VACCINE INSIGHTS

RESPIRATORY DISEASES

SPOTLIGHT

What's next for COVID vaccines?

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"...several exciting [COVID-19 vaccines] are being pursued, which have the potential to confer broad and durable protection across the spectrum of coronavirus strains."

VIEWPOINT

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While first-generation COVID-19 vaccines were highly successful, waning immunity and the rapid evolution of the virus mean that new approaches are needed. In this Viewpoint, we describe several promising strategies with the potential to overcome the limitations of current vaccines.

COVID-19 REMAINS A MAJOR PUBLIC HEALTH CONCERN

The COVID-19 pandemic has created one of the largest global health crises in nearly a century. As of today, the number of confirmed cases has reached over 770 million and the disease has caused nearly 7 million deaths. As grim as these numbers seem, it would have been far worse without the rapid development and implementation of the first generation of COVID-19 vaccines, based primarily on viral vector and modified mRNA technologies. It has been estimated that tens of millions of lives were saved by these vaccines. However, waning immunity in the population has fueled the emergence of heavily spike-mutated and highly contagious SARS-CoV-2 variants and sub-variants that escaped immunity induced by the current clinically proven spike-alone-based vaccines, disrupted the effectiveness of the COVID-19 vaccine booster paradigm, and outpaced the development of variant-adapted spike-alone vaccines. Since early 2020, over 20 variants of concern have emerged and contributed to repetitive surges in morbidity and mortality.

Consequently, COVID-19 remains a major threat to human health, with rates of hospitalizations and deaths rising markedly in the past few months. COVID-19 now accounts for over 3% of all deaths in the US and recently exceeded 6,000 deaths every month [1]. While it is difficult to assess true infection rates, since proactive diagnostics and testing have declined and positive home test cases are not reported to authorities, the amount of the virus in wastewater is the only accurate reflection of the amount of virus being circulated in the human population. Recently, this number reached the second-highest level ever recorded [2]. The rate of emergence of new heavily spike-mutated virus variants, such as the recent JN-1, has accelerated. Of particular concern is the dramatically higher rate of change in the virus that facilitates escape from immunity conferred by the current spike-alone-based vaccines [3]. In addition, COVID fatigue and complacency in the general population, due in part to decreasing confidence in the effectiveness of the currently available vaccines, has led to low rates of uptake of the updated vaccines and is compounding the problem. It may be only a matter of time before we return to a much more widespread and severe COVID-19.

This bleak outlook of a prolonged COVID-19 pandemic emphasizes the urgent need for developing a next-generation broad-spectrum pan-coronavirus vaccine capable of conferring strong cross-strain protective immunity that would prevent immune evasion and breakthrough infection. Importantly, an effective vaccine that obviates the need for frequent updates and boosting could restore confidence and increase uptake, thereby providing greater individual protection and a population benefit that could break the transmission cycle.

TOWARD BROAD-SPECTRUM COVID-19 VACCINES

Current COVID-19 vaccines, except for whole inactivated virus vaccines, focus immune responses solely on the surface spike glycoprotein and confer protection mainly via neutralizing antibodies. This approach has been shown to work well when there is a good match between the spike protein in the vaccine and the circulating virus strain, as was the case early during the pandemic. But, unfortunately, this breaks down when there is a mismatch, such as has been the case since the appearance of viral variants. Furthermore, because the spike protein gene is not well conserved across the coronavirus family, the current spike-based vaccines are strain-specific.

Fortunately, several promising strategies have the potential to overcome these limitations.

First, broadly cross-reactive antibodies that can neutralize diverse coronavirus variants and strains have been identified from human samples, similar to those observed in people with HIV. Thus, in principle, it may be possible to elicit such antibodies with a vaccine. Approaches being undertaken to achieve this are utilizing novel antigen design strategies including:

- Mosaic antigen delivery where multiple spike antigens or receptor-binding domains derived from them are presented to the immune system in the context of nanoparticles or virus-like particles [4];
- Identification of naturally occurring consensus sequences presented as a combination of conserved epitopes [5]; and
- Computationally derived cross-reactive sequences identified from large amounts of sequence data using bioinformatics and machine learning approaches [6].

While more cross-reactive antibodies will be an improvement over the relatively narrow immunity induced by the current spike-based vaccines, by themselves such antibodies are unlikely to confer broad protection across the coronavirus family due to the diversity of spike gene sequences and the susceptibility to immune evasion.

Second, the function of T cell responses in protection against COVID-19 is becoming clear. Animal models have demonstrated the protective effect of antigen-specific CD4 and CD8 T cells against live virus challenge and evidence for the important role T cells play in humans is growing [7]. For example, we have demonstrated that preexisting cross-reactive $CD4^+$ and $CD8^+$ T cells directed against conserved coronavirus antigens correlated with good outcomes in COVID-19 patients, suggesting that vaccines capable of inducing such T cell responses could confer cross-protective immunity in humans [8]. Unlike antibodies, which can prevent virus infection, T cells can result in abortive infections by facilitating clearance of virally infected cells and preventing or minimizing disease. Given that these antigens have undergone far fewer mutations than the spike protein throughout coronavirus evolution, vaccines targeting these conserved antigens have the potential to provide a superior breadth of protection than the current spike-only vaccines. A rational strategy is to build on the demonstrated success of antibody-inducing vaccines by the inclusion of non-spike antigens to provide the added benefit of T cell responses targeting conserved epitopes.

Finally, we have not yet taken advantage of an important part of the immune system that is particularly relevant for protection against respiratory pathogens, namely mucosal immunity. Since most viruses, including coronaviruses, enter through mucosal surfaces, the presence of antigen-specific tissue-resident effector and memory lymphocytes could provide a key first line of defense. In addition, because most viruses are also shed via the mucosal route, active local immunity could reduce the levels of virus transmission. The main challenge for the development of successful mucosal vaccines has been inefficient delivery, usually requiring a live organism or viral vector. However, progress is being made in overcoming this limitation with improved non-viral delivery systems for nucleic acid vaccines and recombinant subunit proteins with adjuvant [9]. If successful, this approach would be complementary or synergistic with those targeting broadly neutralizing antibodies against spike and T cell responses against conserved antigens of the virus.

PROSPECTS

In summary, several exciting approaches to designing next-generation COVID-19 vaccines are being pursued, which have the potential to confer broad and durable protection across the spectrum of coronavirus strains. From a technical perspective, based

on our increasing insights into the virology and immunology of coronaviruses, this seems achievable. From a practical perspective, however, for these innovations to make a meaningful difference in the ongoing endemic and prevention of future outbreaks, it will be critical to ensure acceptance of these new vaccines by the general population and sustainable local manufacturing to enable global equitable access. If not, the virus will continue to circulate, evolve, and cause unnecessary morbidity and mortality.

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BIOGRAPHY

JEFFREY B ULMER spent more than 30 years in vaccines R&D at Merck Research Laboratories, Chiron Corporation, Novartis, and GlaxoSmithKline. His most recent leadership positions included Global Head, External R&D; Head, Preclinical R&D; and Program Head, Technical R&D. His scientific focus has been vaccine technology platforms, including DNA and mRNA vaccines, viral vectors, and adjuvants. He received his PhD in Biochemistry from McGill University, and completed his postdoctoral training in the laboratory of Nobel laureate Dr George Palade in the Department of Cell Biology at Yale University School of Medicine. He has published over 210 scientific articles, is an inventor on 11 patents, and is a Fellow of the International Society for Vaccines where he serves as Treasurer. He is currently President, TechImmune LLC (Newport Beach, California).

LBACHIR BENMOHAMED spent over 20 years studying infection and immunity to viruses, including recent SARS-CoVs at Gavin Herbert Eye Institute, School of Medicine, UC Irvine,

CA, USA. His scientific research focus has been studying viral infections, immunity, and immune evasion, with a focus on vaccine development, including mRNA-based vaccines, adenovirus, and adenovirus-associated vector-based vaccines. BenMohamed received his PhD. in Immunology jointly from Université Paris VII—Denis Diderot, Paris, France, and Pasteur Institute. He then completed his postdoctoral training at Pasteur Institute, Paris, France, and Beckman Research Institute, City of Hope Medical Center, Duarte, CA, USA. He later joined the University of California Irvine (UC Irvine) as a faculty back in 2001, where he founded and served as the Director of the Laboratory of Cellular and Molecular Immunology. He has published over 120 scientific articles as a leading and corresponding author, and is an inventor on 6 patents. BenMohamed was awarded many NIH grants to study infection and immunity, and to develop sub-unit vaccines for herpes simplex viruses and Coronaviruses. In 2020–2021, he discovered the universal coronavirus vaccine and is currently awarded multi-million NIH grants to develop a such vaccine. His lab remains one of the most funded research labs at the School of Medicine, UC Irvine. His most recent leadership positions included a professor of Immunology, at Gavin Herbert Eye Institute, School of Medicine, UC Irvine, Vice-President for Research, TechImmune LLC, Newport Beach, CA, USA.

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