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PERSPECTIVE

mRNA Vaccines: Possible Tools to Combat SARS-CoV-2

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Coronaviruses are large, enveloped, positive-strand RNA viruses. Several coronaviruses are pathogenic in humans, including severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and this novel virus, SARS-CoV-2, which has caused the global pandemic currently. Genetic sequencing suggests that SARS-CoV-2 is related to SARS-CoV and its close relatives (Chen *et al*. 2020). There are four genera of coronavirus, including *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus* and *Deltacoronavirus*. Like other *Betacoronaviruses*, the genome of SARS-CoV-2 codes four major structural proteins, including the spike surface glycoprotein which is called S protein, small envelope protein, matrix protein, and nucleocapsid protein. S proteins are type I transmembrane proteins with a large ectodomain and a short endodomain. Coronavirus replication is initiated by the binding of S protein to the cell surface receptor(s). The S protein is composed of two functional subunits, S1 (bulb) for receptor binding and S2 (stalk) for membrane fusion. Specific interaction between S1 and receptor triggers a drastic conformational change in the S2 subunit, leading to the fusion between the virus envelope and the cellular membrane and release of the nucleocapsid into the cytoplasm. Receptor binding is the major determinant of host range and tissue tropism for a coronavirus (Cui *et al*. 2019). SARS-CoV-2 is able to use human angiotensin-converting enzyme 2 (ACE2) as an entry receptor in ACE2-expressing cells, indicating that ACE2 is likely the cell receptor of SARS-CoV-2 (Zhou *et al*. 2020). McLellan *et al*. showed biophysical and structural evidence that SARS-CoV-2 S protein binds ACE2 with higher affinity than SARS-CoV S protein (Wrapp *et al*. 2020).

To date, although some repurposed drugs showed inhibitory effect on SARS-CoV-2, no drugs have been licensed to be used in the treatment of SARS-CoV-2 infection or other coronavirus infections in humans, and no vaccines have been licensed to prevent these infections. Just days after Chinese scientists shared the genetic map of SARS-CoV-2, scientists around the world, along with a list of biotech and vaccine companies, promptly launched a race to pursue different types of vaccines to prevent infection with this novel virus. Up to the end of April 2020, at least 115 SARS-CoV-2 vaccine projects have been announced to be in development, including vectored vaccines, oral vaccines, subunit vaccines, inactivated vaccines, peptide-based vaccines, nucleotide-based vaccine, etc. Several SARS-CoV-2 vaccine candidates have recently been approved for clinical phase I or II development (Thanh Le *et al*. 2020).

Among these SARS-CoV-2 vaccine candidates, mRNA vaccines are quite remarkable. What is mRNA vaccine? Unlike traditional vaccines, an mRNA vaccine consists of an mRNA sequence encoding a disease-specific antigen. Once delivered into target cells, the antigen is expressed, processed, presented and recognized by the immune system, and a strong humoral and T cell immune response will be instigated. Compared to vaccine production of whole microbes, live attenuated and subunit vaccines, mRNA vaccines are believed to be faster and less expensive to produce, and they do not involve in any living stage of the pathogenic virus or bacteria. This manufacturing process makes mRNA vaccines a promising bioproduct and potentially fills the gap between the desperate demand for vaccines to control disease outbreaks and epidemics, with the potential to scale and standardize the vaccine manufacturing process. The process of mRNA vaccine development is illustrated in Fig. 1, exemplified by the mRNA vaccine coding the *S* gene of SARS-CoV-2. Currently, most of the components needed for mRNA vaccine

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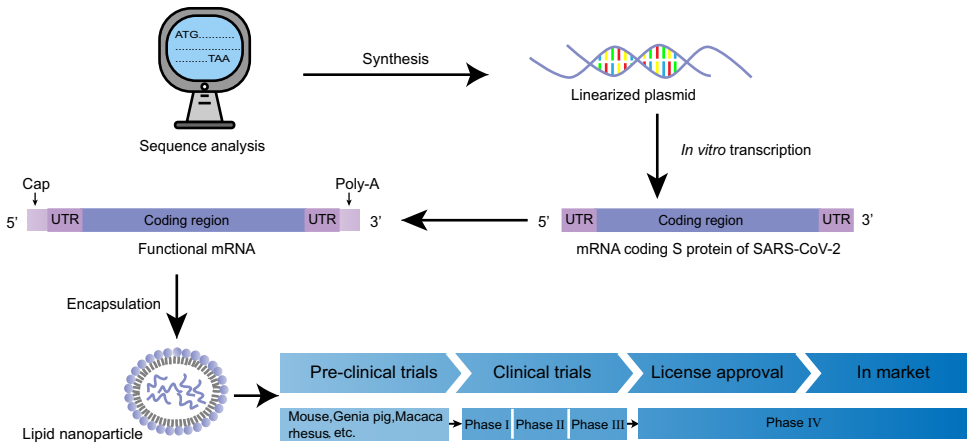

Fig. 1 The streamlined process of the creation of an mRNA vaccine coding the *S* gene of SARS-CoV-2, including the design, formulation, testing, and approval.

production are available at the Good Manufacturing Practices (GMP) grade to satisfy commercialization.

Two forms of mRNA vaccines have been developed, including conventional mRNA vaccines and self-amplifying mRNA (SAM) vaccines. Conventional mRNA encoding target antigen can be synthetically produced, including an open reading frame (ORF) for the target antigen and 5′ and 3′ untranslated regions (UTRs), through a cell-free enzymatic transcription reaction. The *in vitro* transcription reaction includes linearized plasmid DNA encoding the pathogen antigen as a template, recombinant RNA polymerase, and nucleoside triphosphates. A cap analog and a poly(A) tail are added sequentially to the transcriptional product following the reaction to form a functional mRNA. After injection, transient and low levels of antigen expression are driven (Zhang *et al*. 2019). SAM vaccines are derivatives of alphavirus RNA replication, with the structural protein sequences replaced with the antigen gene, generating multiple copies of the antigen-encoding mRNA and expressing high levels of the heterologous gene. Then, *in vitro* transcribed (IVT) mRNA is encapsulated in lipid nanoparticles and delivered into cells. Consequently, humoral and T cell immune responses are stimulated. The immune response mechanism instigated by mRNA remains to be elucidated. The dimension of the immune response is dependent on the quality of the IVT mRNA, delivery vehicle, and administration route.

In the last two decades, mRNA vaccines have been investigated extensively for infectious disease prevention and cancer immunotherapy. Several mRNA vaccines against infectious disease have showed a promising future, such as mRNA vaccines against influenza viruses, rabies virus, HIV, Ebola virus, and Zika virus (Demoulins *et al*. 2016; Maruggi *et al*. 2019). Although clinical trials of mRNA vaccines for infectious disease are still in their early stage, a plethora of publications have shown that mRNA-based vaccines are a promising novel platform that is highly flexible, scalable, inexpensive and cold-chain-free. The growing body of preclinical and clinical results demonstrates that prophylaxis and therapy with mRNA promises to be useful for the prevention of infectious disease and that mRNA vaccines are safe and tolerated in animal models and humans. Despite the great challenges in the creation of new processes to generate mRNA vaccines, such as delivery and translation efficiency, these processes hopefully will be streamlined to establish large-scale production. It is just a matter of time for mRNA vaccines to be used in humans and animals.

Several biopharmaceutical companies have announced promptly the establishment of mRNA vaccine projects for SARS-CoV-2 since its outbreak. On January 23, 2020, the Coalition for Epidemic Preparedness Innovations (CEPI) announced the initiation of three programs to develop vaccines against SARS-CoV-2. Moderna, an mRNA-based biotechnology company, announced that it has received funding from CEPI and would manufacture an mRNA vaccine against SARS-CoV-2 using their mRNA vaccine platform technology, and it has partnered with the National Institute of Allergy and Infectious Diseases (NIAID) to develop a vaccine for the Wuhan strain of coronavirus. The NIAID will conduct investigational new drug (IND)-enabling studies and a phase I clinical study in the U.S. In projects conducted by Moderna, approximately 1000 people have received different versions of mRNA vaccines so far in seven clinical trials designed to prevent illness from other respiratory viruses, including a strain of the flu, respiratory syncytial virus (RSV), and human metapneumovirus (HMPV). mRNA vaccine candidate against SARS-CoV-2 developed by Moderna is the first one entering phase I clinical trial (Moderna 2020).

In February 2019, CEPI agreed to provide up to $34 million in support of CureVac's technology development, which will provide a rapid supply of lipid-nanoparticle-formulated mRNA vaccine candidates that can target known pathogens and prepare for rapid response to new and previously unknown pathogens. The principle of

CureVac's proprietary technology is the use of mRNA as a genetic information carrier to instruct the human body to produce its own proteins capable of fighting a wide range of diseases. Additionally, the Federal Ministry of Education and Research has committed a total of 90 million Euros to support this work (Smith 2020).

Pharmaceutical and biotechnology companies in China have also stepped up to the development of vaccines of SARS-CoV-2. Four SARS-CoV-2 vaccines have been approved for phase I or II clinical trial in China at the end of April of 2020. Several biotechnology companies have announced the development of mRNA vaccines against this mated coronavirus. In early January 2020, Stermirna Therapeutics, cooperating with Shanghai East Hospital of Tongji University, proclaimed that no more than 40 days will be needed to produce vaccine samples based on the new generation of mRNA technology and some preliminary procedures. The samples would be sent for tests and be brought to clinics as soon as possible (Xinhua net 2020). On February 12, 2020, the Institute of Advanced Technology of Shenzhen announced that the first batch of mRNA vaccine against SARS-CoV-2 was being prepared under GMP standards. The mRNA matching the requirement for the clinical trial would be ready in April 2020 (SIAT 2020). On February 14, Zhuhai Lifanda Biotechnology announced that an antibody against antigen encoded by mRNA was detected in mouse serum at day 12 after the mice had been immunized. Data on rhesus macaques immunized with mRNA vaccine candidates would be obtained soon. The mRNA vaccine against SARS-CoV-2 would go into clinical testing within 2–3 months. A GMP factory would be put into use in April, 2020 (cnBeta 2020).

Like other coranaviruses, S protein of SARS-CoV-2 plays an essential role in binding to receptors on the host cell to initiate an infection and determines host tropism. It is also the major target of neutralizing antibodies and it may be the main antigen of development of SARS-CoV-2 vaccines by most related groups. According to the public information, S protein or receptor binding domain (RBD) sites are main antigens edcoded by SARS-CoV-2 vaccine candidates. However, due to the limited information and patent protection on the adaptation of antigens of SARS-CoV-2 vaccines in development, the antigen information of most SARS-CoV-2 vaccine candidates are unclear. The expected immune response, such as antibody or T cell mediated immune response, stimulated by these SARS-CoV-2 vaccines in development are not clear either. Thus accordingly, the protection against SARS-CoV-2 can not to be predicted.

During the development of SARS-CoV and MRES-CoV vaccines, some groups found that enhanced lung inflammation following homologous challenge in mice and nonhuman primates was mediated by S specific IgG (Liu *et al*. 2019; Wan *et al*. 2020). Antibody-dependent enhancement (ADE) was initially found to be induced by dengue vaccine (Katzelnick *et al*. 2017). ADE was also observed in other vaccines later, such as influenza vaccine (Winarski *et al*. 2019). ADE modulates the immune response and can elicit sustained inflammation, lymphopenia, and/or cytokine storm, one or all of which have been documented in severe cases and deaths. ADE also requires prior exposure to similar antigenic epitopes. Currently, immunologists are worrying that SARS-CoV-2 mRNA vaccines based on S protein maybe induce ADE, which will blur the adaptation in the prevention and control of SARS-CoV-2 pandemic. However, in a recent paper, Qin *et al*. reported inactivated SARS-CoV-2 vaccine was safe in nonhuman primate and has not induced ADE in macaques (Gao *et al*. 2020). The other obstacle to developing a successful SARS-CoV-2 mRNA vaccine is the abundant glycosylation sites on the S protein which facilitate the escaping of SARS-CoV-2 from neutralization by the S protein specific antibodies (Vankadari and Wilce 2020).

As a novel vaccine platform, mRNA vaccine technology is not mature to be used in immune prophylaxis and therapy. It still needs improvement and has uncertainty in the SARS-CoV-2 mRNA vaccine development. The mechanisms of immunity induction of mRNA vaccine *in vivo* are under elucidation. Published results showed mRNA vaccines stimulated potent immune response, but in human, the immune response is not strong enough with low dose of antibodies (Pardi *et al*. 2018b). The delivery tool and administration route determine the dimension of immune response by mRNA vaccine (Pardi *et al*. 2018a).

So far, there at least 14 SARS-CoV-2 mRNA vaccine projects had been announced globally (WHO, 27 May 2020). Regularly, the general stages of the development cycle of a vaccine include the exploratory stage, the preclinical stage, clinical development, regulatory review and approval, manufacturing, and quality control. The process of the creation, testing and production of a vaccine in mass quantities can take many years because the industry is highly regulated. For mRNA vaccines against SARS-CoV-2 infection, developers should speed up the process to make them available as soon as possible. However, until a safe, effective vaccine is commercial available, the best protection from infection with SARS-CoV-2 is to follow the suggestions of public health experts.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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