BACKGROUND

Since its emergence in December 2019 in Wuhan, China, the SARS-CoV-2 virus has caused more than 1.3 million cases and nearly 75,000 deaths globally as of April 06, 2020.1 Currently, no vaccine or proven treatment exists for this virus or any coronavirus. The rapid spread and unprecedented dramatic rise of COVID-19 deaths and cases has led many research groups worldwide to explore potential vaccine candidates against SARS-CoV-2.2-4 The World Health Organization (WHO) has worked to develop a Research and Development Blueprint that outlines key areas for research and innovation to address gaps in controlling COVID-19.5 Additionally, as of April 4, 2020, WHO has identified more than 60 vaccine candidates currently being investigated against the SARS-CoV-2 virus across a range of platforms, including nucleic acid, live attenuated, protein subunit, and viral vector (Table 1).6 Of these, 2 are undergoing phase 1 clinical trials, while the remaining candidates are preclinical.

Table 1: Overview of Vaccine Candidates Currently Being Investigated for SARS-CoV-2 Infection2

<table>
<thead>
<tr>
<th>Platform</th>
<th>Number of Vaccine Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>5</td>
</tr>
<tr>
<td>RNA</td>
<td>9</td>
</tr>
<tr>
<td>Inactivated</td>
<td>3</td>
</tr>
<tr>
<td>Live attenuated</td>
<td>2</td>
</tr>
<tr>
<td>Nonreplicating viral vector</td>
<td>8</td>
</tr>
<tr>
<td>Protein subunit</td>
<td>23</td>
</tr>
<tr>
<td>Replicating viral vector</td>
<td>5</td>
</tr>
<tr>
<td>Virus-like particle</td>
<td>2</td>
</tr>
<tr>
<td>Unknown or other</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>63</strong></td>
</tr>
</tbody>
</table>

Each vaccine platform has its own set of advantages and disadvantages. For example, nucleic acid vaccines can be easier to design, but DNA vaccines may not be as immunogenic, and mRNA vaccines may be more unstable.4 Additionally, viral vector vaccines and subunit vaccines generally exhibit higher safety profiles and are more immunogenic, but viral vector vaccines may have reduced efficacy due to preexisting immunity to the vector, and subunit vaccines may be too expensive.4

KEY EXAMPLES OF CANDIDATE VACCINES

Eight vaccine candidates are receiving funding from the Coalition for Epidemic Preparedness Innovations (CEPI).3 CEPI is a philanthropic alliance among public, private, and nonprofit civil organizations that has multiple functions for supporting vaccine development, including funding research into the development and use of platform technologies and investigational vaccines against novel pathogens.4 Given the abundance of vaccines under development, this fact sheet will focus on the vaccine candidates for which research is currently being funded at least in part by CEPI, as well as candidates that are undergoing clinical trials. Vaccine candidates are listed by developer below.

Phase I Clinical Trials

- **CanSino Biological, Inc., and Beijing Institute of Biotechnology**
  
  CanSino Biological, Inc., a China-based company, is collaborating with the Beijing Institute of Biotechnology to develop a nonreplicating viral vector vaccine2 and has recently begun phase I clinical trials, with more than 100 participants aged 18 to 60 years old, in a hospital located in Wuhan, China.7-8 The vaccine candidate uses a nonreplicating adenovirus type 5 viral vector containing the gene encoding the antigenic SARS-CoV-2 spike protein.7 The viral vector delivers the spike protein gene into human cells, leading to production of the protein that is designed to trigger an immune response.8 CanSino, Inc., has successfully developed an Ebola vaccine using the same viral vector approach, which Chinese regulators approved in 2017.9,10 Despite this past approval for other candidates, possible limitations exist. The type of adenovirus used in this candidate is a virus associated with the common cold, and, consequently, it is possible that people may already have been exposed to the viral vector, which could hinder human cell uptake of the viral vector or even lead to possible safety concerns if immunization triggers an inappropriate immune response.10

- **Moderna, Inc./National Institute of Allergy and Infectious Diseases (NIAID)**

  US company Moderna, Inc., in collaboration with NIAID, has developed an mRNA lipid-nanoparticle–based vaccine.7 Clinical trials for the vaccine candidate began in early March, and it is planned that approximately 45 individuals will be enrolled over the course of 6 weeks for an open-label trial based in Seattle, Washington.11 The sequence for the vaccine candidate, called mRNA-1273, was first identified in mid-January and contains genetic code for the SARS-CoV-2 spike protein such that when administered, the mRNA sequence prompts cells to start producing the antigenic SARS-CoV-2 spike protein, thus initiating an immune response. The advantages of using mRNA vaccines, compared to more traditional attenuated or inactivated formulations, is that these vaccines do not contain infectious material and are easier to develop and manufacture.12 Despite these possible advantages, mRNA vaccine candidates, including those in development by Moderna, have not made it past phase III clinical trials.10
Fact Sheet: Vaccines in Development to Target COVID-19 Disease

- University of Oxford
The Jenner Institute, based at the University of Oxford, UK, is working to leverage their ChAdOx1 nonreplicating simian adenoviral vaccine vector against SARS-CoV-2. The institute has recently begun recruiting for a phase 1 clinical trial, with the goal of recruiting approximately 500 people. CEPI has also previously funded this group to develop vaccines against a range of other emerging diseases, including MERS. ChAdOx1 platform consists of a transgenic nonreplicating virus vector that would express and lead to host cell expressing and displaying the antigenic coronavirus spike protein upon immunization, thus prompting an immune response. An advantage of viral vector vaccines is their ability to produce humoral and T-cell-mediated responses.

- Inovio Pharmaceuticals, Inc.
Inovio Pharmaceuticals, a US-based pharmaceutical company, has developed a DNA vaccine candidate called INO-4800 that can be delivered to cells intradermally. Administration of this vaccine candidate requires the use of an electroporation device called CELLECTRA, which uses a small electrical current to make the human cells more permeable and thus enables proper entry and incorporation of the DNA molecule into the cell. The company announced on April 6, 2020, that the US FDA had approved its Investigational New Drug application and that it planned to recruit its first clinical trial participants as early as that day. The trial will enroll up to 40 healthy adults in Philadelphia, PA, and Kansas City, MO. The company recently received additional support from the Bill and Melinda Gates Foundation to accelerate the development and production of the electroporation device. Using an approach similar to the development of other CEPI-funded Lassa and MERS experimental vaccines by Inovio, this candidate consists of plasmid DNA that, upon administration, prompts human cells to produce the antigenic SARS-CoV-2 spike protein. While DNA vaccines carry certain advantages, including optimal development speeds and thermostability, past trials have shown that producing sufficient immunogenicity can be a challenge. Additionally, administration can often require larger volumes of DNA vaccine compared to more traditional vaccine types, and it requires the use of an electroporation device, which can be inconvenient. The company has announced that 1 million doses are expected to be produced by the end of the year.

Preclinical Candidates

- CureVac, Inc.
CureVac AG, a pharmaceutical company headquartered in Germany, focuses on developing mRNA-based vaccines and therapies and received funding from CEPI in 2019 to develop a mobile unit for rapid mRNA production for lipid-nanoparticle formulated mRNA vaccine candidates, potentially at the site of an outbreak. This platform could be used against long-known pathogens, such as yellow fever and rabies viruses, or against novel pathogens, such as SARS-CoV-2. Vaccines relying on this platform contain mRNA that, on being injected into the vaccine recipient, initiates cells to produce protein antigen from the pathogen of interest, thus stimulating an immune response. The advantages of using mRNA vaccines, compared to more traditional attenuated or inactivated formulations, is that these vaccines do not contain infectious material and are easier to develop and manufacture. News of CureVac executives being approached by members of the Trump administration and the European Union to purchase vaccine brings to light issues of ensuring equitable supply of vaccine once it becomes potentially available for clinical use.

- Novavax, Inc.
The US-based company Novavax has received funding from CEPI to investigate and fund a phase I trial for a recombinant protein subunit nanoparticle vaccine. The vaccine consists of a recombinant SARS-CoV-2 spike protein and the company’s Matrix-M saponin-based adjuvant. This adjuvant is a mixture of saponin and lipid molecules and induces the migration of antigen-presenting cells to the injection site on immunization. Clinical trials are expected to begin in late spring of 2020. Like several of the vaccine developers listed above, Novavax, Inc., has also conducted research to develop vaccines against MERS and SARS.

- University of Queensland and Glaxo Smith Kline (GSK)
The University of Queensland is partnering with GSK to develop a subunit vaccine consisting of a SARS-CoV-2 spike protein stabilized with a protein “molecular clamp.” This approach uses an antigenic protein that is shaped in such a way that it “clamps” onto virus protein and helps trigger an immune response. GSK and Dynavax are working on developing adjuvants to incorporate into the vaccine candidate as well. GSK has also announced a separate collaboration with Clover Biopharmaceuticals, based in China, to produce a subunit vaccine with its pandemic adjuvant system and an S-trimer protein that resembles the SARS-CoV-2 spike protein.

- University of Hong Kong
On March 18, 2020, CEPI announced it was providing funding to the State Key laboratory for Emerging Infectious Diseases of the University of Hong Kong to pursue preclinical testing of their vaccine. The vaccine candidate consists of a live attenuated influenza virus vaccine strain that can express an antigenic element of the SARS-CoV receptor binding domain on its surface, to induce immunogenicity against the SARS-CoV-2 virus. Notably, the vaccine can be administered as a nasal spray. A similar approach has been used by the research group to develop MERS candidate vaccines that have been undergoing proof of concept studies in animal models.

- Institut Pasteur
On March 19, 2020, CEPI announced its most recent support of a consortium led by the Institut Pasteur in Paris and including the University of Pittsburgh and Themis. The funding will support initial preclinical testing and manufacturing, as well as preparatory work for phase I studies. The vaccine candidate consists of a replicating measles viral vector. The institute has previously designed SARS vaccine candidates using the human measles vector, and collaborator Themis has developed potential phase III Chikungunya and phase I Lassa fever candidates using CEPI funding.

Considerations for Vaccines to Address COVID-19 Pandemic
The rate at which potential vaccine candidates against SARS-CoV-2 have been identified is unprecedented, with some
candidates starting phase I clinical trials in less than 2 months, showing the promise that platform technologies bring. Despite this initial progress, substantial technical and logistical hurdles may lie ahead. No SARS or MERS vaccine candidates have successfully completed clinical trials. These vaccines have proven to be challenging to develop due to technical issues, including possible enhancement of respiratory disease in vaccine recipients. There have also been financial constraints, as large-scale epidemics of these pathogens have ended or been reduced, thereby affecting funding prioritization.35,36

While the rate of identifying potential vaccine candidates is more rapid than ever before, further experiments and clinical trials to ensure safety and efficacy of vaccines will take at least a year to multiple years. Once a vaccine candidate is approved for clinical use, rapid wide-scale manufacturing will be a challenge. Furthermore, equitable allocation of a high-demand vaccine product across the world will be incredibly challenging, as currently there is a lack of established systems to adjudicate allocation decision making for novel emerging pathogens.35 Future efforts should focus on supporting manufacturing and innovative approaches to vaccination.

REFERENCES


