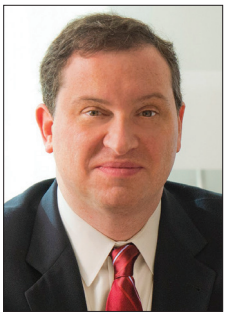
COVID-19 Vaccine Development



My letter in the February 2022 issue of *Clinical Advances in Hematology & Oncology* called for Dr Anthony Fauci to address inherent deficiencies in our national approach to dealing with COVID-19 and any future pandemics. The first issue my letter raised was the need for improved education of the public, encouraging Americans to participate in protecting the health of their fellow citizens (although I recognize that my suggestion to increase the dissemination of accurate information will likely have little effect in our currently politicized environment). The second issue that my letter raised was the need to create processes that will expedite the development of variant-specific vaccine boosters. As it turned out, shortly after I submitted my letter, an essay by Dr Fauci and his colleagues appeared in the January 27 issue of the *New England Journal of Medicine* (Morens DM. *N Engl J Med*. 2022;386[4]297-299), in which the authors discussed the need for a universal coronavirus vaccine, given the history of coronavirus pandemics (SARS, MERS, and COVID-19) and the likelihood of more to come.

The essay focuses on coronaviruses, which not only have proved to be sources of pandemics but also possess characteristics that make them likely culprits in future pandemics. These characteristics include a global enzootic reservoir, pre-adaptation to human infection by binding to angiotensin-converting enzyme 2 receptors, the ability to mutate rapidly and evolve genetically because of the low-level fidelity of their RNA polymerase, and a high degree of contagiousness. The authors suggest that the keys to successful management are to fully characterize the coronavirus "ecosystem" in order to identify species that have not yet jumped to humans but might do so in the future, and to identify antigen targets for developing a universal coronavirus vaccine.

Although I am not an expert in vaccine development, I am wondering if a better approach can be found. The greatest challenge is the need for timeliness. COVID-19 was first reported internationally in December 2019, and the Pfizer-BioNTech and Moderna vaccines both received Emergency Use Authorization in December 2020. This one-year time course is a true tour de force of modern medicine. With the lessons and skills learned, we are likely to be able to replicate these results in the future as long as the key antigen to target is identified correctly and expeditiously. The problem is that COVID-19 spread around the world, causing 1.6 million deaths during that first year alone, according to the World Health Organization, decimating economies and depressing living standards. In the 15 months since the approval of these vaccines in the United States, more than 4 million additional lives have been lost. How do we prevent the next pandemic? More importantly, how do we protect against the next COVID-19 subvariant?

Vaccines will always be more advantageous than therapeutic monoclonal antibodies. Vaccines, which are administered before the infection occurs, allow the immune system to start fighting the infection immediately, when the infectious burden is minimal. Additionally, with epitope spreading, the immune system will generate a broader array of antibodies that will target not just the initial antigen, but other similar ones as well. As a result, vaccines produce antibodies directed against similar—but not exact—versions of the target antigens. In contrast, therapeutic monoclonal antibodies are highly specific, so much so that two formulations directed against COVID-19 have already been rendered obsolete by COVID-19 mutations—casirivimab and imdevimab (REGEN-COV) from Regeneron and bamlanivimab and etesevimab from Eli Lilly.

The problem with vaccines is that time is necessary to develop them and obtain approval. The impact of timeliness will be seen in the relevance of vaccine to the circulating variant. Because of the technological hurdles that must be overcome to design, approve, and produce a vaccine, can we ever be truly successful at preventing a pandemic? Is there any precedent for manufacturing vaccines ahead of time and approving them within a system that is less laborious and deliberate than the one we currently have? There actually is an example, one that is repeated every single year—the flu vaccine. Each year, different antigens are included in the flu vaccine and delivered to the market in time for the season. Why can't the same be done for vaccinations against COVID-19 and its variants? As it turns out, RNA vaccines are extraordinarily well suited to this type of process. Each vaccine would only have to differ from each other only by several RNA bases.

We will have to ask ourselves to be comfortable skipping the proof of efficacy, which we already do for the flu vaccine. We will also have to be comfortable with the potential for adverse events related to the choice of the antigen target, but we also do this with the flu vaccine. The 1918 flu pandemic killed more than 50 million people. Let's prevent COVID-19 from doing the same.

Sincerely,

Richard R. Furman, MD