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First-in-Human Study of DNA Antibody Replicas Generate Efficient and Long-Lasting Biologic Production of Human Antiviral Antibodies

PHILADELPHIA — (OCT. 21, 2025) — A multidisciplinary team of scientists led by The Wistar Institute, including Perelman School of Medicine at the University of Pennsylvania, AstraZeneca and Inovio Pharmaceuticals, published today in *Nature Medicine* a breakthrough in biologic antibody production that happens directly in human subjects in this encouraging first clinical trial of its kind.

Funded by the Defense Advanced Research Projects Agency and Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense, researchers have demonstrated that designed DNA cassettes (small genetic elements) through direct delivery instruct human tissues to produce, assemble, and secrete functional human monoclonal antibodies that persist in the bloodstream for more than a year. Detailed studies of these expressed antibodies show they function effectively, bind correctly to their specific viral target and are well tolerated by the host, an important outcome.

The DNA "cassettes" were designed to mimic native human antibodies in sequence and assembly upon delivery. The two antibodies were detected in 100% of evaluable participants, with serum concentrations reaching a peak of 1.61 µg/mL—a level comparable to some FDA-approved biologic therapies. Sustained antibody expression was observed in all participants during the 72 weeks of follow-up, supporting this novel approach to disease protection and treatment.

"While FIH studies require cautious interpretation, and rigorous validation, the long-term expression of biologic antibodies with demonstrated fidelity and functionality in all volunteers without induction of anti-drug antibodies represents an important development for the biologics field." said **David B. Weiner, Ph.D.**, Executive Vice President of The Wistar Institute, director of Wistar's Vaccine & Immunotherapy Center, W.W. Smith Charitable Trust Distinguished Professor in Cancer Research, and senior author of the study.

As the FDA and other regulatory agencies have requested solutions for the complex biologic production of cell based medicines, this study supports that direct delivery of highly focused DNA, which is already utilized as the seeds to create the cell lines that produce biologics in laboratories, could eliminate steps and excipients in biologic production moving to direct patient production by using the native human biologic production process in their cells.

Traditional antibody or biologics face limitations: They can be expensive to manufacture, store, and distribute; are made in laboratories utilizing many excipients that are time-consuming to approve; and provide only temporary protection lasting weeks to months. During the COVID-19 pandemic, these challenges became particularly apparent when, by the time several antibody treatments were

developed, approved, and distributed, they had been rendered ineffective due to the rapid development of viral escape.

In the clinical trial, led by **Pablo Tebas, M.D.**, a professor of Infectious Diseases at Penn and the study's lead clinical investigator, forty-four healthy adults received between one and four doses of synthetic plasmids encoding two COVID-19 neutralizing antibodies. Thirty-nine out of thirty-nine evaluable participants showed detectable levels of DMAbs produced in vivo up to 72 weeks later. Additionally, no anti-drug antibodies (ADAs) were detected in any participant throughout the duration of the study—a significant advantage over other delivery methods.

"For the first time, we've shown that the human body itself can be turned into a factory to safely produce long-lasting, fully functional antibodies," said Tebas. "This approach could simplify biologic therapies, lower costs, and extend protection for patients who need it most. In our study we were able to give up to four doses in some subjects, in total >200 administrations in the cohort, and did not observe the development of ADAs. We hypothesize that the design of the antibody constructs with high fidelity to normal human antibodies, the lack of foreign proteins or other components that may trigger the immune system, the consistency of antibody production by their own cells,and the targeted delivery of the DNA plasmids into muscle cells by INOVIO's CELLECTRA delivery system without the use of chemical adjuvants, lipid nanoparticles or viral vectors, contributed to this positive outcome. These among others remain areas for continued investigation by the team."

One important application of this approach is for persons who cannot benefit from or take traditional vaccines for various reasons. These could include cancer survivors, transplant recipients, and persons with certain autoimmune diseases, for example. The study reported sustained antibody expression after a single dose. This could reduce the cost of therapy and patient experience through lowering the number of treatments, potentially eliminating expenses associated with protein biologic production and infusion.

Tebas also emphasized that the approach proved to be generally well-tolerated. Most side effects were limited to mild, temporary injection site reactions typical of any intramuscular injection. This was the primary objective of the clinical trial.

"Our sample size was limited, and we looked at up to 72 weeks of expression and tested a limited set of formulations, said Tebas." We are excited to share our findings to bring more eyes to this study and further advance the field."

This study represents the value of deep collaboration, a hallmark of Wistar research to address complex biologic issues. Weiner, Tebas, and their respective labs have collaborated for years on developing first-in-human trials of novel DNA immunogens and vaccines. In this study, Weiner and The Wistar Institute provided the foundational DNA platform technology, while Tebas and Penn used their extensive experience to guide the clinical process and regulatory navigation. They both have collaborations in the DNA space with Inovio Pharmaceuticals, which developed the specialized CELLECTRA® delivery system and oversaw production of the DNA plasmids, and with AstraZeneca which shared its antibody designs and expertise in biologic development. This project received

extensive support and guidance through the U.S. Defense Advanced Research Projects Agency, which funded the project through its reduction to practice focus.

“It was an honor to work together with this exceptional team whose combined skills and dedication to bring new creative solutions for patients benefit underpin this project’s important findings.” said Weiner.

The implications of these findings extend far beyond COVID-19. Weiner suggests that this platform could potentially deliver long-acting treatments for cancer, autoimmune diseases, and other conditions currently requiring frequent clinic visits for antibody infusions. It could be particularly valuable for immunocompromised patients who don’t respond well to traditional vaccines, offering them extended protection through their now own cells antibody production. The approach could also be a viable delivery method for long-term hormone medications like GLP-1s or for enzyme replacement diseases, as well as multicomponent gene editing approaches for inherited disease applications.

“This proof-of-concept in some ways strengthens concepts for biologics delivery,” Weiner said. “We’ve shown that the DNA antibody replicas can reliably deliver to human cells to produce complex biological molecules with high fidelity and are well tolerated. The platform’s simplicity, scalability, and independence from cold storage potentially offer advantages for patient equity and accessible treatments.”

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Penn and Dr. Weiner have either received, or may receive in the future, financial consideration related to the licensing of certain Penn intellectual property to INOVIO. Dr. Weiner is a member of the Scientific Advisory Board and Board of Directors for INOVIO.

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