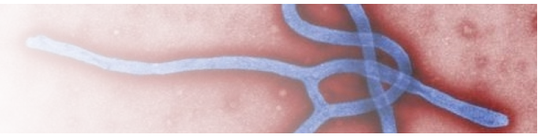

DARPA
ADEPT : PROTECT
Advancing National Security Through Fundamental Research

ADEPT : PROTECT



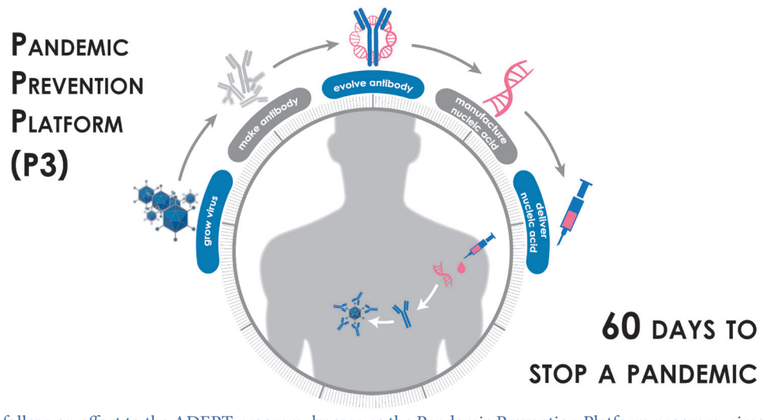
THE NEED AND OPPORTUNITY

A primary objective of DARPA's Biological Technologies Office (BTO) is to better ensure the health, and thereby the force readiness, of the country's military service community. The COVID-19 pandemic, which rapidly spread worldwide from an initial outbreak in China at the end of 2019, highlights one of the most perilous vulnerabilities to deployed military personnel and civilians: lack of protection and medical countermeasures (MCMs) against endemic and emerging biothreats. The Zika outbreak in 2015-2016, the more recent Ebola outbreak in the Democratic Republic of Congo, and mosquito-borne viruses such as Chikungunya and Dengue are among these threats.

Vaccines are the traditional mainstay of long-term infection prevention, while antibody approaches have at times been used to treat active infections. In one antibody-based approach that is being applied on a small scale in the current pandemic, blood serum with presumably protective antibodies obtained from those who have recovered from an infection is infused into patients. In more recent decades, monoclonal antibodies manufactured in cultured immune-system cells have been used to treat certain cancers and immune disorders. However, these treatments have suffered from shortcomings – including slow development, expensive manufacture, and dependence on continuous cold storage – that have prevented widespread use by the military.

THE DARPA SOLUTION

In 2012 with the ADEPT:PROTECT program*, DARPA began investing in the development of gene-encoded vaccines, a new category of preventive measures based on DNA or RNA. In this approach, genes that encode immune-stimulating antigens, such as the spike proteins on the surfaces of viruses like the one (SARS-CoV-2) that causes COVID-19, are delivered directly to a recipient's body. There, the instructions carried in the DNA or RNA elicit the body's own cells to manufacture the antigenic viral protein, which, in turn, elicits an immune response to the virus.



A follow-on effort to the ADEPT program, known as the Pandemic Prevention Platform program, aims to take pandemics off of the list of humanity's angsts with a range of technologies and practices marked by early detection of an outbreak and, within 60 days, development and widescale deployment of protective countermeasures.

Gene-based vaccines have shown great promise as a means to provide safe, reproducible, long-term immune protection. For vaccines to work, however, they often require more than one dose and it often takes weeks to months before a recipient's immune system builds up sufficient protection again the vaccine's viral target. With these biomedical realities come threats to warfighters if they deploy to pathogen-rife regions before having established relevant immunity and threats to military missions due to delayed deployment of personnel until they achieve immune protection.

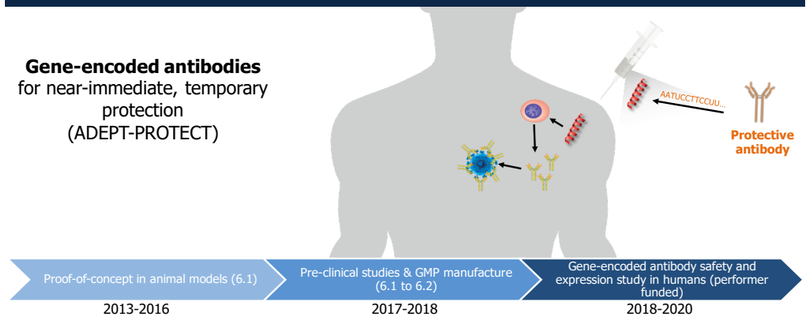
For a vaccine to confer immunity, it must lead to the production within a recipient of highly potent antibodies that can neutralize the pathogen. DARPA initiated the ADEPT:PROTECT program (most often referred to more simply as ADEPT) with the intention of bushwhacking a novel pathway to near-immediate protection against pathogens for which vaccines are not yet available and to confer interim-term protection during the development of a vaccine, which can take years.

THE IMPACT

DARPA's investments in this space led directly, with the biotechnology firm Moderna as a contracted performer on the program, to a first-ever human clinical trial with an RNA vaccine in 2019.

Earlier proof-of-concept experiments funded under ADEPT primarily with 6.1 funding (for basic research) demonstrated that delivery of antibody-making instructions — by way of messenger ribonucleic acid (mRNA), deoxyribonucleic acid (DNA), or another genetic-information-carrying tactic that relies on small viruses known as adenovirus-associated viruses (AAVs)

DARPA pioneered the use of the body as a bioreactor to produce prophylactic antibodies to protect against biothreats



— led to the production of antibodies that conferred protection in test animals exposed to the mosquito-borne Chikungunya (ChikV) virus.

In a more applied phase of technology development, Moderna was converted to 6.2 funding (applied research) to begin pre-clinical studies in non-human primates with an RNA-encoded antibody against ChikV and to produce the countermeasure using Good Manufacturing Practices (GMP), which regulatory agencies such as the Food and Drug Administration often require.

Moderna subsequently used company funding to conduct a Phase I clinical trial with 22 healthy volunteers using an mRNA-encoded ChikV antibody. This marked the first safety demonstration of an RNA-based medical countermeasure. Moderna reported these promising results of its clinical study in 2019. The trial demonstrated platform safety as well as the ability to generate protective levels of functional antibody in humans. In response to COVID-19, Moderna in March 2020 initiated human trials of gene-encoded antibodies that target SARS-CoV-2.

Research by Moderna and other ADEPT performers has provided proof-of-concept results that simultaneously delivering gene-encoded antibody treatment and vaccine confers the recipient with immediate immune protection while a long-term immune response develops.

LOOKING AHEAD

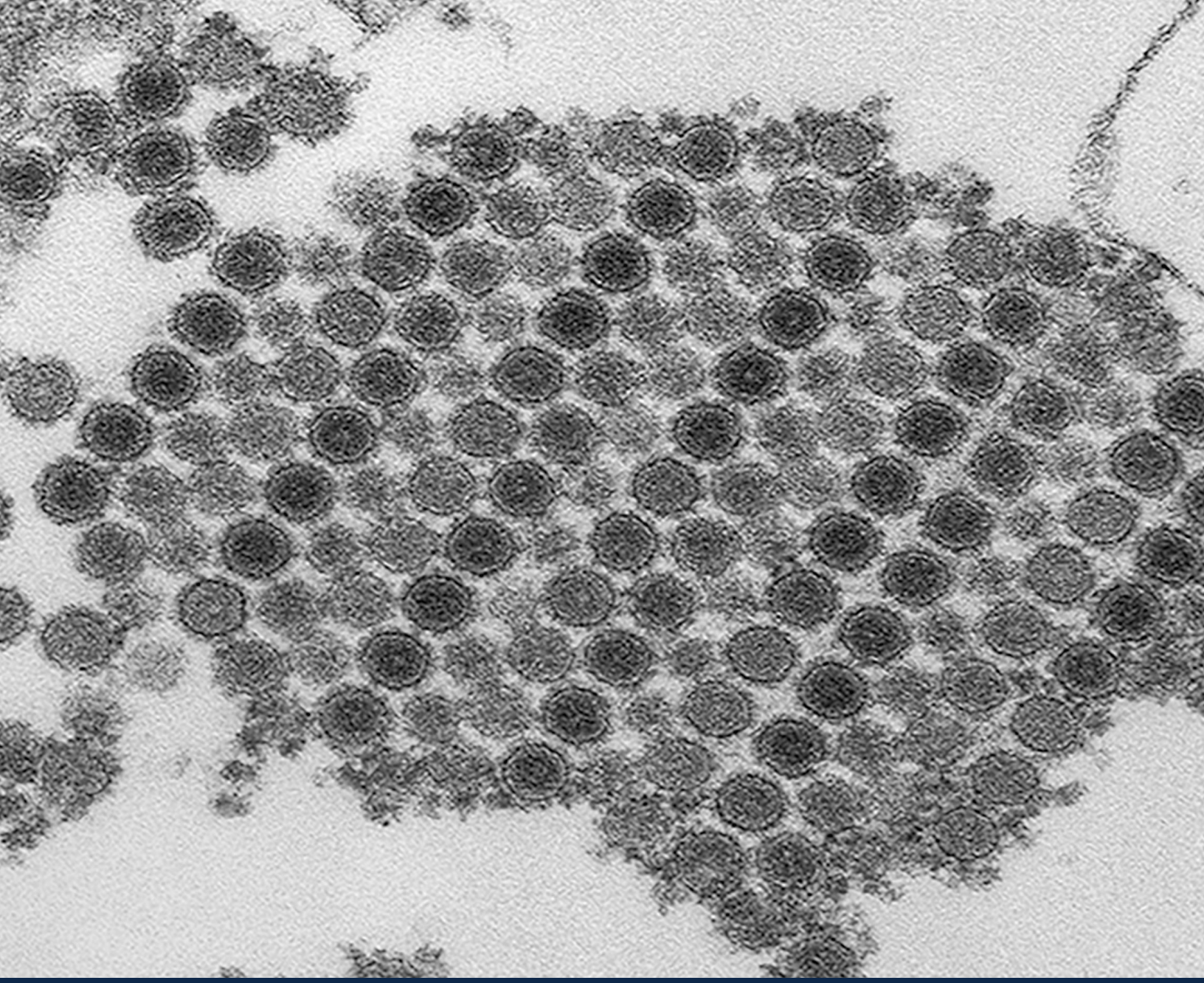
DARPA's R&D investments to de-risk the pathway to gene-based medical countermeasures have spurred like-minded innovators. In addition to Moderna, several other companies, including AstraZeneca and Inovio, have made major investments in this budding biomedical field. These DARPA investments also spurred the biotech firm RenBio to work toward optimizing the delivery of gene-based MCMs for increased efficacy and tolerability. Other government agencies – including the DoD's Joint Program Executive Office for Chemical, Biologic, Radiological, and Nuclear Defense (JPEO-CBRND), the Biomedical Advanced Research and Development Authority (BARDA), and the National Institute of Allergy and Infectious Disease (NIAID) – also have recognized the power of gene-encoded antibody technology to fight a range of biothreats and infectious diseases.

Progress in the ADEPT program has earned supplemental 6.2 funding from the U. S. Congress in response to the 2014 Ebola virus outbreak in West Africa. To address current and future Ebola outbreaks, these funds were directed toward development, manufacture, and/or clinical evaluation of several MCMs, including one based on a monoclonal antibody referred to as mAb-114, which was previously discovered by scientists at NIAID's Vaccine Research Center. This therapeutic antibody was authorized for emergency use (EUA) in the 2017 Ebola outbreak in the Democratic Republic of Congo, where it conferred significant survival benefits over other EUA-sanctioned Ebola therapeutics. To enable continued availability of mAb-114, DARPA and JPEO-CBRND in 2018 co-funded the manufacture of additional doses at Ology Biosciences through its DoD-funded Advanced Development and Manufacturing (ADM) facility.

ADEPT investments also were foundational to an ambitious follow-on DARPA program, the Pandemic Prevention Platform (P3). Its goal is to prevent pandemic outbreaks by creating a platform capable of identifying, testing, and mass-producing MCMs within 60 days of the detection of an outbreak. The emergence of COVID-19 in late 2019 and its pandemic spread in 2020 reinforced the importance of ADEPT and P3 in the most forceful of terms possible. P3 is part of a yet more comprehensive portfolio of DARPA programs that stand a chance of ultimately delivering a technology framework that could quash just about any outbreak of a known or emerging infectious disease before it could grow into a pandemic.

DARPA pioneered the original concept of MCMs based on the encoding of antibodies in RNA and DNA. The agency helped usher the technology from the laboratory to clinical testing and to the verge of clinical practice in 2020. With ADEPT, P3, and related programs, DARPA seeks nothing less than to deliver the knowledge and know-how needed to protect U.S. warfighters and the general citizenry from threats posed by any dangerous pathogen, whether previously encountered or new to humankind.

*Autonomous Diagnostics to Enable Prevention and Therapeutics: Prophylactic Options to Environmental and Contagious Threats (ADEPT: PROTECT)



Transmission electron micrograph of numerous Chikungunya virus particles.
(Photo courtesy of the CDC)

DARPA

www.darpa.mil