Phage display-based gene delivery: A viable platform technology for COVID-19 vaccine design and development

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Researchers at Rutgers Cancer Institute of New Jersey, Rutgers New Jersey Medical School (NJMS) and the Center for Theoretical Biological Physics (CTBP) at Rice University in Houston, Texas, have demonstrated that a technology with favorable biological attributes

known as phage display could be a viable platform for the development of new vaccines to protect against COVID-19. Findings from the proof-of-concept work were published online in the *Proceedings of the National Academy of Sciences (PNAS)* journal.

Currently approved vaccines against COVID-19 worldwide include mRNA-based vaccines, non-replicating adenovirus vaccines, and an inactivated SARS-CoV-2 vaccine among others. While being broadly effective, these vaccine types suffer many challenges, particularly in rapid large-scale production and distribution, with the requirement for strict storage at low-temperatures (a so-called "cold chain"), use of needles for administration, and a currently unknown ability to confer long-term protection in the face of emerging viral variants.

One completely unexplored alternative is the design and development of phage display-based vaccines, which represent an inexpensive and versatile tool for large-scale immunization. Bacteriophage (phage) are viruses that naturally only infect bacteria; thus they are generally considered safe for use in humans. Phage particles are easy to genetically engineer or modify and produce in large quantities; capable of stimulating both cellular and humoral immunity; and are stable under harsh environmental conditions (pH and temperature).

In this study, the authors developed two independent phage display-based vaccination approaches against SARS-CoV-2, the virus that causes COVID-19. The first is a peptide-directed phage particle that can be administered in an aerosolized form by inhalation. It is engineered with an epitope from the SARS-CoV-2 spike (S) protein together with a small ligand peptide to ensure it crosses from the lungs into the systemic circulation, where it produces a strong antibody response in mice. In the second approach, they engineered chimeric adeno-associated virus-phage (AAVP) particles to deliver the gene encoding for the entire S protein, which also stimulates a systemic and specific antibody response

in mice.

This dual proof-of-concept experimentation demonstrates that phage display-based vaccine approaches are versatile platforms that could be used for rapid production of COVID-19 vaccines that are cost-effective, needle-free, and can be safely stored long-term at room temperature. Combined with a theoretical structural biology approach to identify effective epitopes, this work provides a new framework for vaccine development. Further research and development of prototype COVID-19 investigational vaccines and alternative methods of application such as inhalation are ongoing.

"In the development of new vaccination strategies, the structure and strength of the local healthcare system is a key consideration. As such the global COVID-19 pandemic has raised awareness of public health inequity and the need for a rapid and accessible immunization process. In this context, the favorable biological attributes of phage particles might represent a potentially practical yet affordable alternative," shares the study's senior author Renata Pasqualini, Ph.D., resident member of Rutgers Cancer Institute and professor and founding chief of the Division of Cancer Biology, Department of Radiation Oncology at Rutgers NJMS.

The study's other senior author, Wadih Arap, MD, Ph.D., director of Rutgers Cancer Institute at University Hospital Newark and professor and chief of the Division of Hematology/Oncology, Department of Medicine, Rutgers NJMS, notes, "Bacteriophage-based therapy has a long and rich history in medicine because native phage particles are not infectious to human cells. The new appeal here is that we were able to modify the phage particles so that they may now target cell surface receptors; moreover, another potential application of this platform technology is the possibility of an inhaled vaccine administration."

"One of the challenges in designing these vaccines is that when we insert the different SARS-CoV-2 spike epitopes into the phage particles, the structure of these peptides needs to stay intact as in the original protein. In this collaboration, we demonstrated that the epitopes that show the smallest deviations from the original structure are the ones most effective in creating immune protection," adds José N. Onuchic, Ph.D., Harry C. and Olga K. Wiess Chair of Physics and professor of chemistry and biosciences at Rice University, who is a corresponding author on the study with Drs. Arap and Pasqualini.

"This initial success allows us to create a synergistic theoretical/experimental framework to discover new possible epitopes to improve these vaccines not only for SARS-CoV-2 but for other diseases as well," adds Dr. Onuchic, who is also co-director of the CTBP at Rice University.

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