Lasting immunity and protection from new single-shot, room-temperature stable COVID-19 vaccine

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An international collaboration led by Luk H. Vandenberghe, Ph.D., in the Department of Ophthalmology at Mass Eye and Ear, a member of

Mass General Brigham, reported that a novel, gene-based COVID-19 vaccine leveraging a unique adeno-associated viral vector (AAV) platform was highly effective at eliciting neutralizing antibody responses and cellular immunity from a single dose. The vaccine provided nonhuman primates near-complete protection against a live SARS-CoV-2 viral challenge led by immunology researcher, Roger Le Grand, Ph.D., of the French Alternative Energies and Atomic Energy Commission (CEA).

With support from Novartis Gene Therapies, the AAVCOVID vaccine was shown to be producible with efficient, scalable, and industry-established manufacturing processes. The investigators further demonstrated that the vaccine product is stable at room-temperature storage conditions for up to one month, facilitating potential future distribution of the vaccine.

The new research, published September 8 in *Cell Host & Microbe,* represents the first peer-reviewed study to demonstrate AAVCOVID vaccine's preclinical effectiveness and the maintenance of immunity at peak levels for at least 11 months from a single-dose immunization. The study authors hope these findings support a move towards clinical trials with a goal of global distribution in parts of the world that are currently underserved by vaccination.

"Our findings, bolstered by long-term durability and protection data, show the AAV vaccine platform may address some of the ongoing elements of the health crisis and should warrant further study in clinical trials," said AAVCOVID principal investigator Luk H. Vandenberghe, Ph.D., director of the Grousbeck Gene Therapy Center at Mass Eye and Ear and Associate Professor of Ophthalmology at Harvard Medical School. "More durable and accessible vaccine options are of paramount need as the pandemic persists globally. We further believe our data validate this novel platform for consideration of other health threats for

which vaccines are pursued."

Durable immune response and vaccine potency observed

In the new study, two AAVCOVID vaccine candidates with different SARS-CoV2 virus spike-based antigens were analyzed in a battery of experiments to measure effectiveness, duration of response, potency and stability. The candidates were derived from genetic data collected on the Wuhan strain of the SARS-CoV-2 virus. One vaccine candidate, AC1, was found to be superior in its ability to produce sustained immune responses in mouse and nonhuman primate models.

Early studies in mice revealed a single injection of the AC1 AAVCOVID candidate induced significant neutralizing antibody and T-cell levels, with antibody levels persisting for more than six months.

Next, to gain a better sense of how the vaccine might work in people, the AC1 AAVCOVID candidate was studied in a nonhuman primate model. The AC1 vaccine led to antibody levels that peaked at week 11 and remained at peak for at least 11 months. The antibodies were detected in lung tissues, which may suggest mitigating some of the pulmonary effects of COVID-19 infection. The vaccine also induced long-term functional memory T-cell responses.

No adverse effects were observed in either animal model.

Further testing established the feasibility of large-scale manufacturing of the vaccine in already available industry processes through Novartis Gene Therapies. The researchers also tested cold-chain storage requirements, or the need to keep the vaccines at specific low temperatures to retain potency. They analyzed the vaccine's potencies

when stored at -112^{0}F (-80^{0}C), 39^{0}F (4^{0}C) or 77^{0}F (25^{0}C) to approximate freezing, refrigerated and room temperatures, respectively. The vaccine was shown to be stable after one month at room temperature, with stability at colder temperatures exceeding three months.

Immune protection supported by challenge study

Led by Dr. Le Grand, SARS-CoV-2 viral challenge studies were conducted with the AC1 vaccine candidate in nonhuman primates at the Infectious Disease Models and Innovative Therapies (IDMIT) department at CEA in Fontenay-aux-Roses, France. Compared to unvaccinated animals that showed COVID-19 infection in the nose, trachea and lung, the animals that received an AC1 immunization nine weeks prior to the challenge all demonstrated near-complete protection against COVID-19 infection. In particular, the upper airways were highly protected from COVID-19, as no major lung damage was seen in immunized animals, while two controls showed lesions caused by the virus.

"The remarkable efficacy induced in the nonhuman primate model after a single injection of the AAVCOVID vaccine does represent an important step in the development of a COVID-19 vaccine. Many possibilities are offered by the platform for antigen engineering. Rapid production scalability and easy distribution make AAV vaccines of particular interest for new pathogen threats readiness,″ explained Roger Le Grand, Ph.D., executive director of IDMIT.

The different variants of COVID-19, including the Delta variant, were also neutralized by serum from the AC1 candidate in vaccinated animals. Consistent to other Wuhan-based vaccines currently in market, variants are neutralized to a lesser amount as compared to the ancestral strain.

AAV-based platform may address persisting global challenges in pandemic response

AAVCOVID is a vaccine strategy that employs an AAV vector—a well-studied class of viral vectors used in approved gene therapies—to deliver genetic sequences for antigens of the SARS-CoV-2 virus spike protein to elicit a sustained immune response. The vaccine employs a specific AAV designed by Dr. Vandenberghe called rh32.33, which offers favorable inflammatory properties needed for vaccines and lacks pre-existing immunity in humans. This vaccine is the first COVID-19 vaccine developed on the AAV technology. While other viral vector vaccines exist, it is highly distinct from adenoviral vaccines, several of which are currently approved worldwide for COVID-19.

"It is exciting to see the progress in developing this AAV vaccine platform against SARS Co-V-2, and the potential it holds for future vaccine development against other pathogens," said Joan W. Miller, MD, Chief of Ophthalmology at Mass Eye and Ear, Mass General Hospital, and Brigham and Women's Hospital, and Chair of Ophthalmology and David Glendenning Cogan Professor of Ophthalmology at Harvard Medical School. "This is a wonderful example of successful international collaborative research, which is especially critical when addressing a global pandemic like COVID-19."

The new study showed that an AAVCOVID vaccine can address some of the biological and logistical hurdles that have persisted since the pandemic began, and more than six months since vaccines became approved for use.

There remains a critical need for additional vaccination strategies, as rollouts of approved vaccines have been uneven worldwide, especially in low- and middle-income countries. Most COVID-19 vaccines require

two injections, and the need for a booster may become a reality, as the duration of effectiveness has been reported to wane over time. A single-dose vaccine that offers one-year-immunity can not only offer a solution that is more desirable for adherence, but also decrease billions of dollars in global healthcare costs associated with the production of multiple-dose and booster vaccines.

An AAV-based vaccine can also leverage existing manufacturing facilities used to produce and distribute AAV-based gene therapies.

Cold storage also remains a challenge in many parts of the world, and AAVCOVID's ability to retain potency and stability for up to one month at room temperature could address some of these challenges.

"We believe an AAVCOVID vaccine has the potential to provide a more accessible option for people across the globe, especially to those with limited access to medical care," said first study author Nerea Zabaleta Lasarte, Ph.D., a postdoctoral research fellow at the Grousbeck Gene Therapy Center at Mass Eye and Ear. "The AAV-based platform provides a new approach to vaccines never used before, and outside-the-box strategies that can get more inoculations to a greater number of people regardless of where they live remain profoundly needed."

Future study of vaccine platform and new delivery methods

The peer-reviewed findings build on preprint results published earlier this year that showed efficacy and potency at three-month tests, and the team plans to continue to collect data on the duration of response from a single-dose injection.

The team will also explore additional delivery options for the vaccine,

including for needleless vaccine delivery. The temperature stability of AAVCOVID observed in the study could lend itself to easier-to-distribute formulations of the vaccine, such as in liquid drops or pills that can be shipped to far reaches of the globe commercially.

AAVCOVID researchers hope their findings can compel additional study in clinical trials.

More information: Nerea Zabaleta et al, An AAV-based, room-temperature-stable, single-dose COVID-19 vaccine provides durable immunogenicity and protection in non-human primates, *Cell Host & Microbe* (2021). DOI: 10.1016/j.chom.2021.08.002

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