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In: Angewandte Chemie-International Edition 59(43): 18885-18897

**To refer to or to cite this work, please use the citation to the published version:**

Ye T., Zhong Z., Garcia-Sastre A., Schotsaert M., De Geest B. (2020) Current Status of COVID-19 (Pre)Clinical Vaccine Development

Angewandte Chemie-International Edition 59(43): 18885-18897

DOI: 10.1002/anie.202008319

## Current status of COVID-19 (pre)clinical vaccine development

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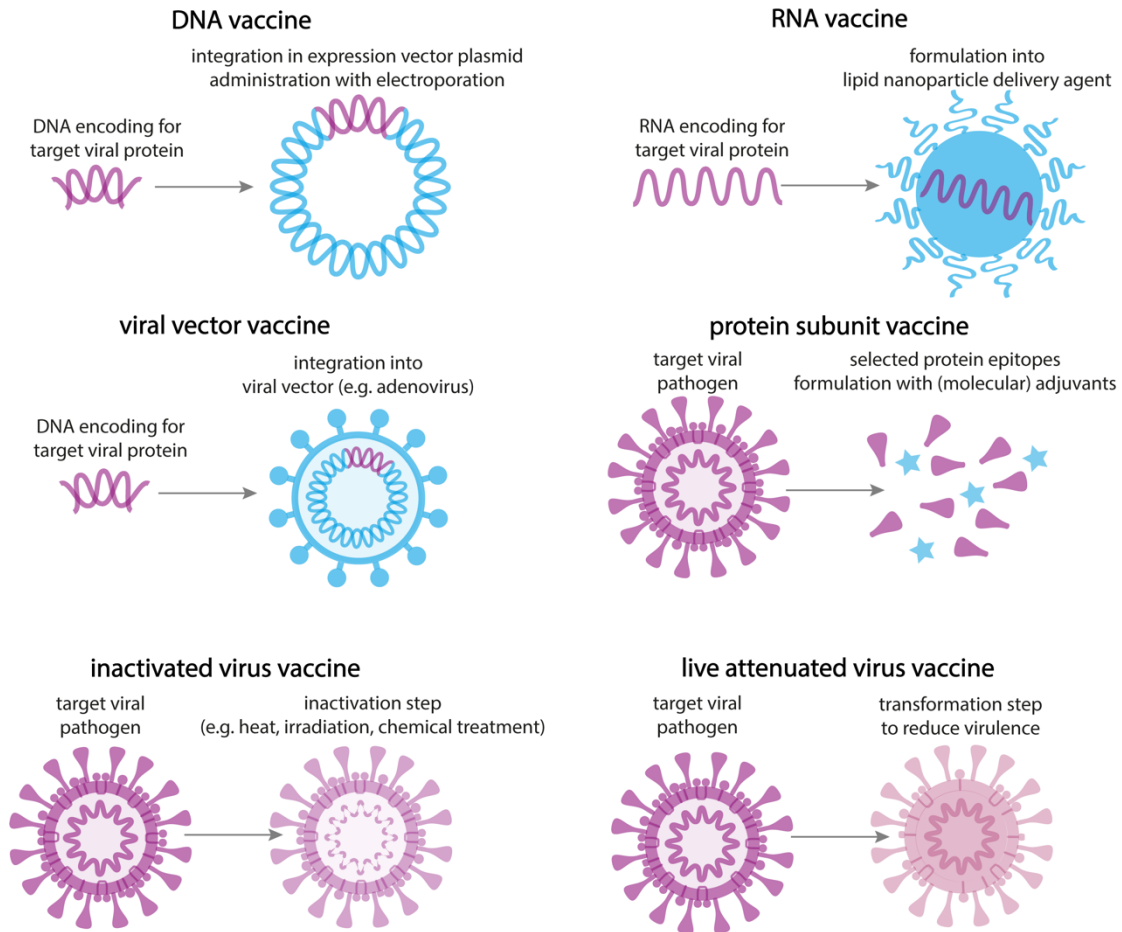
### ABSTRACT

The current COVID-19 pandemic has a tremendous impact on daily life world-wide. Despite the ability to dampen the spread of SARS-CoV-2, the causative agent of the diseases, through restrictive non-pharmaceutical interventions, it is believed that only effective vaccines will provide sufficient control over the spread of the disease and revert societal live back to normal. At present, a double-digit number of efforts are devoted to the development COVID-19 vaccines. Here, we provide an overview of these (pre)clinical efforts and provide background information on the technologies behind these vaccines. In addition, we discuss potential hurdles that need to be addressed prior to mass scale clinical translation of successful vaccine candidates.

### Introduction

The ongoing 2019–2020 pandemic of coronavirus disease 2019 (COVID-19) is due to an infectious respiratory disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Although non-pharmaceutical interventions, such as social distancing and confinement, appear to slow down the spread of SARS-CoV-2, there are no signs that these measures will completely stop the pandemic. <sup>[1]</sup> Hence, there is common ground for the hypothesis that only an effective vaccination campaign will have the power to stop the current pandemic. The goal of such campaign is to establish broad protective immunity in a sufficiently large number of individuals in order to reach herd immunity which stops further transmission of the pathogen. Based on animal model research from previous SARS (SARS-CoV-1) and MERS (Middle East Respiratory Syndrome) outbreaks, it is believed that a suitable vaccine should induce humoral immunity through neutralizing antibodies. In addition, induction of cellular immunity by such vaccines might increase its efficacy <sup>[2-4]</sup>. Although some SARS-CoV-1 and MERS clinical trials have resulted in the induction of promising immune responses, these have been small, and no efficacy trial has been conducted to date for any human coronavirus vaccine. <sup>[5,6]</sup> Given the

urgent need for a vaccine against COVID-19, so far over 200 vaccine candidates are under development and in different stages of (pre)clinical testing. In this report, we aim at giving an overview of the general approaches and challenges regarding the current COVID-19 vaccine development endeavors and discuss the progress of specific candidates and their (pre)clinical evaluation based on the antigen source, formulation strategy, epitope and route of administration (**Table 1**).

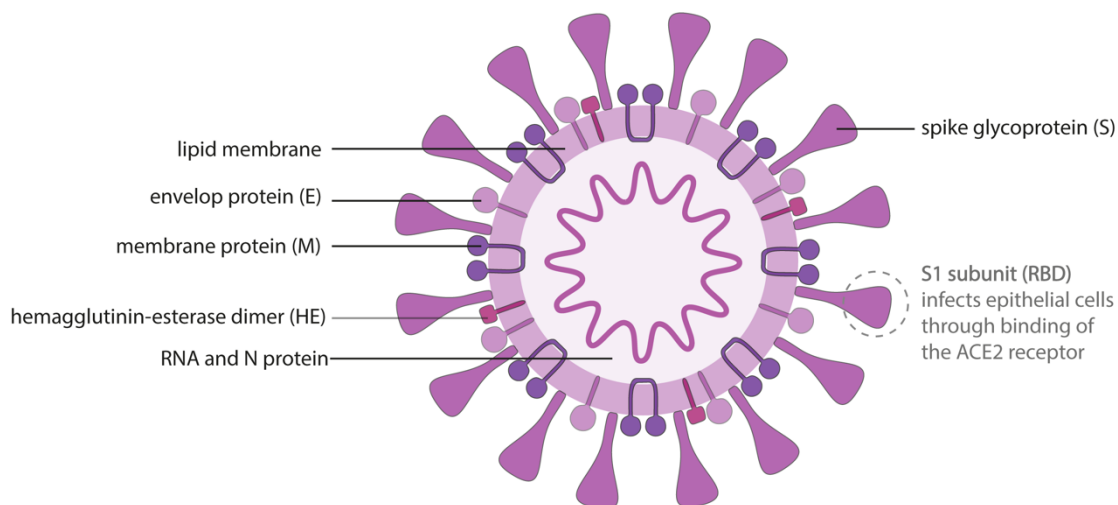


**Figure 1.** Schematic overview of the different types of vaccines.

In general, the vaccine candidates group into five different platforms, comprising classical approaches such as inactivated or live attenuated viruses, protein subunits, and more recent technologies such as engineered viral vectors and nucleic acid based antigens including DNA and mRNA (**Figure 1**). Besides the identification of a suitable antigen against which neutralizing antibodies should be mounted, formulation strategies will also determine the success of the multitude of vaccine candidates. These strategies encompass the use of adjuvants, encapsulation methods to deliver the vaccine at the right tissue and intracellular compartments. Moreover, vaccination approaches need to be compatible with the existence of scalable production systems. Adjuvants generally act by activating the innate immune

system and by skewing adaptive immune responses and are usually essential vaccine components. These include mainly aluminum-based or saponin-based adjuvants and Toll-like receptor (TLR) agonists.<sup>[7,8]</sup> In this context, GlaxoSmithKline (GSK) plays an important role with its proprietary adjuvant technology. GSK has reported to provide its collaborators Sanofi Pasteur, Clover Biopharmaceuticals Inc., University of Queensland and Inovax with their AS03 adjuvant.<sup>[9]</sup> AS03 contains  $\alpha$ -tocopherol and squalene in an oil-in-water (o/w) emulsion, and promotes spatio-temporal co-localisation of antigen, resulting in longer-lasting immunity and a reduction in the amount of antigen required per dose.<sup>[10,11]</sup> Biomaterials, including polymers and lipids, are crucial for the construction of delivery systems that adequately address extracellular stability and intracellular delivery challenges associated to nucleic acid based antigens, and also for some protein subunit vaccines. In addition, delivery systems can also be used to prolong the exposure of the vaccine to the immune system.

Coronaviruses are enveloped, single and positive stranded RNA viruses. Their genomic RNA (~26-32 kilobases) encodes a nonstructural replicase polyprotein and structural proteins, including spike, envelope, membrane and nucleocapsid proteins (**Figure 2**). The spike glycoprotein (SP) is naturally presented as a heavily glycosylated trimer and is required for both target cell binding and viral membrane fusion, making it or its minimal receptor-binding domain (RBD) an ideal vaccine target epitope, while nucleocapsid protein (N protein) also holds the potential to elicit immune protection according to experience with SARS vaccine development.<sup>[12,13]</sup>



**Figure 2.** Schematic illustration of the SARS-CoV-2 virus structure.

Finally, the route of administration could also affect the quality of the induced immune response. SARS-CoV-2 depends for entry on angiotensin-converting enzyme 2 (ACE2) which is expressed mainly on the surface of epithelial cells in the respiratory tract and also in the intestine.<sup>[1,14]</sup> Therefore, oral or nasal delivery of the vaccine, instead of parenteral injection, is being considered to elicit robust mucosal immune responses. However, the physicochemical barriers created by mucosal surfaces are a

formidable hurdle to overcome, and can be hugely different between individuals, hence advocating less for these routes of administration.<sup>[15]</sup> Intramuscular injection is the most common route of vaccine administration since it allows for induction of immune responses while being less prone to local adverse reactions compared to subcutaneous or intradermal injection. However, novel vaccine delivery methods such as microneedle technology have also shown great potential because of their safety, comfort for patients and effectiveness, and could offer distinct advantages in less developed regions in case they are designed in way that the cold chain can be avoided.<sup>[16]</sup>

### **Nucleic acid-based vaccines**

Nucleic acid (DNA and RNA) based vaccines carry a nucleotide sequence encoding the protein of interest. This approach uses the host cellular machinery to generate foreign antigens that can be presented in the context both major histocompatibility complex (MHC) class I and class II molecules of antigen-presenting cells (APCs), thereby eliciting both humoral and cellular immune responses. Interestingly, although there is currently no nucleic acid-based vaccine available on the market, nucleic acid vaccines do show great promise in the COVID-19 vaccine race. Firstly, they have the potential for rapid, inexpensive and scalable manufacture, which is essential in setting of a pandemic outbreak. Secondly, nucleic acids instruct host cells to synthesize SP without the struggling with protein folding, purification, solubility and inappropriate glycosylation issues that are commonly associated with recombinant protein synthesis, thereby matching better with virus' own glycoprotein coat.<sup>[17,18]</sup> Importantly, DNA/RNA requires a delivery system to reach its target (i.e. cell nucleus for DNA and cytoplasm for RNA). In the context of nucleic acid based COVID-19 vaccine development, liposomes and lipid nanoparticles (LNP), together with electrophysiological methods such as electroporation are the most explored system to deliver the DNA/RNA at the required intracellular location.<sup>[19,22]</sup> In this context an important role exists for so-called ionizable cationic lipids, with a pKa typically below neutral pH, that condense mRNA into nanoparticles and deliver their payload into the cellular cytoplasm upon endocytosis.

#### **RNA vaccines**

mRNA technology has emerged as a novel platform for vaccine development. mRNA-based vaccines hold several attractive advantages. For example, mRNA triggers rapid and immediate antigen expression in the cytoplasm without the need for crossing the nuclear membrane. In addition, there is no potential risk of infection or insertional mutagenesis. mRNA expression is rapid and transient as mRNA can be safely degraded by normal cellular processes.<sup>[23]</sup> But it also involves concerns related to its instability, high innate immunogenicity and inefficient in vivo delivery. At present, these drawbacks are becoming resolved to some extent by engineering of the RNA sequence, combining novel adjuvants and developing highly efficient and non-toxic carrier systems that mediate intracellular delivery of mRNA. Two major types of RNA are currently studied in a vaccine context: non-replicating mRNA and virally derived, self-amplifying RNA (saRNA). Conventional mRNA-based vaccine encodes the antigen of

interest, whereas saRNA also encodes a viral replication machinery that enables intracellular RNA amplification and abundant protein expression, hence minimizing the required dose of RNA.<sup>[24,25]</sup> A saRNA-LNP vaccine expressing SP of SARS-CoV-2 has been recently tested in animals and demonstrated that it can lead to comparable levels of SP-specific antibody titers and viral neutralization as found in recovered COVID-19 patients.<sup>[26]</sup>

In March 2020, the first SARS-CoV-2 vaccine candidate, mRNA-1273, was announced by the NIAID and Moderna to be evaluated in a clinical trial (NCT04283461) fueled by their prior efforts on coronavirus vaccine development. After the genetic information of SARS-CoV-2 recently became available, mRNA encoding SP of the virus was synthesized and formulated into LNP using their existing mRNA delivery system. The latter is composed of a proprietary ionizable lipid (SM-102) and three commercially available lipids.<sup>[27,28]</sup> Accomplishing a phase I trial with promising outcome (not published yet), Moderna has started clinical trial II (NCT04405076) with amended dose levels. Meanwhile the phase III study protocol is finished and the study is expected to be launched in July 2020.<sup>[29]</sup>

BioNTech and Pfizer are jointly developing BNT162 as a SARS-CoV-2 mRNA vaccine into clinical trial on April 14<sup>th</sup> (NCT04368728). They will evaluate four vaccine candidates representing different mRNA formats including a nucleoside modified mRNA (modRNA), a uridine containing mRNA (uRNA) and a saRNA, to express the larger SP or the smaller optimized RBD. All the mRNAs will be formulated as LNP.<sup>[30]</sup> Recently, the companies have released the safety and immunogenicity data of one candidate, i.e. BNT162b1, expressing trimerized RBD. In this case, the mRNA was modified with 1-methylpseudouridine to dampen innate immune sensing and increase mRNA translation in vivo. Their safety data showed that, upon intramuscular injection, only mild to moderate local reactions and systemic events were observed, with the severity being in a dose-dependent manner. After receiving two shots (10 or 30 µg) of BNT162b1 vaccine, SARS-CoV-2 specific neutralizing titers reached respectively 1.8- and 2.8-fold of that of a panel of COVID-19 convalescent human sera. These results support further evaluation of this mRNA vaccine candidate.<sup>[31]</sup>

The CureVac mRNA vaccine candidate utilizes nucleotides without chemical modifications in the mRNA, encodes the full-length SP and is formulated as LNP. This vaccine has been evaluated in various animal models and the obtained data indicated that the induced neutralizing antibody titers were comparable to sera from patients who recovered from COVID-19. Additionally, it also elicited specific T cell responses that may contribute to combating viral infection. Starting in June 2020, a clinical trial I (NCT04449276) is conducted in Germany and Belgium.<sup>[32]</sup>

Arcturus and their collaborator at Duke-NUS are developing a saRNA based on Arcturus's STARR (Self-Transcribing And Replicating RNA) technology and take advantage of a delivery platform developed at Duke-NUS allowing for rapid effectiveness and safety screening of vaccines. The saRNA is encapsulated with the LUNAR® (lipid-enabled and unlocked nucleic acid modified RNA), an ionizable and biodegradable LNP platform.<sup>[33]</sup> They expect their vaccine to elicit an immune response using much

lower doses than traditional mRNA vaccines due to a sustained protein expression through the use of saRNA, as it was observed for their other products in development.<sup>[34]</sup>

### DNA vaccines

DNA vaccines are relatively easy to manufacture and are fairly stable. However, DNA needs to cross the nuclear membrane to become translated, which is a major barrier for DNA-based therapeutics. Moreover, DNA vaccines could possibly result in insertional mutagenesis and cell transformation because of its chromosomal integration by non-homologous recombination. Hence, formulation and delivery strategies are of particular relevance for DNA vaccines.<sup>[35]</sup>

Inovio initiated their clinical phase I trial of DNA vaccine candidate INO-4800 (NCT04336410), fueled by their experience gathered from INO-4700, a MERS-CoV vaccine which was shown to be well-tolerated and capable to induce strong antibody and T cell responses.<sup>[6]</sup> INO-4800 is composed of optimized DNA plasmids that are designed to express the SP of SARS-CoV-2. Moreover, to improve the DNA vaccine potency, Inovio's DNA medicines deliver plasmids intradermally by electroporation (CELLECTRA®), which uses a brief electrical pulse to reversibly open small pores in the cell membrane to allow the plasmids to enter.<sup>[22]</sup> In this context it is noteworthy that in vivo electroporation of DNA has reported to transfect both immune cells and stromal cells, including fibroblasts and endothelial cells.<sup>[36]</sup> Currently, following immunization of mice and guinea pigs with INO-4800, both SP-specific antibody responses and T cell responses were observed. Furthermore, antigen-specific IgG has been detected in bronchoalveolar lavage fluid and serum and showed functional neutralizing activity against SARS-CoV-2. The preliminary dataset identifies INO-4800 as a potential COVID-19 vaccine candidate, supporting further translational study.<sup>[37]</sup>

Symvivo's bacTRL platform designed orally administered, genetically modified probiotic bacteria that colonize the gut, directly bind to intestinal epithelial cells and constitutively replicate, secrete and deliver plasmid DNA encoding antigenic transgenes and neutralizing nanobodies targeting the SP of SARS-CoV-2. They have concluded preclinical testing and initiated clinical trial (NCT04334980) in April 2020 evaluating a bifidobacterial monovalent SARS-CoV-2 DNA vaccine called bacTRL-Spike to rapidly induce both cellular and humoral immunity against SP.<sup>[38]</sup>

### Viral vector vaccines

Viral vector-based vaccines rely on the delivery of one or more antigens encoded in the context of an unrelated, modified virus. This strategy either employs live (replicating but often attenuated) or non-replicating vectors, among which adenovirus (Ad) vectors, measles virus, vesicular stomatitis virus (VSV) and modified vaccinia Ankara (MVA) are the most commonly used.<sup>[18]</sup> Adenoviruses allow insertion of up to 7-8 kb, supporting the expression of most target antigens as a multivalent vaccine. Ad type-5 (Ad5) has been extensively used and shows superior ability to induce exceptionally potent CD4<sup>+</sup> and

CD8<sup>+</sup> T cell as well as antibody responses. Moreover, pre-existing immunity against the viral vector itself, which is often considered as a factor to hamper the vaccine potency, only has limited influence on the immunogenicity of Ad5-based vaccines.<sup>[39-41]</sup> Innovatively, researchers from the KU Leuven made use of the live-attenuated yellow fever 17D (YF17D) vaccine as a vector to express SARS-CoV-2 SP, which elicited potent immune responses in mice.<sup>[42]</sup> Non-replicating vectors are more used as they cannot cause an ongoing infection in the vaccinated individual, but may need more doses than replicating viral vectors. Viral vector vaccines also have specific advantages. Indeed, delivery of the target antigen as genetic information allows for faithful antigen generation. Furthermore, viral vectors mimic a natural infection and induce potent immune responses, often without the need for additional adjuvants. However, viral vectors are genetically modified organisms (GMOs) and are therefore treated with caution.

The Chinese biotech company CanSino Bio is developing a COVID-19 vaccine based on a non-replicating Ad5 vector. Their platform has been previously successfully applied for the development of a vaccine against Ebola. A single intramuscular vaccination of the Ad5-nCoV was found sufficient to induce humoral and T-cell responses, while no serious adverse events were noted within 28 days post-vaccination according to the accomplished the phase I trial outcome (NCT04313127).<sup>[43]</sup> A phase II clinical trial subsequently started on April 10<sup>th</sup> 2020 (NCT04341389). This study will examine adverse reactions as well as serum levels of neutralizing antibodies against the SP for up to six months.<sup>[44]</sup>

A chimpanzee adenovirus vaccine vector (ChAdOx1) was developed at the Jenner Institute in Oxford. As a non-replicating and non-human adenoviral vector, it largely avoids pre-existing immunity. Hence, the chimpanzee adenoviral vector is safe in use and has proven to elicit a robust humoral and cellular immune response in mice and in rhesus macaques upon administration of a single injection.<sup>[45]</sup> This team of researchers has previously developed a vaccine for MERS which showed promise in clinical trial I, in which ChAdOx1 MERS was safe and well tolerated, whereas a single dose was able to elicit both humoral and cellular responses against MERS-CoV.<sup>[46]</sup> The phase I trial (NCT04324606) of ChAdOx1 COVID-19, involving over 1000 participants, is currently completed, and a phase II/III trial (NCT04400838) is launched to determine the efficacy, safety and immunogenicity of the ChAdOx1 candidate in a population with a broader age range.

Janssen Pharmaceutical Companies of Johnson & Johnson is expediting its COVID-19 vaccine program based on Janssen's AdVac® and PER.C6® technologies which provide a cost-effective manufacturing system for high-yield, faster and large-scale production of Ad vector vaccines. This approach has also been used for the development of an Ebola vaccine, which is currently deployed in Africa. The Ebola vaccine is a heterologous two-dose vaccine with Ad26.ZEBOV and MVA-BN-Filo, the first to prime the immune system and the second to boost the immune system to mount long-lasting immunity.<sup>[47,48]</sup> Its selected non-replicating Ad26 vector-based vaccine candidate will enter clinical evaluation in the U.S. and in Belgium in the second half of July 2020.



## Protein subunit vaccines

Subunit vaccines are based on only a limited number of viral proteins, often the major protein in the capsid or the envelope needed to confer protective immunity. Examples of these include the SP or RBD of SARS-CoV-2. Therefore, subunit vaccines are considered safer than full pathogen-based vaccines. However, single proteins, when expressed and purified in the absence of other viral components, are much less immunogenic. Besides lack of immune-stimulatory viral compounds, also a partial misfolded conformation of the protein, relative to the native protein, could be responsible for this reduced immunogenicity. Therefore, subunit vaccines often require higher dosing, booster administrations and co-administration of adjuvants to enhance antigen-specific immunity.<sup>[49,50]</sup> Virus-like particles (VLPs) are a highly effective type of subunit vaccines that mimic the overall structure of a virus. VLPs are formed by structural viral proteins which have the inherent property to self-assemble into protein nanoparticles, and mimic the morphology of the pathogen. Conferring improved delivery to lymphoid tissue and multivalent antigen display, usually means that VLP elicits stronger humoral and cellular response.<sup>[51,52]</sup> To date, subunit vaccines have been produced for a number of targets using mammalian, plant, insect or bacterial cells.<sup>[53]</sup>

Sanofi Pasteur is leveraging their previous work on the development a SARS-CoV-1 vaccine to unlock a fast path for developing a COVID-19 vaccine. Sanofi Pasteur uses its recombinant DNA in vitro platform that produces an exact genetic match to SP. The DNA sequence will be combined into a baculovirus expression platform, the basis of Sanofi's licensed recombinant influenza vaccine, which allows for rapid production of large quantities of antigen.<sup>[54]</sup> Sanofi Pasteur plans to initiate phase I clinical trials in the second half of 2020.<sup>[55]</sup>

A team from the University of Queensland announced a subunit vaccine candidate for which they used a technique called a 'molecular clamp'. It's a novel thermally-stable trimerisation domain, that can constrain a recombinant protein (i.e. SP of SARS-CoV-2) to its prefusion, trimeric conformation, expecting to expose the conserved stem domain to the immune system, while simultaneously stimulating an improved cross-reactive immune response to conserved epitopes.<sup>[56]</sup> Clinical trials are expected to be initiated in July 2020.<sup>[57]</sup>

The University of Pittsburgh School of Medicine has announced a potential vaccine against SARS-CoV-2 using the SP as antigen based, on their previous experience on SARS and MERS vaccine development. When tested in mice, the vaccine produced antibodies specific to SARS-CoV-2 at quantities thought to be sufficient for viral neutralization.<sup>[58]</sup> This lab uses a microneedle array, i.e. a fingertip-sized patch of 400 tiny needles that delivers the antigen into the skin. The patch is applied as band-aid, and subsequently the needles, which are entirely composed of sugar, and antigen dissolve into the skin. This system was reported to be scalable, by manufacturing of the antigen by a "cell factory", i.e. layer-upon-layer of cultured cells engineered to express SP. Researchers are now in the process of applying for an investigational new drug approval from the FDA in anticipation of starting a phase I clinical trial.<sup>[59]</sup>

Novavax, a late-stage biotech company, has developed a SARS-CoV-2 subunit vaccine (NVX-CoV2373) produced from the full-length SP, stabilized in the prefusion conformation. Matrix-M was used as adjuvant to enhance the immune response by promoting antigen absorption.<sup>[7]</sup> In mice and nonhuman primate (baboons) models, NVX-CoV2373 with Matrix-M adjuvant induced a Th1 dominant B- and T-cell response, hACE2 receptor blocking antibodies as well as SARS-CoV-2 neutralizing antibodies. This vaccine successfully protected immunized mice against SARS-CoV-2 challenge without evidence of vaccine-associated enhanced respiratory disease.<sup>[60]</sup> These results support the ongoing phase I/II clinical evaluation of the safety and immunogenicity of NVX-CoV2327 (NCT04368988).

### **Inactivated and live attenuated virus**

The majority of the currently available human vaccines are based on inactivated or live attenuated viruses. Live attenuated vaccines, engineered from much less virulent version of the pathogen, are often able to induce strong, long-lasting cellular and humoral immunity as observed with the natural live virus. However, risk exists of reversion to virulent wild-type strains which can lead to disease, especially in immunocompromised individuals. On the other hand, inactivated vaccines (or killed vaccines) cannot replicate and cause disease and thus, are non-infectious and safer. One animal trial on SARS-CoV-2 inactivated vaccine has been conducted, resulted in specific neutralizing antibodies while no significant T-cell immunity was found.<sup>[61]</sup> As these are less potent than live vaccines in inducing protective immunity, multiple doses and administration of boosters of the inactivated vaccine may be required to ensure durable protection.<sup>[49]</sup> Additionally, the efficacy of inactivated virus vaccine can be dampened when crucial viral neutralizing epitopes are destroyed during the inactivation process.

Codagenix and the Serum Institute of India are co-developing a live-attenuated vaccine against SARS-CoV-2. Codagenix uses viral deoptimization to synthesize a "rationally designed," live-attenuated vaccine, starting from the digital sequence of the viral genome. This viral vaccine still requires animal testing prior to initiating clinical trials.<sup>[62]</sup>

Dynavax Technologies is collaborating with Sinovac Biotech to develop an inactivated COVID-19 vaccine in combination with the FDA approved adjuvant CpG 1018 (NCT04352608). The latter is a short, unmethylated CpG oligodeoxynucleotide with immunostimulatory function through TLR9 signalling.<sup>[7]</sup> Mid of June 2020, Sinovac revealed promising preliminary data, reporting that in a phase I/II study, more than 90% of the 600 healthy volunteers showed antigen-specific immune response. In July 2020, Phase III trials are expected to start in Brazil.<sup>[63]</sup>

### **Conclusions and perspectives**

The global efforts in vaccine development in response to the COVID-19 pandemic are unprecedented in terms of scale and speed, with a licensed vaccine hopefully to become available in one year and a half. However, several technical difficulties in this race are noted. First of all, studies with SARS and

MERS suggested COVID-19 vaccine research should focus on establishing animal models that recapitulate replication, pathogenesis and transmission in humans. Animal models that include ferrets and NHPs are a good choice but with high cost and limited source. The golden Syrian hamster model may be good alternative as they are smaller, easier to handle and pathology with coronavirus infection has been described.<sup>[64]</sup> However, human ACE2 transgenic mice developed encephalitis when used as a model to study SARS-CoV, which was not observed in humans.<sup>[65]</sup> Secondly, a paradoxical phenomenon called antibody-dependent enhancement (ADE) has been described for flaviviruses.<sup>[66,67]</sup> During ADE, viruses exploits virus-specific antibodies in the human host to enter into host cells. This phenomenon complicates vaccine development for flaviviruses, and should be considered as a potential risk when developing a vaccine against a new emerging pathogen like SARS-CoV-2. It is important to find out the level of protection and absence of ADE during (re-)infection provided by immunity against SARS-CoV-2, induced by natural infection or vaccination. This to optimize protection and to avoid that vaccines or convalescent people develop more severe disease than non-vaccinated individuals.<sup>[68]</sup> Previous animal experiments on vaccines against SARS and MERS also report the occurrence of ADE.<sup>[69,70]</sup> Hence, prior to clinical trials, the vaccine's potential risk to aggravate disease should be fully evaluated in animal models.

Another possible complication is whether SARS-CoV-2 can change antigenically through genetic mutations and thereby avoid immunity.<sup>[71]</sup> At present it is not yet known whether SARS-CoV-2 mutations will affect viral antigenicity and if this would allow the virus to escape neutralizing antibodies as witnessed for influenza viruses (antigenic drift). In that case, a vaccine that targets more conserved epitopes such as RBD on the virus would be necessary for long-term protection by vaccination. Robbiani et al. recently reported that most convalescent plasmas obtained from individuals who recover from COVID-19 do not contain elevated levels of neutralizing antibodies, but RBD-specific neutralizing antibodies were found in all tested individuals.<sup>[72]</sup> Despite the urgent pursuit for a vaccine to master the current COVID-19 pandemic, we still do not know how long specific immunity will last in the human body after being vaccinated. Evidences showed that antibody titers in individuals that survived SARS-CoV or MERS-CoV infections often waned after 2–3 years.<sup>[73,74]</sup> Longitudinal studies of host immune responses to SARS-CoV-2 are required to understand the best immune correlates of protection, which in turn will guide further vaccine development.

**Table 1.** Selected COVID-19 vaccine candidates.

Type	Current stage of development	Formulation strategies	Epitope	Route of administration	Developer
mRNA/saRNA	<b>Clinical trial Phase I/II</b> (NCT04368728)	Formulated in LNP	SP/RBD	IM	BioNTech/Fosun Pharma/Pfizer <sup>(60)</sup>
mRNA	<b>Clinical trial phase II</b> (NCT04283461)	Formulated in LNP	prefusion stabilized SP	IM	Moderna/NIAID <sup>(68)</sup>
	<b>Clinical trial phase I</b> (NCT04449276)	Formulated in LNP	SP	IM	Curevac <sup>(75)</sup>
	<b>Clinical trial phase I</b> (ChiCTR200003411)		RBD		Academy of Military Sciences/Walvax Biotech
	Pre-clinical	Naked mRNA	SP		China CDC/Tongji University <sup>(76)</sup>
	Pre-clinical	Encoding VLP/SP	SP/RBD		Fudan University/ Shanghai JiaoTong University <sup>(77)</sup>
	Pre-clinical	Liposome RNA Encoding VLP	SP		Translate Bio/ Sanofi Pasteur <sup>(78)</sup>
saRNA	Pre-clinical	Formulated in LNP	SP		Arcturus/Duke-NUS <sup>(84)</sup>
	<b>Clinical trial phase I</b> (ISRCTN17072692)	Formulated in LNP	SP	IM	Imperial College London <sup>(79)</sup>
DNA	<b>Clinical trial phase I</b> (NCT04336410)	Plasmid DNA	SP	ID and EP	Inovio Pharmaceuticals <sup>(22)</sup>
	<b>Clinical trial phase I</b> (NCT04334980)	Genetically modified probiotic bacteria with a plasmid DNA	SP	Aral	symvivo <sup>(88)</sup>
	<b>Clinical trial phase I</b> (NCT04445389)		SP	IM	Genexine, Inc.
	<b>Clinical trial phase I/II</b> (CTRI/2020/07/02635)	Plasmid DNA		ID	Zydus Cadila

	<b>Clinical trial phase I</b> (JapicCTI-205328)	Plasmid DNA		IM	Osaka University/ AnGes
	Pre-clinical	A fragment of DNA		IM and EP	Takis/Applied DNA Sciences/Ewivax <sup>(79)</sup>
	Pre-clinical	Plasmid DNA	SP		Zydus Cadila <sup>(80)</sup>
	Pre-clinical	Delivered by bacteriophage		IN	University of Waterloo <sup>(81)</sup>
	<b>Clinical trial phase II</b> (NCT04313127)	Ad5 Vector	SP	IM	CanSino/Beijing Institute of Biotechnology <sup>(43)</sup>
	<b>Clinical trial phase II / III</b> (NCT04400838)	Chimpanzee adenovirus vaccine vector (ChAdOx1)	SP	IM	University of Oxford
	<b>Clinical trial phase I</b> (NCT04437875)	Ad26 Vector	SP	IM	Gamaleya Research Institute
	Pre-clinical	Ad vectors, alone or with MVA boost		IM	Janssen Pharmaceutical Companies <sup>(47)</sup>
	Pre-clinical	Modified Vaccinia Virus Ankara vector Encoding VLP			GeoVax/BravoVax <sup>(82)</sup>
	Pre-clinical	Ad vector	SP	IN	Altimmune <sup>(83)</sup>
	Pre-clinical	Ad vector			Greffex <sup>(84)</sup>
	Pre-clinical	Ad5 vector	SP	Oral	Vaxart <sup>(85,86)</sup>
	Pre-clinical	DelNS1 live attenuated influenza virus (LAIV) vector	SP	IN	University of Hong Kong <sup>(87)</sup>
	Pre-clinical	MVA vector	SP		DZIF – German Center for Infection Research <sup>(88)</sup>
	Pre-clinical	MVA vector; Encoding structural proteins	SP		Centro Nacional Biotecnología <sup>(89)</sup>
Replicating Viral Vector	Pre-clinical	Recombinant measles virus (rMV)	Codon-optimised SP		Zydus Cadila <sup>(80)</sup>
	Pre-clinical	Measles virus vector	SP		Institute Pasteur/Themis/Univ. of Pittsburg <sup>(90)</sup>

	Pre-clinical	Horsepox virus vector	SP		Tonix Pharma/Southern Research <sup>(91)</sup>
	Pre-clinical	Recombinant vesicular stomatitis virus (VSV) vector	SP		IAVI/Batavia <sup>(92)</sup>
Protein Subunit	<b>Clinical trial phase I</b> ( NCT04405908)	Adjuvant: AS03, Alum	Trimeric SP	IM	Clover Biopharmaceuticals Inc./GSK <sup>(93)</sup>
	<b>Clinical trial phase I</b> (NCT04453852)	Adjuvant: Advax-SM	SP		Vaxine Pty Ltd
	<b>Clinical trial phase I</b> (NCT04445194)			IM	Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd.
	Pre-clinical		RBD		Vaxil Bio <sup>(94)</sup>
	Pre-clinical		SP		AJ Vaccines <sup>(95)</sup>
	Pre-clinical	Activated by T-Cell called li-Key	RBD		Generex/EpiVax <sup>(96)</sup>
	Pre-clinical		SP		EpiVax/Univ. of Georgia <sup>(97)</sup>
	Pre-clinical	Baculovirus expression system ; Adjuvant: AS03	SP	IM	Sanofi Pasteur/GSK <sup>(98)</sup>
	Pre-clinical	GP-96 backbone	SP	ID	Heat Biologics/Univ. Of Miami <sup>(99, 99)</sup>
	Pre-clinical	Molecular clamp stabilized trimeric SP ; Adjuvant: AS03	SP		University of Queensland/GSK <sup>(97)</sup>
	Pre-clinical	Chimeric soluble protein	SP and N protein	Oral	MIGAL Galilee Research Institute <sup>(100)</sup>
	Pre-clinical	MPLA adjuvant	SP	ID	University of Pittsburgh School of Medicine <sup>(101)</sup>
	Pre-clinical	Formulated as microspheres	Peptide antigen		Flow Pharma Inc <sup>(101)</sup>
	Pre-clinical		RBD		Baylor College of Medicine <sup>(102)</sup>
	Pre-clinical	Formulated in LNP	Peptide antigen		IMV Inc <sup>(103, 104)</sup>
	Pre-clinical	Adjuvant:AS03	truncated SP		Innovax/Xiamen Univ./GSK <sup>(105)</sup>
Pre-clinical		SP		WRAIR/USAMRIID <sup>(106)</sup>	

VLP	<b>Clinical trial phase I</b> (NCT04368988)	Baculovirus/insect cells expression system; Adjuvant: Matrix-M™	SP	IM	Novavax <sup>600</sup>
	Pre-clinical	Drosophila S2 insect cells expression system	SP	IM	ExpreS2ion/ AdaptVac <sup>(107,108)</sup>
	Pre-clinical	Plant derived VLP	SP	IM	Medicago Inc <sup>(109)</sup>
	Pre-clinical	FastPharming System™; Coated with oligomannose			iBio/CC-Pharming <sup>(10)</sup>
Live Attenuated Virus	Pre-clinical	Gene rationally designed vaccines	Viral proteins		Codagenix/Serum Institute of India <sup>(62)</sup>
Inactivated virus	<b>Clinical trial phase I/II</b> (NCT04352608)	Chemically inactivate whole virus; Adjuvant : CpG 1018™	Viral proteins	IM	Sinovac/Dynavax Technologies Corporation <sup>(63)</sup>
	<b>Clinical trial phase I/II</b> (NCT04412538)		Viral proteins		Chinese Academy of Medical Sciences
	<b>Clinical trial phase I</b> (ChiCTR2000032459)		Viral proteins		Beijing Institute of Biological Products
	<b>Clinical trial phase I</b> (ChiCTR2000031809)		Viral proteins		Wuhan Institute of Biological Products

IM: Intramuscular; ID: Intradermal; IN: Intranasal; EP: Electroporation; LNP: lipid nanoparticle; VLP: virus-like particle; SP: spike glycoprotein; N protein: nucleocapsid protein; RBD: receptor binding domain

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