In the Know

Update on COVID-19 Vaccine Development

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The hallmark of many public health programs that have the goal of disease eradication is the development of an effective vaccine. Since the outbreak of SARS-CoV-2 in the Hubei province of China in late 2019, there have been myriad research programs initiated with the express aim of developing an effective vaccine to protect large populations against COVID-19.

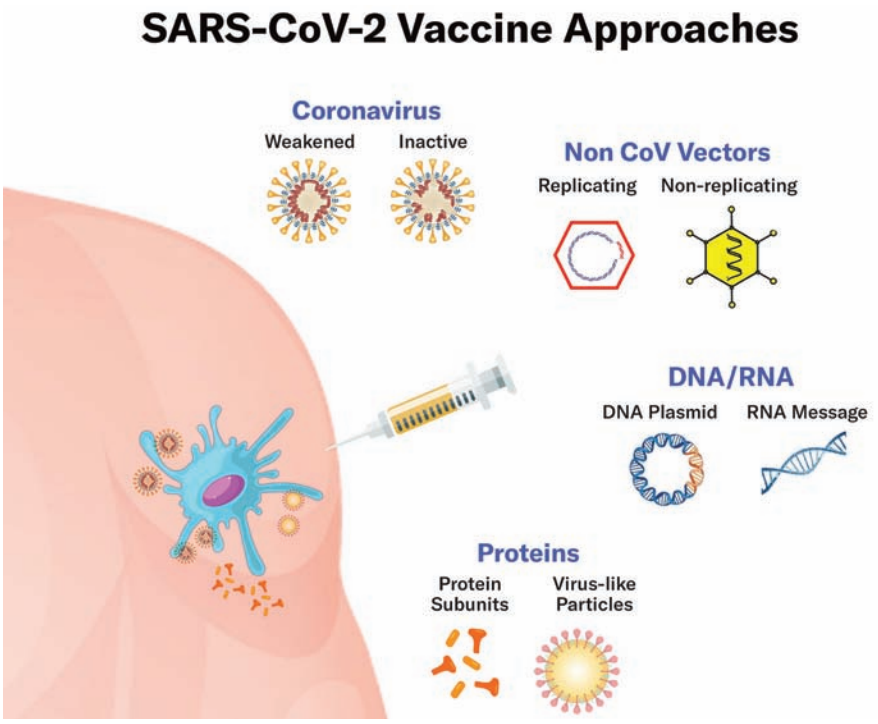
In an April 9, 2020 letter in *Nature Reviews Drug Discovery*, Tuang Le and colleagues from the Coalition for Epidemic Preparedness Innovations presented information on a number of ongoing vaccine-based clinical studies (*Nature Reviews Drug Discovery* 2020;19:305-6). As of April 8, 2020, the authors noted that there were 115 total vaccine candidates, 78 of which were confirmed as active, while the remaining 37 were classified as unconfirmed. Of the 78 vaccine candidates with documented activity, 56 (72%) were undergoing development by private or industrial entities; the remaining 22 (28%) are being advanced by academic, non-profit, or public sector (i.e., governmental) organizations.

Several different platforms are being evaluated for the development of SARS-CoV-2 vaccines. As illustrated in a *Nature* article, these vaccine candidates are loosely categorized into four basic types: virus-based, viral vector-based, protein-based, and nucleic acid-based (*Nature* 2020;580:576-7). Some programs have advanced to human-based phase 1 clinical studies.

Virus vaccines

A number of vaccines are derived from the infectious viruses themselves. These are divided into two main types: weakened (also referred to as attenuated) and inactivated. Weakened virus vaccines employ "live" viruses that have been weakened by passage through a foreign host (often another animal or an embryonated egg). The main advantage to using this type of vaccine is that the immune response generated tends to be quite vigorous, engaging all phases of the immune system. Some disadvantages include the potential risk to the immunocompromised for severe complications, and in rare circumstances, mutations may result in virulence reemergence.

The other main type of virus-based vaccine is termed inactivated, meaning the viruses or viral fragments generating immunity are no longer transmissible. Inactivated virus vaccines are further split into subtypes, based on their method of inactivation. Whole virus vaccines are inactivated using thermal or perhaps chemical methods; split virus vaccines are produced by detergent-based membrane disruption; subunit vaccines are produced by isolation of the best immune response-inducing antigens. The response to this type of vaccine is usually not as robust as that obtained with an attenuated vaccine, often requiring the use of an adjuvant and more frequent boosters.



SARS-CoV-2 vaccine approaches. The vaccine presents the spike protein to the dendritic cells, which trigger the adaptive immune response to SARS-CoV-2. The spike protein can be expressed on the surface of a weakened or inactive coronavirus, delivered as RNA by a non-coronavirus viral vector and manufactured in host cells, delivered as either a DNA plasmid or an RNA message and manufactured in the host cells, or injected directly either as immunogenic protein subunits or attached to a particle that looks like a virus to the immune system but lacks genetic material. All of these approaches are being explored in an effort to develop an effective vaccine.

PiCoVacc (NCT04352608)

In a recent report from *Science*, researchers present preclinical data for and the pilot-scale production of the inactivated SARS-CoV-2 vaccine PiCoVacc (*Science* 10.1126/science.abc1932 (2020)). They noted effectiveness of the generated antibodies against 10 representative strains of SARS-CoV-2, hinting at possibly broad applicability of the vaccine. Inoculated macaques were partially or fully protected against challenge with SARS-CoV-2; importantly, there were no observations of antibody dependent enhancement (more on that phenomenon later).

Viral vector vaccines

In this approach to immunization, vaccines utilize a virus, typically a measles or an adenovirus vector, to produce viral proteins (in this instance, SARS-CoV-2 proteins) for immunization. There are approximately 25 different research groups exploring various viral vector approaches to vaccines for SARS-CoV-2. This vaccine class is divided into two distinct groups: replicating (viral replication occurs within cells) or non-replicating (replication can't occur because essential genes are deactivated). Replicating vaccines tend to have a more vigorous immune response and be safer; however, that response could be weakened by prior immunity to the viral vector. Although there are currently no approved non-replicating vaccines, the technology has been utilized for some time in gene therapy.

Ad5-nCoV (NCT04313127)

Ad5-nCoV is a recombinant adenovirus type-5-vectored COVID-19 vaccine that expresses the spike (S) protein of SARS-CoV-2. In a recently *Lancet* article, researchers presented safety and immunogenicity data for Ad5-nCoV from a single-center phase 1 dose-escalation, non-randomized open-label clinical study (*Lancet* 2020; 395(10240):1845-54).

LV-SMENP DC (NCT04276896)

LV-SMENP-DC consists of dendritic cells (DCs) that have been modified via lentivirus (LV) vectors that express the SARS-CoV-2 minigene SMENP as well as genes affecting immune modulation. Cytotoxic T lymphocytes (CTLs) will be activated by the aforementioned DCs presenting SARS-CoV-2-specific antigens.

Protein vaccines

A number of vaccines utilize either the portions of viral proteins (termed subunits) or the empty protein shells (referred to as virus-like particles [VLPs]) to elicit an immune response in the inoculated. There are more than 20 different research teams employing the protein subunit approach for SARS-CoV-2 vaccine candidates. Most of these focus on the spike (or S) protein, or, in particular, a fairly conserved portion of that protein called the receptor binding domain that facilitates entry into host cells via surface-bound ACE2 receptors. This type of vaccine does not produce as vigorous an immune response and may require an adjuvant or the use of additional boosters.

VLP vaccine candidates tend to elicit strong immune responses and, in addition, there is no risk for infection, as viral genetic materials are absent; however, manufacturing for this type of vaccine can be somewhat problematic. Five teams are evaluating VLP approaches for SARS-CoV-2 vaccines.

Nucleic acid vaccines

Approximately 20 research teams are in the process of developing vaccines based

Continued on page 18

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In the Know

Continued from page 17

on the delivery of nucleic acids (DNA or RNA) encoding whole or partial SARS-CoV-2 protein sequences. Entry of the nucleic acids into cells across the cell membrane can be facilitated by the use of electroporation (application of an electric charge) or encapsulation of the genetic materials in lipid-based nanoparticles.

mRNA-1273 (NCT04283461)

The vaccine candidate mRNA-1273 is a novel lipid nanoparticle-covered messenger RNA (mRNA)-based vaccine that encodes for the full-length stabilized spike protein of SARS-CoV-2. The phase I study, which is evaluating the safety, immunogenicity, and reactogenicity of mRNA-1273, is being conducted at sites in Atlanta (Emory University), Seattle (Kaiser Permanente), and Bethesda (NIAID/NIH).

INO-4800 (NCT04336410)

INO-4800 is a DNA-based construct that targets the spike (S) protein of SARS-CoV-2. In a *Nature Communications* (https://doi.org/10.1038/s41467-020-16505-0) article, scientists reported results from preclinical *in vitro* and *in vivo* studies of INO-4800. As a testament to the rapidity of development for this type of vaccine, once the nucleic acid sequence SARS-CoV-2 had been determined, within three hours, the design for INO-4800 was complete. *In vivo* studies showed that animals treated with INO-4800 produced measurable antigen-specific T cell responses, functional SARS-CoV-2-neutralizing antibodies, and blocked binding of the viral S protein to the ACE2 receptor.

Antibody dependent enhancement (ADE)

One phenomenon that has been encountered in SARS and other vaccine-based studies (e.g., dengue virus) is antibody dependent enhancement (ADE), a condition whereby non-neutralizing antibodies can bind to the virus and thus facilitate its entry into a host cell, producing disease enhancement via macrophage activation and the release of inflammatory cytokines. In a recent *Nature Reviews Immunology* comment, researchers from Yale University present data from previous studies for this potentially important phenomenon (*Nature Reviews Immunology* April 21, 2020).

Prior studies have shown that ADE, when encountered in SARS-CoV infection, is caused by engagement of the Fc receptors (FcRs) present on the surface of numerous immune system cells (*J Virol* 2011; 85:10582–97). Consequently, the *in vivo* presence of non-neutralizing SARS-CoV-specific antibodies may permit viral entry into cells expressing FcRs in a mechanistically distinct process that is independent of ACE2 expression.

One particularly interesting study showed that mice inoculated with vaccines based on the SARS-CoV S and nucleocapsid (N) proteins had differing outcomes (*J Immunol* 2008;181:6337–48). Both vaccines elicited the respective immune responses in vaccinated mice to a similar degree; however, re-challenge of the N-protein vaccinated mice increased lung pathology with elevated pro-inflammatory cytokine secretion. Consequently, the authors from Yale speculate that antibodies targeting different epitopes on the S protein or other SARS-CoV-2-based proteins could also vary in the degree to which they induce ADE or the desired neutralization. ■

Table 1: Anti-SARS-CoV-2 Vaccine Candidates

Vaccine Candidate	Vaccine Description	NCT Registry	Clinical Trial Phase	Development Organization
PiCoVacc	Inactivated virus	NCT04352608	Phase 1	Sinovac Biotech
CDX-005	Live attenuated virus		Preclinical	Codagenix/Serum Institute of India
Ad5-nCoV	Adenovirus type 5 vector	NCT04313127	Phase 1	CanSino Biologics
LV-SMENP-DC	Lentiviral vector-modified dendritic cells/cytotoxic T lymphocytes	NCT04276896	Phase 1	Shenzhen, Geno- Immune, Medical Institute
AZD1222 (formerly ChAdOx1 nCoV-19)	Non-replicating attenuated chimpanzee adenovirus vector	NCT04324606	Phase 2	AstraZeneca/Oxford University
Ad26.COV2-S, recombinant	Non-replicating adenovirus vector		Phase 1/2a	Johnson & Johnson
NVXCoV2373	Prefusion protein virus with Matrix M® adjuvant		Phase1/2 (1-Australia; 2-US)	Novavax
mRNA-1273	Lipid nanoparticle-encapsulated mRNA	NCT04283461	Phase 1	Moderna
BNT162	mRNA lipid nanoparticle formulation	NCT04380701	Phase 1/2	Pfizer/BioNTech
INO-4800	Nucleic acid (DNA)	NCT04336410	Phase 1	Inovio Pharmaceuticals

Your Input, Please

Anesthesiology is one of the most rewarding professions in medicine. It can also be one of the most stressful. For many, unfortunately, the COVID-19 pandemic has introduced a variety of new stressors.

However, anesthesiologists have proven to be resilient and resourceful, as evidenced most recently by how the profession has responded, for instance, to ventilator shortages and ICU staffing needs in COVID hot spots.

In this unprecedented time, we are conducting a brief survey that seeks to identify the primary concerns in your practice. We will use the data collected for future *ASA Monitor* content that we hope will help drive solutions.

We invite you to fill out the brief survey at **asamonitor.pub/survey**. Your input is very much appreciated.