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Progress and Concept for COVID-19 Vaccine Development

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The recent outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), previously known by the provisional name 2019 novel coronavirus (2019-nCoV), in the city of Wuhan in China's Hubei province in 2019–2020 has been causing significant numbers of mortality and morbility in humans with the coronavirus infection diseases (COVID-19) with fever, severe respiratory illness, and pneumonia.[1–3] Till April 8, 2020, there have been over 1 431 973 confirmed cases globally, leading to at least 82 085 deaths. These SARS-CoV-2 isolates belong to the *Betacoronavirus* genus of the Coronaviradae family which is an enveloped single-stranded RNA virus containing a 30 kb genome with 14 open reading frames including four major viral structure proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins.[4–7] The S gene sequences of SARS-CoV-2 isolates have a 93.1% nucleotide sequence identity to the *Rhinolophus affinis* bat coronavirus RaTG13, but only less than 75% nucleotide sequence identity to the severe acute respiratory syndrome coronavirus (SARS-CoV). The viral S sequences of SARS-CoV-2 compared to SARS-CoV have three additional short insertions in the N-terminal domain, and four out of five key residues changes in the receptor-binding motif of S protein receptor binding domain (RBD).[6,7] Although both SARS-CoV-2 and SARS-CoV share the same human cellular receptor-angiotensin converting enzyme II, SARS-CoV-2 appears to be more readily transmitted from human to human.[1,8,9]

The S protein is the major target for COVID-19 vaccine development, mainly based on the elicitation of virus neutralizing antibodies as the immune correlates to vaccine protection. The current status of COVID-19 vaccine development includes, i) three phase I vaccine candidates, ii) 11 preclinical vaccine candidates, and iii) 26 research-stage vaccine candidates (**Table** 1; [https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker?feed=Regulatory-Focus?utm_source=Facebook&utm_medium=social&utm_campaign=Regulatory-Focus]). Most of these vaccine candidates are based on the S antigen either as inactivated vaccines, subunit vaccines, viral vectored vaccines, and nucleic acid-based DNA or mRNA vaccines. Among these vaccine candidates, the Coalition for Epidemic Preparedness Innovations (CEPI) has provided funding to develop COVID-19 vaccines using the following platform technology: a) Curevac Inc. (mRNA), b) Inovio Pharmaceuticals Inc.

Table 1. The current status of COVID-19 vaccine development.

Company	Vaccine candidates	Status
Moderna	mRNA-1273	Phase I NCT04283461
CanSino Biologics	Ad5-nCoV	Phase I ChiCTR2000030906
Inovio	INO-4800 (DNA)	Phase I NCT04336410
Pfizer and BioNTech	BNT162 (mRNA)	Pre-clinical
Novavax	Recombinant nanoparticle vaccine	Pre-clinical
CureVac	mRNA-based vaccine	Pre-clinical
Generex	Ii-Key peptide vaccine	Pre-clinical
Vaxart	Oral recombinant vaccine	Pre-clinical
Imperial College London	Self-amplifying RNA vaccine	Pre-clinical
Medicago	Plant-based vaccine (VLP)	Pre-clinical
Takis Biotech	DNA-based vaccine	Pre-clinical
J&J and BARDA	AdVac and PER.C6 systems	Pre-clinical
Altimmune	Intranasal vaccine	Pre-clinical
University of Saskatchewan	Not revealed	Pre-clinical
Clover and GSK	S-Trimer	Research
Heat Biologics	gp96-based vaccine	Research
CSL and University of Queensland	Molecular clamp vaccine	Research
Sanofi	Not revealed	Research
iBio	Plant-based vaccine	Research
ExpreS2ion Biotechnologies	Not revealed	Research
EpiVax	Ii-Key peptide vaccine	Research
Codagenix	Live attenuated vaccine	Research
Zydus Cadila	DNA and/or live attenuated recombinant vaccine candidate	Research
Sinovac	Formalin-inactivated and alum-adjuvanted candidate vaccine	Research
Geovax and Bravovax	Modified Vaccinia Ankara virus like particles (MVA-VLP) vaccine	Research
University of Oxford	Chimpanzee adenovirus vaccine vector (ChAdOx1)	Research
Greffex	Adenovirus-based vector vaccine	Research
Walter Reed and USAMARIID	Not revealed	Research
MIGAL	Modified avian coronavirus vaccine	Research

(*Continued*)

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Table 1. Continued.

Company	Vaccine candidates	Status
Vaxil Bio	Protein subunit COVID-19 vaccine candidate	Research
AJVaccines	Not revealed	Research
Baylor	Re-purposed SARS vaccine; S1 or RBD protein vaccine	Research
Institut Pasteur	Not revealed	Research
Tonix Pharmaceuticals and Southern Research	Horsepox vaccine with percutaneous administration	Research
Fudan University, Shanghai Jiao Tong University, and RNACure Biopharma	mRNA-based vaccine	Research
Arcturus Therapeutics and Duke-NUS	Self-replicating RNA and nanoparticle non-viral delivery system	Research
University of Pittsburgh	Not revealed	Research
ImmunoPrecise	Not revealed	Research
Peter Doherty Institute for Infection and Immunity	Not revealed	Research
Tulane University	Not revealed	Research

(DNA), c) Moderna, Inc. (mRNA), d) University of Queensland (molecular clam), e) Novavax (nanoparticles), f) University of Oxford (adenovirus vector), g) University of Hong Kong (live-attenuated influenza virus), and h) Institute of Pasteur (measles vector) to accelerate the development of vaccines and enable equitable access to these vaccines for people during outbreaks [https://cepi.net/covid-19/].

To date, many previous studies of SARS-CoV, Middle East respiratory syndrome-related coronavirus (MERS-CoV), and other coronavirus vaccines revealed several safety concerns associated with the use of coronavirus S-based vaccines, including inflammatory and immunopathological effects such as pulmonary eosinophilic infiltration and antibody-dependent disease enhancement (ADE) following subsequent viral challenge of vaccinated animals.[10–21] The anti-S antibodies for ADE may facilitate uptake by macrophage expressing FcR, leading to macrophage stimulation and the production of proinflammatory cytokines (IL-6, IL-8, and MCP1) and loss of tissue-repaired cytokine (TGFβ).[22] Moreover, the Th2-associated immunopathology has been documented for the inactivated vaccines of respiratory syncytial virus after viral challenge[23–25] and the inactivated vaccines of MERS-CoV after virus challenge.[20] Thus, the safety and the potentially harmful responses in vaccines to develop ADE antibodies against any coronaviruses should be carefully assessed in human trials.[26] It has been proposed that the neutralizing epitope-rich S1 region, or the RBD region, instead of the entire full-length S protein as an alternative target for MERS-CoV vaccine development.[27] Whether the use of S1 or RBD antigen of SARS-CoV-2, or the selection of Th1-skewed adjuvants rather than alum adjuvant, can avoid the inflammatory, immunopathological, and ADE effects, requires further studies from animal models and human trials. These findings are particularly important for developing a safe and effective COVID-19 vaccine.

Suh-Chin Wu

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Conflict of Interest

The author declares no conflict of interest.

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