



Preventing Pandemics

*With a mandate to anticipate next-generation threats,
DARPA has helped lay technological foundations for ending
COVID-19 and preventing future pandemics*

PREVENTING PANDEMICS

The public health community has long known that pandemics are sure bets, that they are certain to intermittently visit upon us devastating degrees of illness, death, and economic loss. The current COVID-19 pandemic is just the latest in a series of pandemics that historians have traced back thousands of years. Caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), COVID-19 has become the worst pandemic since the flu pandemic of 1918-1919, which killed tens of millions of people around the globe. As January 2021 was coming to a close, COVID-19 was closing in on 100 million infections and already had surpassed 2.1 million deaths worldwide, including well over 25 million infections and 420,000 deaths in the United States.

It's DARPA's job to anticipate and, if possible, develop technologies for pre-empting and even eliminating threats that are likely to challenge the DoD's ability to carry out its mission in the coming years and decades. With our warfighters deploying potentially anywhere in the world, infectious disease is prominent among those challenges. In the past 15 years, DARPA has stepped up its commitment to delivering the scientific understanding and technologies required for preventing, diagnosing, and treating infectious disease in timeframes much faster than have been possible so far – weeks and months, rather

than years. Now those investments are undergirding history's most rapid mobility of innovation for quashing a raging pandemic. And given the broad applicability of these technologies, this spate of public-health research will contribute to the desperately needed technology base for meeting infectious disease threats in the future, whether they are localized outbreaks or fast-growing epidemics and pandemics.

Underscoring this point, representatives Jim Langevin and Elise Stefanik, the chairman and ranking member of the House Armed Services Committee's Subcommittee on Intelligence and Emerging Threats and Capabilities, note in a joint op-ed published in *The Hill* on May 21, 2020, "DARPA's investments in biotechnology and pandemic preparedness have given us our best chance at developing a rapid testing and treatment capability for COVID-19. DARPA's projects aimed to revolutionize how our country develops capabilities using the properties of biology to protect our women and men in uniform, while simultaneously preparing the nation to prevent and defend against biological threats."

Just as massive wildfires can be prevented by putting out smaller fires before they spread, so too can localized outbreaks of disease be quashed or prevented before they grow into pandemics. With that dynamic in mind, DARPA has been managing

an audacious portfolio of projects designed to generate pandemic-stopping know-how and to act on that knowledge by dramatically reducing the time it takes to scale-up the means for preventing, diagnosing, and treating any infectious disease that might arise, even ones the world has never seen before.

The pillars of DARPA's pandemic portfolio fall into the categories of prevention, diagnostics, and treatments.

PATHWAYS TO PREVENTION

Effective vaccines prevent people from getting sick even if they are exposed to an otherwise infectious agent, whether it be a seasonal flu virus, the measles virus (Rubeola), or SARS-CoV-2. Vaccines do this by mimicking a viral or bacterial threat in a way that mobilizes the immune system into behaving as though the host is under attack and then retaining an ability to counter such attacks in the future. Conventional vaccines achieve this effect by exposing the immune system to key pathogen-borne proteins along with stimulating the immune system (e.g., with adjuvant). Nearly all existing vaccine strategies, however, require laborious, expensive, and lengthy development time to counter each new threat.

This is where DARPA's groundbreaking push to develop so-called nucleic-acid

vaccines has been transformational. In 2012 with its ADEPT:PROTECT program* (and usually known for short as ADEPT), DARPA began investing in the development of gene-encoded vaccines, a new category of preventive measures based on DNA or RNA. DNA is the celebrity biological molecule that encodes genes; RNA is a related molecule that shuttles the DNA code from the cell's nucleus to cellular machinery that converts that genetic information into proteins that do the cell's work, including neutralizing infectious agents. In this new vaccine strategy – which is at the basis of the highly effective COVID-19 vaccines that have begun to protect millions of people – genes that encode immune-stimulating antigens, such as the now infamous spike protein on the surface of SARS-CoV-2, 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. "This

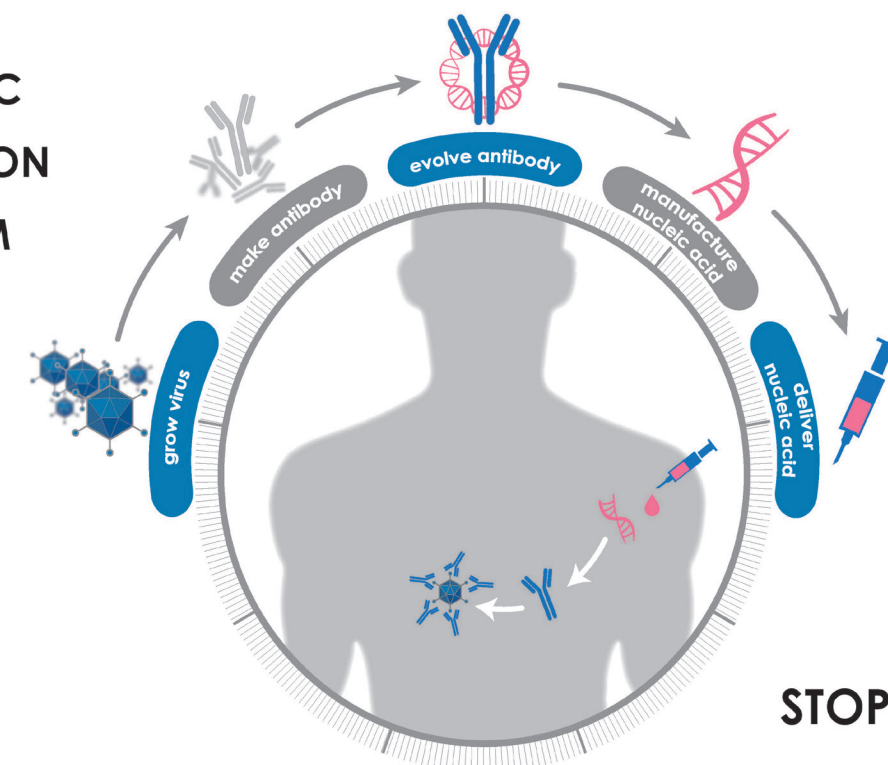
is a remarkably simple and elegant biological process," says program manager Amy Jenkins, who now oversees the P3 program along with other programs that could transform and empower society's responses to infectious-disease threats.

DARPA's investments in this R&D space helped to reinforce an entire community of nucleic-acid vaccine researchers and led directly, with the biotechnology firm Moderna as a contracted performer on the ADEPT program, to some of the first experimental vaccines based on so-called messenger RNA (mRNA). Initial targets for these new vaccines included emerging diseases such as Chikungunya (ChikV). 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 this RNA-based medical countermeasure. Moderna reported these promising results of its clinical study in 2019. The

trial also demonstrated that this new type of vaccine could elicit protective levels of antibodies in humans.

As the COVID-19 outbreak began early in 2020, former DARPA performers and others swiftly adapted their new nucleic acid vaccine platforms to create RNA and DNA vaccine candidates against SARS-CoV-2. Moderna's RNA vaccine was the first COVID vaccine to enter clinical trials and advanced in July 2020 to Phase 3 studies in 30,000 subjects. On December 18, 2020, the Moderna vaccine received FDA Emergency Use Authorization (EUA) approval for the prevention of COVID-19. Inovio, another DARPA performer, reported positive findings for its DNA vaccine, with efficacious immune response observed in 34 of 36 (94%) subjects enrolled in the Phase I safety study. The company initiated Phase 2/3 studies to determine efficacy and dose protocols on November 16, 2020.

PANDEMIC PREVENTION PLATFORM (P3)



**60 DAYS TO
STOP A PANDEMIC**

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.

In addition to DARPA, the Department of Health and Human Services (HHS) and the Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND) have both invested heavily in clinical development and/or manufacturing to bring these nucleic-acid vaccines to the clinic, and – in the case of Moderna’s RNA vaccine – to the American public.

Another pillar of prevention in public health is the detection of even low levels of disease agents and DARPA has been developing potentially game-changing technologies in this arena too. The DARPA SIGMA+ program, for one, is on its way to delivering networked sensors that can detect chemical, biological, radiological, nuclear and explosive threats. One of the SIGMA+ projects seeks to reduce the time to sample and monitor even low levels of environmental pathogens from thirty minutes to a few seconds. In response to the pandemic, DARPA program manager Mark Wrobel has tasked researchers to update the sensors with the ability to identify molecular signatures for SARS-CoV-2. This will open the way to sensor systems that persistently monitor for the virus in large public spaces such as airports, transportation hubs, and hospitals. To further that cause, DARPA is working with researchers in the SIGMA+ program to collect additional field data and to soon move toward operational demonstrations of the technology.

In tandem with this maturing research, DARPA has initiated the SenSARS program to rapidly survey technologies that may provide real-time detection of SARS-CoV-2 in offices, classrooms, conference rooms, and buildings to help accelerate a safe return to work and school for the U.S. population. With the same view on returning to normalcy, DARPA responded to a request from the Commander of USTRANSCOM to evaluate the risk of aerosol exposure to SARS-CoV-2 among individuals in military and commercial aircraft. All military aircraft

(KC10, KC46, KC135, C5, C17, and C130J) were tested within one week and USTRANSCOM received valuable risk-assessment data by the end of April 2020 to guide military transport safety measures. Commercial aircraft (B737-800, A319, B767-300, and B777-200) were also tested to assess exposure risk to crew members and passengers. Those studies, coordinated with aircraft manufacturers, involved aerosol sources placed in different seat locations to represent “sick” individuals and highly spatially-resolved sampling and analysis to map out the movement of aerosolized particles throughout the aircraft.

Testing on military aircraft found that smoke barriers offer excellent protection to particle penetration between cabin zones, especially in the KC135, KC46, and KC10. Testing on commercial aircraft cabins indicated that even those passengers in neighboring seats to a “sick” passenger are at extremely low exposure risk due to the high air-exchange rates (25 CFM per passenger), HEPA filtration, and downward air flow. More specifically, the analysis suggested that all passengers within 40 rows of a COVID-19 infected individual in a commercial aircraft (B777-200 and B767-300) with the specified HVAC settings would experience at least a 99.7% reduction in exposure risk (or 3 orders of magnitude). The average exposure risk reduction was 99.99% for passengers in the B777-200 and B767-300 while in flight with the specified HVAC settings.

Several commercial aircraft operators immediately acted on this information to minimize exposure risk in their flights. All of the testing data has been made available to the public through the USTRANSCOM website to help manufacturers and commercial aircraft carriers in their own studies to evaluate countermeasures and risk-mitigation strategies for improving the safety of passengers during the pandemic.

PATHWAYS TO DIAGNOSIS

In partnership with prevention, diagnosis is a critical aspect of pandemic response. Rapid discovery, validation, and manufacture of diagnostic tools that the public-health community can use to detect any disease threat, anytime, anywhere is the *raison d’être* of two DARPA programs: Detect It with Gene Editing Technologies (DIGET) and Epigenetic CHaracterization and Observation (ECHO).

Current diagnostic tools screen blood, saliva, and other body fluids from infected individuals to detect molecular signatures – usually nucleic acids (DNA and RNA) or protein – of a virus. With DIGET and ECHO, DARPA is supporting innovators whose sights are on new diagnostic technologies that detect ultra-low amounts of viral nucleic acid as well as the subtle but detectable “genetic marks” that past and current infections can leave behind along gene-carrying chromosomes and that reflect an individual’s likely response to an infection.

When the COVID-19 outbreak began spreading early in 2020, DARPA recognized the potential for the ECHO and DIGET programs to aid in the fight against the pandemic through rapid and early detection. DARPA program managers quickly refocused their diagnostic research teams to target the novel coronavirus as a test of their developing technologies. In one uplifting result in light of the large amount of disease transmission from symptom-free people infected with SARS-CoV-2, a test developed in the ECHO program demonstrated 99.1% accuracy in diagnosing COVID-19. By harvesting specific cells from saliva, mucus, or blood, this technology has shown that it is not only possible to diagnose COVID-19 36 hours earlier than conventional tests, but also that within the first five days of infection, the severity of a patient’s yet-to-show symptoms can be predicted based on these genetic marks. This

means that ECHO researchers are on track to delivering diagnostic and prognostic tools that are likely to help guide individualized quarantine and treatment protocols.

ECHO program performers already have received EUA approval for a direct viral saliva test. This is the first manufacturer’s EUA for diagnosis of COVID-19 from saliva. The performers will be submitting an EUA application to the FDA in February 2021 for additional host-based diagnostics. Meanwhile, DARPA is coordinating further development of the saliva test in partnership with NIH’s RADx (Rapid Acceleration of Diagnostics) program.

Somewhat earlier in the DARPA pipeline are next-generation diagnostics based on CRISPR technology, which usually is associated with gene editing. DARPA program managers are instead pursuing it as an approach to detecting virus-revealing nucleic-acid sequences. CRISPR-based diagnostics may offer advantages compared to state-of-the-art technologies. For example, they appear more amenable to simultaneous analysis of multiple pathogens, allowing a single test to distinguish, for example, SARS-CoV-2 infections from the flu and other respiratory infections.

DARPA also has been supporting other diagnostics-based efforts, including ones that reveal how the technology can help move society back toward normalcy. Among these studies is one undertaken with the U.S. Marine Corps and the Naval Medical Research Center and known as CHARM, which stands for COVID-19 Health Action Response for Marines (CHARM). 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. Data from this investigation led to updated CDC quarantine guidelines that reduced the necessary quarantine period from 14 to 10 days for individuals testing



DARPA researchers at Vanderbilt University working on antibody discovery.

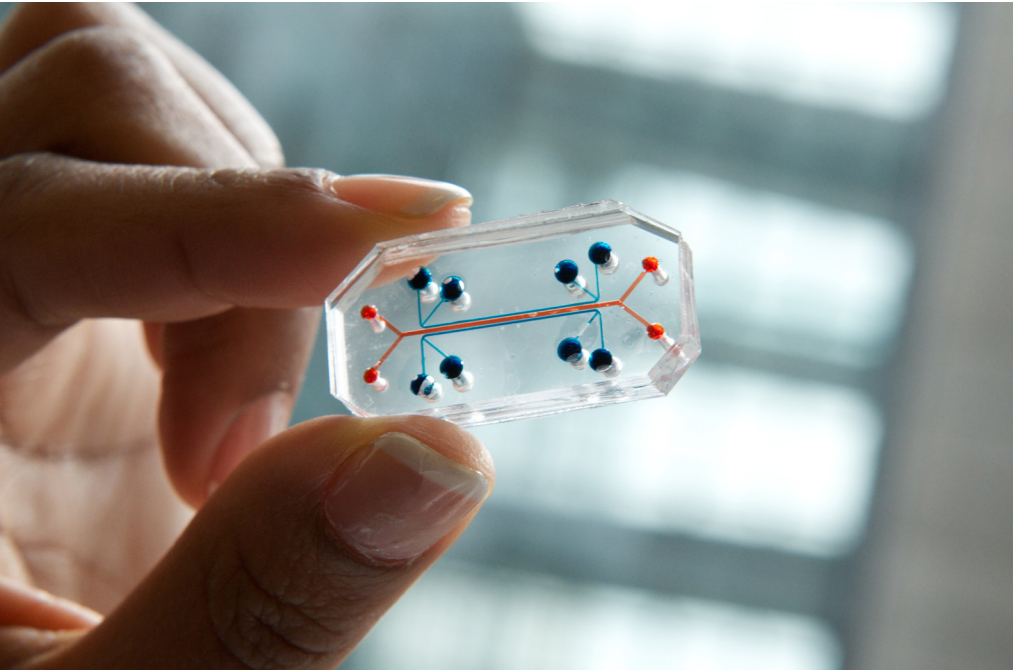
positive for COVID-19, as outlined in a November 2020 *New England Journal of Medicine*.

PATHWAYS TO ANTIBODY-BASED TREATMENTS AND PROPHYLACTICS

If it becomes too late to prevent an infection, and if a diagnosis confirms a patient has COVID-19, then it falls to treatment to save the patient and minimize additional transmission. Through novel antibody treatments, rapid drug discovery, and domestic manufacture of key medicinal compounds known as active pharmaceutical ingredients (APIs), DARPA has been leveraging its ongoing research base to hasten the availability of COVID-19 treatments.

A key part of P3, notes program manager Jenkins, always has been to develop antibody-based countermeasures for preventing disease outbreaks from spreading by treating those who are vulnerable to exposure — perhaps because they are in the vicinity of infected individuals — with pathogen-stopping antibodies. “The ability to use these same preventive antibodies [to treating those who do become infected] is an awesome side-effect of their utility and so that became a focus for COVID-19 because we had few other treatment options,” said Jenkins.

More specifically, a primary treatment and prophylaxis strategy DARPA is pursuing capitalizes on the successful immune responses of people who have recovered from COVID-19. When people fight off a viral infection, their immune systems manage to identify and then mass-manufacture antibodies. These are specialized protein molecules with astonishing abilities to specifically bind to molecular motifs on pathogenic particles such as viruses. That antibody response hobbles the virus particles and flags them for destruction by other components of the immune system. Those who have recovered



Among the many organ-on-chip modules that have been delivered under the MPS program is this Lung-on-a-Chip, which was developed by researchers at the Wyss Institute. (Photo courtesy of the Wyss Institute)

from COVID-19 have antibodies in their blood that bind to SARS-CoV-2. In fact, they often have thousands of different antiviral antibodies that range in effectiveness in neutralizing the virus. By identifying the most powerful antibodies, it is possible to develop targeted and potent antibody-based treatments and prophylactics.

Years before the current pandemic, DARPA had scored a success in manufacturing an antibody that binds to the Ebola virus. It became the basis of one of the two approved Ebola treatments and is a large part of the reason why Ebola is becoming a manageable infectious disease rather than one dreaded for its pandemic potential. However, the actual Ebola antibody-discovery work, performed by the National Institutes of Health, took years. In FY2016, DARPA initiated the P3 program aimed squarely at the rapid discovery, testing, and manufacture of antibody treatments to fight any emerging disease threat. Using influenza, Zika, and MERS (Middle East Respiratory Syndrome) as test cases, researchers in the P3 program demonstrated how to find and manufacture neutralizing antibodies in

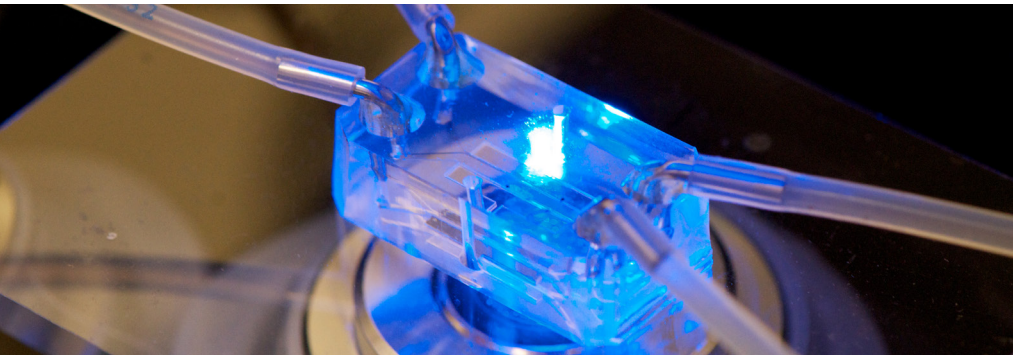
less than 90 days as opposed to the years it previously had taken.

As the COVID-19 outbreak began early in 2020, DARPA alerted P3 research teams to be ready to address the novel coronavirus as the next test. Once blood samples were recovered from some of the earliest COVID-19 patients, it took only three weeks for potent antibodies to be discovered. Manufacturing of these antibodies started soon after that. The first clinical trial of a P3-discovered antibody product began on June 1, 2020 – under 90 days from receipt of the first blood samples. Two additional P3-discovered antibodies were combined into a “cocktail” or combination product, and this treatment entered clinical studies in August 2020. HHS and JPEO-CBRND have both invested significant funds with major drug manufacturers to make and test P3-derived antibody products.

Following successful Phase 1 clinical safety trials, both of these antibody products – bamlanivimab, the antibody discovered by AbCellera Biologics and licensed by Eli Lilly; and AZD7442, the combination product comprised

of two antibodies discovered by scientists at Vanderbilt University and licensed by AstraZeneca — entered large-scale Phase 2/3 clinical studies in August and November 2020, respectively. Based on the results, bamlanivimab received FDA EUA on November 9, 2020, for treatment of recently diagnosed COVID-19 among individuals at high risk of developing severe disease. Studies evaluating AZD7442’s clinical efficacy are ongoing. Additionally, P3 performers are developing RNA-encoded monoclonal antibodies targeting SARS-CoV-2 and are aiming for clinical studies in 2021.

Another potential route for rapidly discovering treatments amidst the sudden arrival of new infectious agents is to mine already FDA-approved drugs for ones that might be repurposed into effective treatments. DARPA started taking steps to make this possible a decade ago when the agency initiated its MicroPhysiological Systems (MPS) program. That led to a pathbreaking drug-screening technology based on human “organ-on-a-chip systems,” which are versatile laboratory surrogates for whole-animal and human clinical tests. Now these commercially-available systems are being used to rapidly screen drugs to treat COVID-19. Adding to this drug-screening strategy is work in DARPA’s Panacea program that yielded the first published human/ SARS-CoV-2 protein interactome map. This data-rich tool describes how the proteins in and on SARS-CoV-2 particles interact with human cells and it has been used worldwide in the fight



An organ-on-chip module developed by the Wyss Institute undergoes testing. (Image courtesy of the Wyss Institute)

against COVID-19. The drug Zotatiffin, a protein-synthesis inhibitor identified by Panacea performers with their interactome map, is entering a Phase 1 clinical trial with investment support from the Defense Health Agency.

It is one thing to discover new pharmaceutical treatments; manufacturing and distributing them in amounts sufficient to treat everyone who can benefit is another. Indeed, the COVID-19 pandemic has highlighted vulnerabilities in the U.S. pharmaceutical supply chain. With its programs aimed at transforming how chemists synthesize molecules and manufacture chemicals in sufficient quantities, DARPA also is tackling this practical part of outbreak prevention and management. Under DARPA’s Make-It program, for example, researchers are developing and commercializing technology that directly addresses these supply vulnerabilities to enable an end-to-end, deployable, and scalable capability for the production of medicines made from readily available ingredients that can be sourced within the U.S.

The Make-It technology began taking shape under DARPA’s Battlefield Medicine program nearly a decade ago. That program sought to establish proof-of-concept for a field-deployable pharmacy kit to assist military medical personnel treating service men and women in forward operations. Researchers in the program demonstrated the ability to produce four active pharmaceutical ingredients,

or APIs, which are the critical ingredients for final drug formulations. Under Make-It, researchers automated and expanded production to enable the flexible and scalable manufacture of a broad range of APIs. Current efforts focus on addressing regulatory approval requirements and adapting the technology for producing critical medicines and precursors needed to treat critical-care COVID-19 patients.

PREVENTING PANDEMICS

When DARPA initiated research on rapid disease response more than a decade ago, no one could predict what diseases would emerge and when, only that they would. Now, the results of these DARPA projects are playing a leading and catalytic role in today’s fight against COVID-19. In typical DARPA fashion, the agency conducted technology development efforts years before they were needed, leading to high-impact technologies that are key to mitigating the current pandemic. Perhaps even more consequential is the generic nature of many of these disease-fighting technologies, i.e., the applicability to what the World Health Organization refers to as “Disease X,” which signifies an infectious and contagious illness that no one has seen before. COVID-19 is just the latest Disease X. There will be more of them and DARPA’s extensive and continuously growing platform of pandemic-stopping technologies – spanning from prevention to diagnostics to treatment – will be ready to use in humanity’s defense.

*Autonomous Diagnostics to Enable Prevention and Therapeutics (ADEPT); Diagnostics on Demand (DxOD); Prophylactic Options to Environmental and Contagious Threats (PROTECT)



A researcher from the University of Nebraska Medical Center suits up to collect samples from a COVID-19 patient.



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