

NIH Contributions to WHO COVID-19 Technology Access Pool and Q&As

NIH Makes COVID-19 Technologies Available to Global Manufacturers Through WHO Program

NIH has licensed COVID-19 technologies arising from NIH intramural research to the Medicines Patent Pool (MPP) for access through the World Health Organization's (WHO) COVID-19 Technology Access Pool (C-TAP). The technologies include the stabilized spike protein used in currently available COVID-19 vaccines, research tools for vaccine, drug, and diagnostic development as well as early-stage vaccine candidates and diagnostics. While NIH's early-stage technology contributions are only one component in the development process and do not alone enable full development of medical countermeasures, such contributions are an important step toward facilitating wider availability of lifesaving interventions around the world. Scientists from the National Cancer Institute (NCI), the National Eye Institute (NEI), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Environmental Health Sciences (NIEHS), and the National Center for Advancing Translational Sciences (NCATS) developed the technologies.

Contributed NIH COVID-19 Technologies:

Vaccine Development

- **[Prefusion coronavirus spike proteins and SARS-CoV-2 prefusion spike proteins and their use:](#)** NIAID scientists and their academic collaborators invented a molecular engineering approach for stabilizing the spike protein of any coronavirus. The spike protein enables coronavirus particles to infect human cells. The strategy, based on previous related research on HIV and respiratory syncytial virus (RSV), involves locking the spike protein into a prefusion conformation, or shape. Stabilizing coronavirus' spike proteins makes them potent and precise immunogens for use in vaccines. NIH was issued a patent for this invention, which covers specific mutations to stabilize pre-fusion coronavirus spike proteins. The SARS-CoV-2 spike protein was stabilized using this patented molecular engineering approach. NIH has licensed this pivotal technology to various companies worldwide for use in their COVID-19 vaccine products.

References:

P Jesper *et al.* [Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen](#). *PNAS* DOI: 10.1073/pnas.1707304114. (2017)

D Wrapp *et al.* [Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation](#). *Science* DOI: 10.1126/science.abb2507 (2020)

Research Tools for Vaccine Development

- **[Structure-Based Design of SARS-CoV-2 Spike Immunogens Stabilized in the RBD-All Down Conformation:](#)** NIAID scientists designed a SARS-CoV-2 spike protein immunogen for use in COVID-19 vaccines. The immunogen includes specific mutations designed to induce antibodies that can bind to SARS-CoV-2 and prevent immune evasion.

Reference: T Zhou *et al.* [Cryo-EM Structures of SARS-CoV-2 Spike without and with ACE2 Reveal a pH-Dependent Switch to Mediate Endosomal Positioning of Receptor-Binding Domains](#). *Cell Host Microbe* DOI: 10.1016/j.chom.2020.11.004 (2020).

- **SARS-CoV-2 Pseudotyping Plasmid:** NIAID scientists developed a plasmid encoding spike proteins of SARS-CoV-2 variants. This research tool can be used to make pseudoviruses, which are harmless proxy viruses. Because SARS-CoV-2 is a potentially lethal and airborne virus, it must be handled in high-containment laboratories ([Biosafety Level 3](#)) that require special airflow, ventilation and decontamination procedures. Research on SARS-CoV-2 countermeasures can be conducted more expeditiously by using pseudoviruses in standard Biosafety Level 2 laboratories.

Reference: K Corbett *et al.* [SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness](#). *Nature* DOI: 10.1038/s41586-020-2622-0 (2020).

Research Tool for Drug Development

- **ACE2 Dimer construct:** NIAID scientists developed a plasmid encoding human ACE2 dimers (two copies of ACE2 that are joined together). ACE2 is the protein on the surface of human cells to which the spike protein of SARS-CoV-2 must bind to infect cells. This research tool can be used in studies testing the binding of spike protein probes to ACE2 and for selecting and isolating antibodies generated against SARS-CoV-2. This tool has been used widely by scientists to study COVID-19 and can be used to study other viruses that bind to ACE2.

References:

T Zhou *et al.* [Cryo-EM Structures of SARS-CoV-2 Spike without and with ACE2 Reveal a pH-Dependent Switch to Mediate Endosomal Positioning of Receptor-Binding Domains](#). *Cell Host Microbe* DOI: 10.1016/j.chom.2020.11.004 (2020)

T Zhou *et al.* [Structure-Based Design with Tag-Based Purification and In-Process Biotinylation Enable Streamlined Development of SARS-CoV-2 Spike Molecular Probes](#). *Cell Rep* DOI: 10.1016/j.celrep.2020.108322 (2020)

Research Tool for Drug and Diagnostic Development

- **Synthetic humanized llama nanobody library and use thereof to identify SARS-CoV-2 neutralizing antibodies:** NCATS scientists have built a library of antibodies called synthetic nanobodies to rapidly identify novel therapeutics. The library will help speed the identification and development of nanobodies into preclinical evaluation and clinical applications. The library's diversity will increase the likelihood of identifying nanobodies against new SARS-CoV-2 variants, as well as future pandemic threats as they emerge. The researchers evaluated the library against the SARS-CoV-2 spike protein, which the virus uses to infect cells. They found that many types of nanobodies could block the virus spike protein, and the viral activity.

Reference: Y. Fu, *et al.* [A humanized nanobody phage display library yields potent binders of SARS-CoV-2 spike](#). *bioRxiv* (pre-print) DOI: 10.1101/2021.10.22.465476

Vaccine Candidates

- **Newcastle Disease Virus-Like Particles Displaying Prefusion-Stabilized SARS-CoV-2 Spikes as a Single-Dose COVID-19 Vaccine:** NIAID researchers designed an investigational virus-like particle (VLP) vaccine for COVID-19. VLP vaccines use virus proteins to form a non-infectious particle that mimics a virus particle but does not replicate. For this vaccine, scientists combined proteins from Newcastle disease virus (which primarily infects poultry) and stabilized SARS-CoV-2 spike proteins. The vaccine candidate induced robust immunity against SARS-CoV-2 in animal models.

Reference: Y Yang *et al.* [Newcastle Disease Virus-Like Particles Displaying Prefusion-Stabilized SARS-CoV-2 Spikes Elicit Potent Neutralizing Responses](#). *Vaccines* DOI: 10.3390/vaccines9020073 (2021)

- **[Parainfluenza virus 3 based vaccine against COVID-19:](#)** NIAID researchers have developed nasal spray vaccine candidates against COVID-19 primarily intended for infants and young children. The vaccines use a viral vector to express the stabilized SARS-CoV-2 spike protein immunogen. The viral vector is a live but weakened chimeric virus consisting of a bovine parainfluenza virus backbone with certain proteins from human parainfluenza virus type 3 (HPIV3). These nasal spray vaccines are expected to induce durable and broad systemic and respiratory mucosal immunity against SARS-CoV-2, and against childhood respiratory infections caused by HPIV3.

Reference: X Liu *et al.* [A single intranasal dose of a live-attenuated parainfluenza virus-vectored SARS-CoV-2 vaccine is protective in hamsters](#). *PNAS* DOI: 10.1073/pnas.2109744118 (2021)

- **[A VSV-EBOV-Based Vaccine Against COVID-19:](#)** NIAID researchers, using a rhesus macaque study model, have taken the existing federally approved vaccine against Ebola virus (brand name Ervebo) and modified it to also protect against SARS-CoV-2, the virus that causes COVID-19. Ervebo uses recombinant vesicular stomatitis virus (VSV)—which is typically not harmful to people—to deliver an Ebola virus protein in a vaccine to generate immunity. The same research group that helped develop Ervebo has added an immune-generating protein from SARS-CoV-2 that provided protection in its macaque model. This is one of several examples of how NIAID scientists are testing the safe and cost-effective VSV delivery method in pre-clinical animal models to introduce proteins that generate protection from different viruses.

Reference: W. Furuyama, *et al.* [Rapid Protection from COVID-19 in Nonhuman Primates Vaccinated Intramuscularly but Not Intranasally with a Single Dose of a Vesicular Stomatitis Virus-Based Vaccine](#). *mBio* DOI: 10.1128/mbio.03379-21 (2022)

Diagnostics

- **[RNASEH-Assisted Detection Assay for RNA](#)**: NCI researchers developed a diagnostic methodology that can detect specific RNA sequences in less than 3 hours and does not require the expensive thermocycler instrument needed for PCR tests. The technology uses low-cost reagents and has potential for point-of-care applications for detection of cellular or viral RNA.
- **Detection of SARS-CoV-2 and other RNA Virus Using a Novel Improved RT-qPCR Method that Increases Detection Sensitivity and Improves Safety**: NEI researchers discovered a technique for isolating SARS-CoV-2 from patient samples that increases yield and safety while reducing cost and prep time. Key to the method is a chelating agent called Chelex 100 resin made by the company Bio-Rad that preserves SARS-CoV-2 RNA in patient samples. The RNA prep method inactivates the virus, making positive samples safer for lab personnel to handle. Once extracted, the RNA is amplified to detectable levels using reverse transcription PCR (RT-qPCR), a widely used lab technique.

Reference: B. Guan *et al.* [Sensitive extraction-free SARS-CoV-2 RNA virus detection using a chelating resin](#). *iScience* DOI: 10.1016/j.isci.2021.102960 (2021)

- **[High-Throughput COVID-19 Diagnostic Test that Detects Both Viral and Host Nucleic Acid](#)**: As part of the NIH [Rapid Acceleration of Diagnostics](#) (RADx) program, NIEHS researchers developed a genetic sequencing-based test that can combine thousands of biological patient samples to test them for SARS-CoV-2 infection and forecast each patient's COVID-19 risk in a single run, helping to overcome time constraints. The method, which detects both the virus and the patient's active genes directly from their swabs, can permit monitoring of at-risk individuals.

QUESTIONS AND ANSWERS:

What are the Medicines Patent Pool (MPP) and the World Health Organization's COVID-19 Technology Access Pool (C-TAP)?

MPP, initiated in 2010 and funded by Unitaid, licenses medicines and health technologies with the aim of increasing access to and facilitating development of essential medicines—including HIV, hepatitis C, tuberculosis and COVID-19 treatments—for people living in low-and middle-income countries. In 2010, NIH contributed the first patent to MPP through a royalty-free license agreement related to the HIV medicine darunavir.

C-TAP, which began in May 2020, aims to boost global supply of vaccines, treatments, and diagnostics for COVID-19 specifically by facilitating the sharing of intellectual property, knowledge, and data with quality-assured manufacturers that have capacity to scale up production. Licensing of patents through C-TAP is handled by MPP.

Why is NIH contributing to this effort?

Controlling COVID-19 and addressing other public health needs are only possible if all communities around the world have access to lifesaving vaccines, treatments, and diagnostics. While NIH's early-stage technology contributions are only one component in the development process and do not alone allow full development of medical countermeasures, such contributions are an important step toward facilitating wider availability of lifesaving interventions around the world.

What is the purpose of the licensing process?

While NIH does not manufacture products for commercial sale, NIH scientists regularly make discoveries that can be transferred to the private sector for further research and development and eventual commercialization. This can include inventions with intellectual property protection or pending protection (discoveries claimed in a patent or patent application) as well as biological materials which are not in the public domain and for which patent protection cannot or will not be obtained. NIH technology transfer experts have negotiated license agreements with MPP which state that NIH will not take action to exclude MPP sub-licensees from making, using, or selling a potential invention. NIH has already directly granted numerous non-exclusive licenses for a key COVID-19 technology (the stabilized spike protein) used in vaccines and diagnostics; however, licensing this technology and others to MPP will facilitate even wider access.

Will NIH's contributions allow manufacturers to make "generic" versions of the currently available COVID-19 vaccines?

While NIH's early-stage technology contributions are only one component in the development process and do not alone enable full development of medical countermeasures, the contributions are an important step toward facilitating wider access to lifesaving interventions around the world. Vaccines are [biologics](#), or complex mixtures, and are different from conventional drugs, which are chemically synthesized and have defined structures. Numerous technologies—sometimes from several scientists and institutions—comprise a vaccine, and the U.S. government does not own all of the rights relevant to any of the existing COVID-19 vaccines. For example, some currently available COVID-19 vaccines contain an immunogen (the part of a vaccine that stimulates the immune system) developed by NIH scientists and their academic collaborators, while other components of the vaccines have been developed by the pharmaceutical companies that manufacture and sell the vaccine products. Aside from the intellectual property, pharmaceutical companies also use specialized processes and methods to manufacture the product at scale. Therefore, in some cases, additional developers and rights holders beyond NIH would need to contribute to C-TAP to ensure manufacturers have the necessary tools and know-how to produce specific vaccines at scale.

How will this affect U.S. intellectual property?

The United States will retain all its existing rights in any licensed technologies. The licenses will simply allow others to use the technologies as well.

What terms are contained in the licenses to MPP?

[The licenses to MPP are posted on its website.](#) The NIH licenses to MPP allow technology developers to work with MPP and C-TAP to manufacture products using these technologies all around the world for distribution and sale in low-and-middle-income countries. Countries under sanction from the United States are not included.

Will NIH receive royalties from MPP sub-licensees on future sales of products that use NIH technology?

The [Federal Technology Act of 1986](#) authorizes government agencies to license their inventions in exchange for royalties that the agency can use to fund further research. NIH typically receives annual minimum royalty payments and a percentage of the sales of the end product. The law requires that a portion of these royalties go to the inventors according to a statutory formula ([15 U.S.C. 3710c](#)) and the remainder to the NIH Institutes where the inventions were made. NIH-funded universities and research hospitals have similar programs governed by the [Bayh-Dole Act of 1980](#) (35 U.S.C. 202(c)(7)). Royalties to NIH also pay for the cost of obtaining patents.

For the NIH licenses to MPP for inclusion in C-TAP, in most circumstances, NIH will not collect royalties on sales of products licensed in 49 countries classified by the United Nations as Least Developed Countries (LDCs). The agreements between NIH and MPP specify a 0.0% earned royalty rate on patented technology and unpatented materials in LDCs. The one exception is an earned royalty rate for NIH of 0.0-0.5% for products containing the patented stabilized spike protein technology (known as S2P) in LDCs. The ranges are consistent with the financial terms in NIH's current S2P vaccine commercialization agreements.