical data and will transition the most promising candidates into larger clinical trials.
  - ACTIV2 continues to investigate promising candidates for the treatment of outpatients with COVID-19, including investigational mAbs developed by multiple companies. Concurrently, ACTIV3 has initiated multiple clinical trials evaluating promising mAbs for treating people hospitalized with COVID-19.
Priority 3: Develop and test next-generation COVID-19 and pan-coronavirus vaccine candidates

The development of safe and effective vaccines is a high priority of the NIAID research response to COVID-19. NIAID has supported the development and testing of several COVID-19 vaccine candidates that hold promise to significantly alter the course of the COVID-19 pandemic. Despite the rapid development and FDA emergency use authorization (EUA) of several vaccine candidates, the SARS-CoV-2 virus is evolving. New variants are associated with increased transmission efficiency and antigenic variation that may diminish the efficacy of authorized vaccines. To maintain progress and ultimately end the pandemic, it is critically important to complete the clinical evaluation of current vaccine candidates across all ages and populations, rapidly develop and evaluate next-generation vaccine candidates to protect against emerging SARS-CoV-2 variants of highest concern, and invest in the fundamental discovery and development of vaccine approaches that provide protection against multiple coronavirus strains. In 2020 NIAID established a new clinical trials network that aims to enroll thousands of volunteers in large-scale clinical trials testing a variety of investigational vaccines and monoclonal antibodies intended to protect people from COVID-19. The COVID-19 Prevention Network (CoVPN) was established by merging four existing NIAID-funded clinical trials networks: the HIV Vaccine Trials Network (HVTN); the HIV Prevention Trials Network (HPTN); the Infectious Diseases Clinical Research Consortium (IDCRC); and the AIDS Clinical Trials Group (Box 2).

- Continue to advance promising candidates through clinical testing across all ages and populations

Although unprecedented progress has been made, much remains to be learned about the vaccine products currently under EUA and in late-stage clinical development, the majority of which are technologies that have not been used extensively in humans. Critical questions to be addressed include understanding: vaccine outcomes across all age groups and demographics, the duration of protection of each candidate vaccine, the impact of vaccination on infection and transmission, the safety and efficacy of vaccination in special populations, and the level of protection afforded by a single dose of certain vaccine products. NIAID is planning or has already initiated studies to confirm the safety of vaccine candidates in pregnant women, children, and immunocompromised individuals. Additional studies are planned to understand whether highly allergic individuals are more prone to allergic reactions to the COVID-19 mRNA vaccines than are non-allergic individuals.

- Identify and characterize immunogens that induce a wide breadth of protection

NIAID is supporting the advancement of multiple approaches to identify immunogens with broad protective potential against multiple coronavirus strains. This includes analyses of coronavirus diversity, structural investigations of coronavirus proteins, and identification of broadly reactive B-
and T-cell epitopes. NIAID also supports studies that leverage innovative immunogen identification and design strategies to delineate proteins that elicit broad coronavirus immunity.

- **Develop and evaluate next-generation vaccine candidates that protect against SARS-CoV-2 variants**
  Emerging SARS-CoV-2 variants with multiple changes in critical antigenic regions of the spike protein have the potential to significantly impact vaccine-induced immunity. There is an urgent need to learn the potential impact of these variants on vaccine efficacy and to immediately begin developing next-generation COVID-19 vaccine candidates to protect against emerging variants, should they be needed. NIAID is working with industry, academic, and community partners to develop and evaluate vaccine candidates to protect against currently circulating variants of highest concern. Preclinical *in vitro* studies and studies in animal models are underway. Phase 1 clinical studies for vaccines against current variants are expected to begin in early spring 2021. NIAID will continue to advance novel vaccine candidates that generate potent immune responses against epitopes from multiple SARS-CoV-2 proteins to potentially expand the breadth of protection against viral variants.

- **Provide adjuvants to support vaccine development**
  Identification and selection of appropriate adjuvants is crucial for developing safe and effective vaccines. NIAID is working with multiple collaborators to provide adjuvants to the research community. These adjuvants include compounds that specifically improve SARS-CoV-2 vaccine efficacy in elderly individuals or modulate host immunity toward protective responses while limiting or preventing harmful inflammatory responses.

**Priority 4: Characterize, prevent, and treat post-acute sequelae of SARS-CoV-2 infection (PASC)**

*As millions recover from initial SARS-CoV-2 infections of varying severity, some individuals do not return to baseline health. Reported symptoms involve nearly all organ systems and include fatigue, dyspnea, cognitive dysfunction, anxiety, and depression. Specific case definitions have not been established and PASC may comprise multiple phenotypes. Although the prevalence of these sequelae remains unclear, the public health impact is potentially large given the sheer number of individuals who have been already or will be infected with SARS-CoV-2. NIAID supports efforts to delineate and characterize the clinical spectrum of PASC and launch investigations on promising interventions to prevent and treat the diverse manifestations associated with this condition across demographic groups.*

- **Identify and characterize the spectrum and epidemiology of PASC**
  Although multiple clinics have been established in the United States and globally, the clinical spectrum and biology underlying recovery from acute SARS-CoV-2 infection are not well characterized. Multiple factors, including age, sex, existing co-morbidities, and host genetic factors, may impact the breadth of post-acute complications. NIAID is conducting retrospective and prospective studies designed to develop strategies for the prevention and treatment of PASC. In addition to characterizing long-term disease manifestations, a clearer picture of the epidemiology of these outcomes will be critical. NIAID is leveraging new and existing infrastructure, including ongoing natural history cohorts, to characterize the incidence and prevalence of PASC more fully and to understand the long-term impact of SARS-CoV-2 infection.
• **Evaluate immune correlates and biomarkers related to long-term outcomes**  
  The biological mechanisms underlying the varied long-term effects of SARS-CoV-2 infection are unknown. Although dysregulated immune responses play a key role in progression to severe disease, the factors leading to diverse long-term sequelae are multifactorial, and mechanistic links with immune responses have not yet been identified. NIAID will continue to support research on the immune and inflammatory responses during acute disease and their role in the development of PASC. This includes supporting *in vitro* studies to evaluate cellular responses to SARS-CoV-2 infection and developing animal models of PASC.

• **Identify and adapt treatments and preventative interventions for PASC**  
  Characterizing the various manifestations of PASC and their potential underlying causes will suggest novel targets for prevention and treatment. NIAID will support the evaluation of promising interventions, including investigations of existing drugs and testing of novel strategies to address these long-term manifestations.

**Conclusion**  
The unprecedented spread and persistence of COVID-19 has created a daunting public health challenge. Building on early advances in our understanding of SARS-CoV-2 and COVID-19, NIAID is focusing its resources to further characterize virus biology, understand immediate and long-term consequences of disease, and develop safe and effective COVID-19 therapeutics and vaccines. The resulting scientific advances will add to our existing prevention and treatment armamentarium for mitigating the current COVID-19 pandemic, as well as serving as a foundation for the development of prevention, diagnostic, and treatment strategies to address future emerging and re-emerging infectious diseases and protect public health from future pandemics.