EDITORIAL

The story behind COVID-19 vaccines

Amid the staggering amount of suffering and death during this historic pandemic of COVID-19, a remarkable success story stands out. The development of several highly efficacious vaccines against a previously unknown viral pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in less than 1 year from the identification of the virus is unprecedented in the history of vaccinology. A frequently asked question is how such an extraordinary accomplishment could have been realized in such a short time frame, when timelines for other vaccines are measured in years if not decades. In fact, concern about this truncated timeline has contributed in part to the hesitancy in accepting these vaccines. What is not fully appreciated is that the starting point of the timeline for SARS-CoV-2 vaccines was not 10 January 2020, when the Chinese published the genetic sequence of the virus. Rather, it began decades earlier, out of the spotlight.

Two activities predate the successful COVID-19 vaccines: the utilization of highly adaptable vaccine platforms such as RNA (among others) and the adaptation of structural biology tools to design agents (immunogens) that powerfully stimulate the immune system. The RNA approach evolved over several years owing to the ingenuity of individual scientists, including Drew Weissman and Katalin Karikó, and the concentrated efforts of several biotech and pharmaceutical companies.

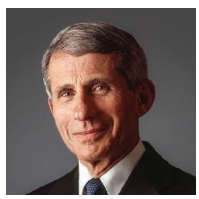
The discovery of an immunogen adaptable to the multiple platforms (messenger RNA and others) used for COVID-19 vaccines resulted from collaboration across different scientific subspecialities. At the Vaccine Research Center (VRC) of the U.S. National Institute of Allergy and Infectious Diseases, a group led by Peter Kwong had for several years used tools of structure-based vaccine design to determine the optimal structural conformation of a trimeric protein on the surface of the virus (the envelope protein) that allows HIV to bind to cells and ultimately trigger the production of antibodies that neutralize many HIV viral strains. Although this sophisticated approach has not yet led to a successful HIV vaccine, it caught the attention of another VRC investigator, Barney Graham, who was interested in generating a vaccine for respiratory syncytial virus (RSV). Graham joined Jason McLellan (of Kwong's team) to adapt a structure-based approach to an RSV vaccine. They identified the prefusion conformation of the viral spike protein as highly immunogenic and created mutations to stabilize that conformation for successful use as an immunogen. This was a huge step toward the creation of a successful RSV vaccine.

VRC researchers and colleagues then built on the RSV advances. Graham's team, including Kizzmekia Corbett, and collaborators in the laboratories of McLellan and Andrew Ward adopted this approach of mutational stabilization of prefusion proteins in their work on the spike protein of the coronaviruses that cause Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). So, when the genetic sequence of the SARS-CoV-2 became available, Graham's team lost no time in joining their long-time collaborators at Moderna to develop an RNA vaccine using a stabilized, prefusion spike protein as the immunogen. Pfizer and BioNTech, where Karikó was working, also used the RNA platform that she and Weissman had perfected and the immunogen designed by Graham to develop an RNA vaccine. Additional companies also used Graham's immunogen in other vaccine platforms that had been evolving for years, to make SARS-CoV-2 vaccines.

> "When the stories...of this pandemic are written, it is important that this history not be forgotten..."

SARS-CoV-2 vaccines based on the new immunogen rapidly moved to clinical trials. Several of these vaccines were tested in phase 3 efficacy trials at a time when the level of community spread of SARS-CoV-2 was extremely high, allowing vaccine efficacy endpoints of greater than 90% to be reached in a timely fashion. The speed and efficiency with which these highly efficacious vaccines were developed and their potential for saving millions of lives are due to an extraordinary multidisciplinary effort involving basic, preclinical, and clinical science that had been under way—out of the spotlight—for decades before the unfolding of the COVID-19 pandemic. When the stories and recounting of this pandemic are written, it is important that this history not be forgotten, as we are reminded once again of the societal value of a sustained and robust support of our scientific enterprise.

–Anthony S. Fauci



Anthony S. Fauci is director of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. afauci@niaid.nih.gov

PHOTO: NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

10.1126/science.abi8397

Science

The story behind COVID-19 vaccines

Anthony S. Fauci

Science **372** (6538), 109.
DOI: 10.1126/science.abi8397