

# DEFENSE ADVANCED RESEARCH PROJECTS AGENCY

## COVID-19

Title: The DARPA Difference: Pivoting to Address COVID

*Updated March 19, 2021*

DARPA continues to work closely with the Department of Defense (DoD), multiple U.S. government agencies, as well as its academic and industry partners, to provide technical and scientific solutions to address the COVID-19 pandemic.

Welcome to the sixth installment of DARPA's ongoing web series highlighting the agency's active programs focused on the diagnosis, detection, treatment, prevention and manufacture of medical countermeasures to combat COVID-19, including:

### Diagnose & Detect:

Diagnosis is a critical aspect of pandemic prevention and response. DARPA research is producing tests that offer earlier, more sensitive, and widely distributable diagnosis of SARS-CoV-2-infected patients.

DARPA began the Detect It with Gene Editing Technologies (DIGET) and the Epigenetic CHaracterization and Observation (ECHO) programs focused on rapid discovery, validation, and manufacture of diagnostics detecting any threat, anytime, anywhere.

DIGET, which recently [awarded a contract to MRI Global](#), is moving forward with its goal to build a multiplexed detection device to screen up to a thousand pathogens at a time, along with a mobile, point-of-need device targeting up to 10 pathogens, including SARS-CoV-2. DARPA's ECHO program is developing diagnostic tests that measure the body's response to viral infection rather than testing for the virus itself.

DARPA [ECHO supported the U.S. Marine Corps and the Naval Medical Research Center](#) as part of COVID-19 Health Action Response for Marines (CHARM). During the 2-month study, DARPA provided near-real-time diagnostic results for over 3,500 Marine recruits to ensure that training at Parris Island could continue through the entirety of 2020 and into 2021. This work led to updated CDC quarantine guidelines reducing the necessary quarantine period from 14 to 10 days for individuals testing positive for COVID-19, as outlined in a [November 2020 New England Journal of Medicine publication](#).

A second CHARM study was posted in January 2021 on the [preprint server MedRxiv](#), demonstrating that COVID-19 reinfection was "common" among those who had the virus. Of the 189 participants that tested positive for antibodies, 19 ended up testing positive for the virus six weeks later, according to the study. In March 2021, the study was accepted for publication in The Lancet.

The team is now focusing on expanding the cohort and tracking long-term host response, in addition to new infections, in the U.S. Marine Corps.

In a separate December 2020 investigation, ECHO performers at Duke University [posted data](#) on chromatin remodeling reflecting disease severity prognosis, and a separate team at Stanford [demonstrated 87.5% accuracy in predicting mortality in COVID](#). These studies demonstrated the potential of the epigenome to both diagnose and predict disease severity in COVID-19 patients at the early, asymptomatic stages of infection.

In addition to the host-based methods under development, in August 2020, ECHO performers received [EUA approval](#) for a direct viral saliva test, the first manufacturer's EUA for diagnosis of COVID-19 from saliva. The saliva test is now being further developed in partnership with the [NIH RADx program](#).

### ***Friend or Foe***

Two preliminary efforts associated with the Friend or Foe program have made critical advances in SARS-CoV-2 detection.

A preliminary effort at the University of Illinois at Urbana-Champaign (UIUC), tasked with developing systems to detect pathogenic bacteria quickly, shifted to target COVID-19. Leveraging digital design and rapid prototyping on production manufacturing systems, the [team demonstrated a point-of-care assay and system](#) that requires only a smartphone to collect and process diagnostic images. The UIUC performer detected SARS-CoV-2 from nasal swab samples in 30 minutes, and developed test cartridges that can quickly scale up to hundreds of thousands of tests.

Researchers at Stanford University are developing biosensors that can quickly spot an attack on a cell membrane – the first step of CoVID-19 (or any) infection. The team is using the platform to identify mechanisms to inhibit CoVID-19 membrane attack; the technology can be readily multiplexed enabling fast high-throughput drug screens.

## **Treat & Prevent:**

DARPA technology contributes to preventing future COVID-19 infections through novel vaccine technology and more pervasive environmental aerosol monitoring, and to treating the disease through novel antibody treatments, rapid drug discovery, and domestic active pharmaceutical ingredient manufacture.

### ***ADEPT/P3***

As part of the ADEPT program in 2011, DARPA began investing in nucleic acid vaccines. The hypothesis was that rather than delivering antigens to the immune system, we could deliver genes that encode the antigen and allow the human body to produce the antigen from its own cells, triggering a protective immune response. In December 2020, former ADEPT performer Moderna's RNA vaccine received [FDA Emergency Use Authorization \(EUA\) approval](#) for the prevention of COVID-19.

In FY2016, DARPA initiated the Pandemic Prevention Platform (P3) program aimed squarely at the rapid discovery, testing, and manufacture of antibody treatments to fight any emerging disease threat. P3 convincingly demonstrated how to find and manufacture antibodies in less than 90 days

(vs. years), using influenza, Zika, and MERS as test cases. As the COVID-19 outbreak began early in 2020, P3 research pivoted to address the novel coronavirus.

In November, 2020, [AbCellera](#) announced that a human monoclonal antibody (mAb) identified as part of the P3 program and in conjunction with the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center (VRC), bamlanivimab (LY-CoV555), had been granted emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA) for the treatment of patients 12 years of age and older with mild to moderate COVID-19 to prevent hospitalization. AbCellera was able to obtain a sample of blood at the end of February 2020 via an intergovernmental panel, and identified over 1,000 potential antibody candidates. The mAb is being developed in collaboration with Eli Lilly and Company.

On January 21, 2021 the company [announced that](#) bamlanivimab reduced the risk of contracting symptomatic COVID-19 among residents and staff of long-term care facilities by up to 80%. This was [followed by a second announcement six days later](#) that the mAb will be evaluated together with VIR-7831, an antibody developed by Vir Biotechnology, Inc., and GlaxoSmithKline, as a potential COVID-19 therapy in low-risk patients with mild to moderate COVID-19. In February, 2021, [bamlanivimab](#), administered with etesevimab also received an EUA for the treatment of mild to moderate COVID-19 in patients aged 12 and older who are at high risk for progressing to severe COVID-19 and/or hospitalization.

A second antibody drug (AZD7442) discovered by Vanderbilt University Medical Center and licensed to AstraZeneca [is in late stage clinical studies](#) to prevent covid-19 disease, and performers at Duke University are aiming for clinical studies this year for their highly potent antibody targeting the receptor binding domain of SARS-CoV-2 which will be delivered as an mRNA construct.

### ***SIGMA+***

The DARPA SIGMA+ program is developing networked sensors to detect a variety of chemical, biological, and explosive threats. Some of this research has tilted to addressing the COVID-19 pandemic.

As part of this program, Battelle Memorial Institute developed a unique signature for the SARS-CoV-2 virus using their Resource Effective Bio-identification System (REBS). The REBS platform is designed to monitor the atmosphere for the presence of biological warfare agents and other pathogens using a technique called Raman spectroscopy. The effort worked to develop a signature for the virus that causes COVID-19 over the last year. This signature is currently being evaluated in several trials that utilize the REBS system and newer REBS+ system that provide a range of performance improvements compared to original REBS systems. This includes sampling times reduced from 30 minutes to just seconds.

The program is also evaluating the potential use of wearable technology to detect COVID-19 and other infectious diseases. The effort, led by RTI International and supported by Garmin® International, Inc., includes a number of studies on whether wearables can provide indications of infection based on an individual's immune response. One such study will track the health of U.S. Navy sailors living in close quarters aboard a ship via a novel "app" to monitor high quality wearable data. The app allows for continuous data collection in areas with limited or no access to Wi-Fi or cellular networks.

In addition to SIGMA+, the new SenSARS Disruptioneering Opportunity seeks to develop high performance, airbreathing pathogen sensors for SARS-CoV-2 and beyond, targeting use in offices, classrooms and buildings. The effort will examine new high sensitivity and high specificity signatures

for SARS-CoV-2, and use those signatures to produce technology readiness level 4 sensor prototypes.

### ***Panacea***

Previously FDA-approved drugs are a second option that could be immediately repurposed as effective treatments. DARPA developed several screening methods to rapidly identify the best previously approved drugs including rapid tests on human organ-on-a-chip systems, identification of drugs that target SARS-CoV-2 interactions with human cells rather than targeting the virus itself, and the use of AI and machine learning methods to design and screen drugs.

The DARPA Panacea program generated and published the first [human: SARS-CoV-2 protein interactome map](#) in the journal *Nature*, which describes how the SARS-CoV-2 proteins interact with human cells. Developed by performers at UCSF's Quantitative Bioscience Institute (QBI) and the Icahn School of Medicine at Mt. Sinai (ISMMS), this map has been used worldwide in the fight against COVID-19. The drug zotatifin, a protein synthesis inhibitor identified by the Panacea performers with their interactome map, is entering a [Phase 1 clinical trial](#) in Q1FY21 with investment support from the [Defense Health Agency](#).

In January 2021, these performers [published findings in Science](#) demonstrating that Plitidepsin, a compound originally discovered in Mediterranean sea squirts, currently used as a therapeutic for the treatment of multiple myeloma, is 27.5-fold more potent against SARS-CoV-2 than remdesivir in vitro. Remdesivir received [FDA emergency use authorization](#) in 2020 for the treatment of COVID-19.

### ***INTERCEPT***

Researchers at Los Alamos National Laboratory (LANL), supported by DARPA's INTERCEPT program, are modeling in-person and population-based spread of COVID-19 by combining clinical data and mathematical modeling to provide a quantitative understanding of the SARS-CoV-2 infection process within infected individuals and derive principles for therapeutic treatments for the purpose of limiting spread, reducing disease severity, and minimizing the risk of resistance. [In a manuscript published in Clinical Pharmacology & Therapeutics](#), the researchers review current literature on using within-host models to understand SARS-CoV-2 infection dynamics and their relationship with infectiousness, immune responses, and disease severity. This work provides an up-to-date synthesis of what is known about quantitative SARS-CoV-2 viral dynamics and their implication to both non-pharmaceutical and pharmaceutical interventions, such as therapeutics and vaccines.

Another INTERCEPT performer, Autonomous Therapeutics, Inc (ATI), is developing therapeutics to provide protection against any coronavirus – from novel mutational strains of COVID-19 to the next (unpredictable) threat. Known as Therapeutic Interfering Particles (TIPs), these broad-spectrum antivirals can be developed and stockpiled before the next threat emerges or is even known. TIP development is being supported by the INTERCEPT effort, with additional backing for clinical transition from leading private investors and a [partnership with BARDA and Johnson and Johnson known as Blue Knight](#).

ATI is also developing non-invasive platform technologies to enable the at-home, self-administered distribution of next-generation, gene-encoded antivirals. The technology would surmount a major barrier to the distribution of leading vaccine and monoclonal antibody approaches, which require intramuscular (IM) or intravenous (IV) delivery in centralized clinical settings.

### ***PREPARE***

On February 3, 2021 a PREPARE performer team at Georgia Tech and colleagues [published a paper in Nature](#) highlighting a new mRNA treatment as a potential therapeutic against both influenza A virus and SARS-COV-2 using Cas13a constructs they developed as part of the program.

## Manufacture:

The COVID-19 pandemic has highlighted vulnerabilities in the U.S. pharmaceutical supply chain. Work being done under DARPA's Make-It program furthers the development and commercialization of technology that directly addresses these vulnerabilities to enable an end-to-end, deployable and scalable capability for the production of medicines made from readily available commodity materials that can be sourced within the U.S.

AMD performers are collaborating with the Walter Reed Army Institute of Research (WRAIR) to apply artificial Intelligence (AI) techniques to accelerate the discovery of drugs to combat SARS-CoV-2. Under this program, the NIH National Center for Advancing Translational Sciences (NCATS) and WRAIR provide medicinal chemistry expertise to MIT and SRI, and also conduct in vitro testing of the AI predictions to validate and inform the models.

Researchers at MIT are concentrating efforts on the development of new AI algorithms that specifically address the problem of data scarcity inherent in studying a novel virus, and are looking to apply such techniques to identify synergistic combination therapies in the future. They recently posted blog posts on results from their model trained to [predict antiviral activity against COVID-19](#), and efforts towards [the development machine-learning tools](#) to aid in identifying molecules with therapeutic effects against the disease.

AMD performers at SRI International are developing AI tools that incorporate chemists' expert knowledge, in addition to that learned through data, to discover analogs of existing therapeutics with potency against SARS-CoV-2. They have also [recently published](#) data on the use of machine learning models to identify inhibitors of the virus.

### Make-It

Under Make-It, Active Pharmaceutical Ingredient (API) production was further automated and expanded to enable the flexible and scalable manufacture of a broad range of APIs. Current efforts are focused on addressing regulatory approval requirements and expanding the capability to enable production of critical medicines and precursors needed to treat critical care COVID-19 patients.

Make-It performers are building a suite of flexible manufacturing capabilities for scalable, resilient production of important medicines:

- On Demand Pharmaceuticals' (ODP) focus is on the production of fine chemical reagents and active pharmaceutical ingredients (APIs), and their technology is based on small-footprint chemical manufacturing devices that were developed in DARPA's Battlefield Medicine and Make-It programs. Their effort is [jointly funded](#) by DARPA and HHS under the CARES Act, and the company enjoyed a visit from FDA Commissioner, Dr. Stephen Hahn, as well as DARPA's Deputy Director, Dr. Peter Highnam, on 3 December.
- SRI International is developing an approach that [enables simple scaling of flow-based pharmaceutical production](#) from bench-top to production scale in a single step.
- Virginia Commonwealth University is building tools to [analyze and optimize](#) U.S. based chemical manufacturing to enable rapid reallocation of existing on-shore process streams to critical APIs in a time of need.

For more information on the highlighted programs, we invite you to visit the appropriate program page. In addition, please continue to follow this space for timely updates on DARPA's efforts

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