Inside the story about the research and development of COVID-19 vaccines

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The ongoing coronavirus threat from China has spread rapidly to other nations and has been declared a global health emergency by the World Health Organization (WHO). The pandemic has resulted in over half of the world's population living under conditions of lockdown. Several academic institutions and pharmaceutical companies that are in different stages of development have plunged into the vaccine development race against coronavirus disease 2019 (COVID-19). The demand for immediate therapy and potential prevention of COVID-19 is growing with the increase in the number of individuals affected due to the seriousness of the disease, global dissemination, lack of prophylactics, and therapeutics. The challenging part is a need for vigorous testing for immunogenicity, safety, efficacy, and level of protection conferred in the hosts for the vaccines. As the world responds to the COVID-19 pandemic, we face the challenge of an overabundance of information related to the virus. Inaccurate information and myths spread widely and at speed, making it more difficult for the public to identify verified facts and advice from trusted sources, such as their local health authority or WHO. This review focuses on types of vaccine candidates against COVID-19 in clinical as well as in the preclinical development platform.

Keywords: COVID-19, Vaccine, SARS-CoV-2, Clinical trials, Vaccine development, Vaccine candidate

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originated in Hubei Province, China, in December 2019 (and possibly earlier, though unrecognized), as a pneumonia-causing disorder [1], most likely the result of natural selection in animal hosts (bats, pangolins) before the zoonotic transition [2]. Seven members of this viral family are now known to infect humans, three of whom have the potential to cause severe respiratory diseases [3]. Coronaviruses (CoVs) are positive-sense, single-stranded Coronaviridae family (subfamily Coronavirinae) RNA viruses that infect a broad range of hosts to produce diseases ranging from the common cold to severe/fatal diseases [4]. The novel virus was initially named "2019-nCoV" by the International Committee on Virus Taxonomy. It was changed to "SARS-CoV-2" since it was found to be the sister virus of an extreme acute respiratory syndrome (SARS-CoV) [5]. The ongoing threat of coronavirus emerging in China has spread rapidly to other countries and has been declared by the World Health Organization (WHO) as a global health emergency [6].

Virus genetic sequencing shows that it is a beta coronavirus that is closely related to the SARS virus [7]. Currently, immunization prevents 2–3 million deaths from more than 20 life-threatening diseases that are now being controlled by vaccinations, and work is underway at an unprecedented pace to make coronavirus disease 2019 (COVID-19) a vaccine-preventable illness [8]. To accelerate the research and development process and to establish new standards and standards to prevent the spread of the coronavirus pandemic and care for those affected, WHO brings together the world's scientists and public health practitioners [7]. In human medical intervention, vaccines are one of the monumental achievements in mitigating the dispersion and effects of infectious diseases [9]. Vaccines are the most useful method for contagious disease prevention because they are more cost-effective than treatment and reduce morbidity and mortality without long-lasting effects [10]. Preventive and therapeutic vaccines will be of fundamental significance as the most obvious way to safeguard public health [11]. Since the coronavirus shares substantial sequence homology with two other lethal coronaviruses, SARS and Middle East respiratory syndrome (MERS), the vaccines identified could potentially promote the design of anti-SARS-CoV-2 vaccines. It is essential to establish safe and effective vaccines to contain the COVID-19 pandemic, eradicate its spread, and eventually prevent its future recurrence [12]. By exposing individuals to antigens, vaccination can produce long-lasting immunity to drive the production of immunological memory before meeting live pathogens. Thus the resulting immunity can be mediated by the activation of humoral antibodies and the effector function of cellular T-cells [13]. The full development path for an effective SARS-CoV-2 vaccine will involve th e cooperation of industry, government, and academia in unprecedented ways, each contributing its strengths [14].

It is a difficult task to develop a SARS-CoV-2 vaccine to control its spread and help remove it from the human population since there is a lack of knowledge on its biological properties, epidemiology, individual immune responses to it, and so forth [15]. The S protein is the critical target of vaccine production since it includes a receptor-binding domain (RBD) and viral functions. It will be essential to confirm the clinical significance of the SARS-CoV-2 binding and neutralizing antibody titers and their ability to predict efficacy [16]. Only in a significant clinical efficacy study would it be possible to confirm the association between antibody titers and defense against COVID-19 [17]. For any frequently used vaccine, there is a theo-

retical risk that vaccination could cause subsequent infection with SARS-CoV-2 more severe. This has been confirmed in feline coronaviruses and has been observed in some SARS-CoV-1 animal vaccine challenge models [18].

The key benefit of next-generation vaccines is that they can be produced based on sequence data alone [19]. If the viral protein(s) that are essential for the defense against infection or disease and therefore for inclusion in the vaccine is established, the availability of coding sequences for the viral protein(s) is sufficient to start the production of the vaccine rather than to rely on the ability to grow the virus [20]. This makes these platforms extremely adaptable and dramatically accelerates the production of vaccines, as is evident from the fact that the majority of currently underway clinical trials of COVID-19 vaccines include a next-generation platform [19]. A prospective pharmaceutical manufacturer must send an application to a regulatory authority such as the Food and Drug Administration (FDA) to examine the new vaccine after a possible vaccine has been announced by a researcher [21].

The demand for immediate therapy and potential prevention of COVID-19 is growing [22] with the increase in the number of individuals affected due to the seriousness of the disease, global dissemination, lack of prophylactics, and therapeutics [23]. Attempts are being made to establish secure and successful methods for prophylactics [24,25]. Several vaccines are in different phases of clinical trials [6], but there is a lack of prophylactics in the present scenario [26]. Several attempts have been made to create COVID-19 vaccines to avoid the pandemic condition as well as the S-protein SARS-CoV-2 has been used for most of the emerging vaccine candidates. In Fig. 1, the overview of vaccine candi-
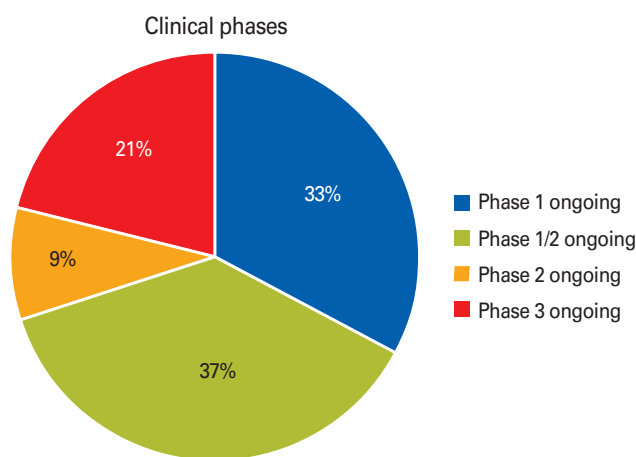

Fig. 1. Overview of vaccine candidates in their respective ongoing clinical phases.
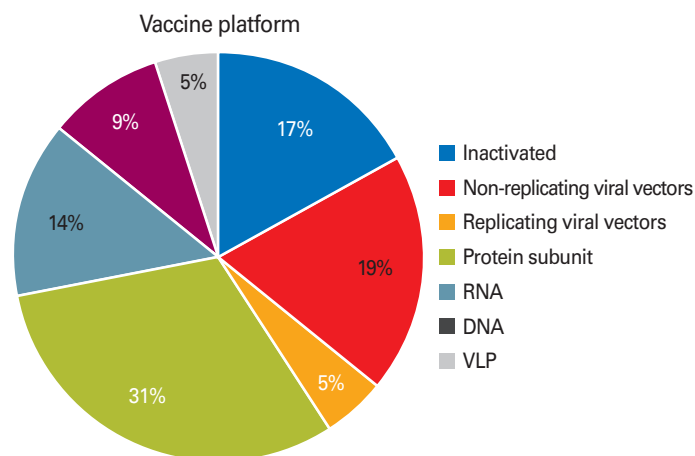
Fig. 2. The overview of global coronavirus disease 2019 vaccine landscape in clinical development. VLP, virus-like particle.

Fig. 3. The overview of global coronavirus disease 2019 vaccine landscape in preclinical development. VLP, virus-like particle.

dates in their respective ongoing clinical phases depicts the percentage of vaccine candidates amongst which the majority of developing vaccines is in phase 1/2. The data shown below in the graph is assessed until 15 October 2020, in the pipeline of vaccine development and registered clinical trials globally.

In Fig. 2, the overview of the global COVID-19 vaccine landscape in clinical development depicts that there are seven major types of vaccine candidates for COVID-19 is illustrated as (inactivated, non-replicating viral vectors, replicating viral vectors, protein subunit, nucleic acid-based, and virus-like particles [VLP]), showing the percentage of candidate vaccines that are currently under clinical development. The nucleic acid-based platform includes both RNA vaccines and DNA vaccines. Among the seven types of vaccine candidates, protein subunit-based vaccines constitute the highest 31% in clinical development. In contrast, VLP-based vaccine and replicating viral vectors comprises the lowest as 5% in the clinical development.

In Fig. 3, the overview of global COVID-19 vaccine landscape in preclinical development depicts that there are 10 significant types of vaccine candidates for COVID-19 is illustrated as (inactivated, replicating bacteria vector, DNA, live attenuated virus, non-replicating viral vectors, protein subunit, t-cell based, replicating viral vectors, RNA, and VLP), showing the percentage of candidate vaccines that are currently under preclinical development. Among the 10 types of vaccine candidates, protein subunit-based vaccines constitute the highest 36% in clinical development whereas T-cell based vaccine and replicating bacteria vector comprises the lowest at 1% in the preclinical development globally.
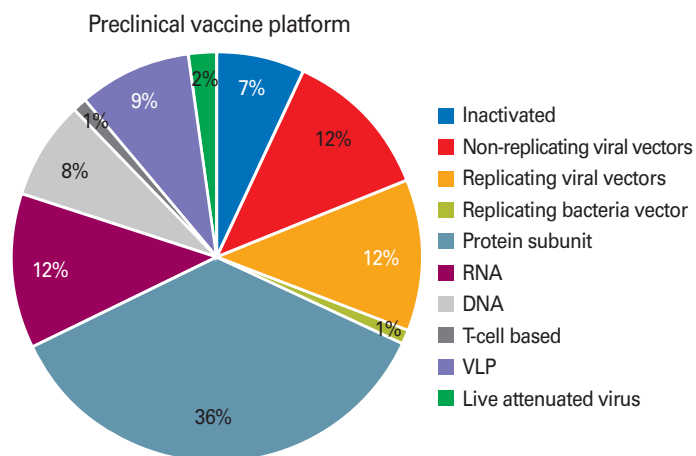
RNA-Based Vaccine

As a result of considerable developments in biotechnology, due to their higher potency, short development cycles, low-cost product, and safe administration, mRNA vaccines represent a substantial improvement over traditional vaccine strategies [27]. The mRNA is an evolving platform that is non-infectious and non-integrated and has almost no possible risk of insertional mutagenesis. Antigen discovery, sequence analysis, and optimization, screening of modified nucleotides, delivery system discovery, and immune response and safety assessment tests are the sequential events in the mRNA vaccine production process [28]. In vaccines, two primary forms of RNA are investigated: virally derived, RNA self-replicating, and mRNA non-replicating. The antigen and the necessary viral replication machinery are typically self-replicating RNAs, whereas conventional mRNA-based vaccines encode only the antigen of interest with 50 and 30 untranslated regions (UTRs) [27].

The immunogenicity of mRNA can be decreased, and changes can be made to enhance the stability of these vaccines [29]. Furthermore, anti-vector immunity is also resisted as mRNA is the minimally immunogenic genetic vector, allowing repeated administration of the vaccine [30]. This platform has empowered the rapid vaccine development program due to its flexibility and ability to reproduce the structure and expression of the antigen as seen in the course of natural infection [31]. A possible benefit of mRNA vaccines is the convenient availability of a portable mRNA "printing" facility for large-scale production of mRNA [32].

mRNA-1273 (Moderna TX Inc.)

It is a vaccine composed of lipid nanoparticle (LNP) encapsulated synthetic mRNA that codes for SARS-CoV-2 full-length, pre-fusion stabilized spike protein (S) [33]. It has the potential to induce an antiviral response that is highly S-protein specific. Also, it is known to be relatively harmless since it is neither composed of the inactivated pathogen nor of the live pathogen sub-units [34]. To perform the phase II trials, the vaccine has received FDA fast-track approval. The company published the interim antibody data for phase I of eight participants who received different levels of dose [33]. For the participants receiving 100 µg dose, neutralizing antibody levels were significantly higher than those observed in convalescent sera. In the 25 µg and 100 µg dose cohorts, the vaccine was found to be primarily safe and well-tolerated. In comparison, three participants reported systemic symptoms of grade 3 following administration of the second 250 µg dose level [26]. The possible benefits of a prophylactic vaccine mRNA strategy include the ability to replicate natural infection to induce a more effective immune response and the ability to incorporate multiple mRNAs into a single vaccine [12].

On 24 February 2020, Moderna declared that it had released the first batch of mRNA-1273 against SARS-CoV-2 for human use, prepared using the methods and strategies outlined in its previous patents. mRNA-1273 vials have been shipped to the National Institute of Allergy and Infectious Diseases (NIAID), a division of the National Institutes of Health (NIH), to be used in the United States in the proposed phase 1 study [35]. In collaboration with researchers at the NIAID Vaccine Research Centre, Moderna reports that mRNA-1273 is an mRNA vaccine targeting a prefusion stabilized form of the S protein associated with SARS-CoV-2, which was chosen by Moderna [32]. Patent application WO2018115527 describes vaccines consisting of mRNA encoding at least one MERS coronavirus antigen, preferably an S protein or an S protein fragment (S1), an envelope protein (E), a membrane protein (M), or a nucleocapsid protein (N), all of which have been successful in inducing an immune response unique to the antigen [33]. Intradermal administration of a LNP-encapsulated mRNA mixture encoding MERS-CoV S proteins into mice has been shown to result in vivo translation and humoral immune response induction [12].

BNT162b1 (BioNTech, Fosun Pharma, Pfizer)

BNT162b1 is a codon-optimized mRNA vaccine that codes for the essential target of the neutralizing antibody virus, trimerized SARS-CoV-2 RBD [29]. The vaccine shows improved immunogenicity due to the addition of the foldon trimerization domain of T4 fibrin-derived to the RBD antigen. In 80 nm ionizable cationic LNPs, the mRNA is encapsulated, which guarantees its efficient delivery [31]. In phase 1/2 clinical trials, elevated levels of RBD-specific immunoglobulin G (IgG) antibodies with a geometric mean concentration were found to be 8 to 46.3 times the convalescent serum titer. Whereas, the SARS-CoV-2 neutralizing antibody geometric mean titers were found to be 1.8 to 2.8 times the convalescent serum panel [29]. With no adverse effects, mild and transient local reactions and systemic events were observed. The data review did not, however, assess the protection and immune response beyond 2 weeks after the second dose administration [31].

Report of available effectiveness, tolerability, and immunogenicity results from an ongoing placebo-controlled, observer-blinded dose-escalation study in healthy adults 18–55 years of age, randomized to receive two 21-day separate doses of 10 µg, 30 µg, or 100 µg of BNT162b1, a nucleoside-modified LNP mRNA vaccine encoding trimerized SARS-CoV-2 spike glycoprotein dose-dependent, usually mild to moderate, and temporary, was the local reactions and systemic events [29]. The BNT162b1 vaccine candidate now being clinically studied integrates such nucleoside modified RNA and encodes the SARS-CoV-2 spike protein RBD, a primary target of virus-neutralizing antibodies [31]. Sera's RBD-binding IgG and SARS-CoV-2 neutralizing titers increased both at the dose level and after the second dose. Geometric mean neutralizing titers were 1.8 to 2.8 times those of a panel of human sera convalescent COVID-19. These findings help further evaluation of this candidate for the mRNA vaccine [33]. By adding a T4 fibritin-derived "foldon" trimerization domain, the RBD antigen expressed by BNT162b1 is modified to improve its immunogenicity by a multivalent display. The RNA vaccine is formulated in LNPs for more effective delivery to cells after intramuscular injection [31]. In Table 1, potential RNA-based vaccine candidates are listed below for COVID-19 which are in the clinical development phase and registered globally [36-45].

Viral Vector-Based Vaccines

Viral vector-based vaccines have a high degree of protein expression and long-term stability, inducing strong immune responses [46]. These include vaccines focused on chemically weakened viruses used to bear antigens or pathogens of

Table 1. Potential RNA-based vaccine candidates for COVID-19 in the clinical development pipeline

No.	Title	Description	Vaccine candidate	Phase trial	Sponsor and collaboration	Reference
1	Safety and immunogenicity study of 2019-nCoV vaccine (mRNA-1273) for prophylaxis of SARS-CoV-2 infection (COVID-19)	This clinical trial is designed to assess the safety, reactogenicity, and immunogenicity of mRNA-1273. It encodes for a full-length, prefusion stabilized spike (S) protein of SARS-CoV-2.	LNP-encapsulated mRNA	Phase 1	NIAID	NCT04283461 [36]
2	Dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 COVID-19 vaccine in adults aged 18 years and older	This clinical study will assess the safety, reactogenicity, and immunogenicity of 2 dose levels of mRNA-1273 SARS-CoV-2 vaccine.	LNP-encapsulated mRNA	Phase 2	Sponsor: Moderna TX Inc. Collaborator: Biomedical Advanced Research and Development Authority	NCT04405076 [37]
3	A study to evaluate efficacy, safety, and immunogenicity of mRNA-1273 vaccine in adults aged 18 years and older to prevent COVID-19	The study was designed to primarily evaluate the efficacy, safety, and immunogenicity of mRNA-1273 to prevent COVID-19 for up to 2 years after the second dose of mRNA-1273.	LNP-encapsulated mRNA	Phase 3	Sponsor: Moderna TX Inc. Collaborator: Biomedical Advanced Research and Development Authority & NIAID	NCT04470427 [38]
4	A phase I clinical trial of novel coronavirus pneumonia (COVID-19) mRNA vaccine (BNT162b1) in China	To evaluate the safety and tolerability profiles of BNT162b1 P/B immunization given 21 days apart on healthy Chinese subjects through 28 days after boost vaccination.	3 LNP-mRNAs	Phase 1	Jiangsu Provincial Center for Disease Prevention and Control	ChiCTR2000034825 [39]
5	A trial investigating the safety and effects of one BNT162 vaccine against COVID-19 in healthy adults	The vaccine BNT162b3 will be administered using a P/B regimen. This trial has been divided into two parts for dose-escalation cohorts in older subjects.	3 LNP-mRNAs	Phase 1/2	BioNTech RNA Pharmaceuticals GmbH	NCT04537949 [40]
6	Study to describe the safety, tolerability, immunogenicity, and efficacy of RNA vaccine candidates against COVID-19 in healthy individuals	This study is a phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study in healthy individuals.	3 LNP-mRNAs	Phase 3	Sponsor: BioNTech SE Collaborator: Pfizer	NCT04368728 [41]
7	A study to evaluate the safety, reactogenicity, and immunogenicity of vaccine CVnCoV in healthy adults	This study aims to evaluate the safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV at different dose levels.	mRNA	Phase 1	Sponsor: CureVac AG Collaborator: Coalition for Epidemic Preparedness Innovations (CEPI)	NCT04449276 [42]
8	Ascending dose study of investigational SARS-CoV-2 vaccine ARCT-021 in healthy adult	To determine safety and tolerability and immunogenicity of investigational vaccine ARCT-021 in healthy adult volunteers.	mRNA	Phase 1/2	Arcturus Therapeutics Inc.	NCT04480957 [43]
9	A clinical trial to assess the safety of a coronavirus vaccine in healthy men and women	The main aim of the study is to assess the safety of the vaccine and its effects on the immune system.	LNP-nCoVsaRNA	Phase 1	Imperial College London	ISRCTN17072692 [44]
10	A phase I clinical trial to evaluate the safety, tolerance, and preliminary immunogenicity of different doses of a SARS-CoV-2 mRNA vaccine in population aged 18–59 years and 60 years and above	To explore the immune persistence of the investigational vaccine at the recommended dose and the specific cellular immune response to the RBD of S protein.	mRNA	Phase 1	People's Liberation Army (PLA) Academy of Military Sciences, Walvax Biotech.	ChiCTR2000034112 [45]

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; LNP, lipid nanoparticle; NIAID, National Institute of Allergy and Infectious Diseases; P/B, prime/boost; RBD, receptor-binding domain.

concern for immune response induction [47]. A possible prophylactic strategy against a pathogen is a viral vector-based vaccine. These vaccines are highly selective in transmitting genes to the target cells, are highly effective in gene transduc-

tion, and are useful in inducing immune responses [48]. They have a long-term and high level of antigenic protein expression and thus have an excellent potential for prophylactic use as these vaccines activate and facilitate cytotoxic T cells, eventually contributing to the elimination of infected virus cells [46]. The generation of immunity to the vector is an essential consideration for the development of virus vectored vaccines, which could impede the antigen-specific response to boost vaccination [49]. Reports from preclinical and clinical trials suggested that adequate safety can be obtained from a single dose [50].

Ad5-nCoV (CanSino Biologics Inc., Beijing Institute of Biotechnology)

A four-fold increase in RBD and S protein-specific neutralizing antibodies was observed within 14 days [51]. Ad5-nCoV is a recombinant type-5 adenovirus (Ad5) replication-defective vector expressing the recombinant SARS-CoV-2 spike protein. It was prepared by cloning, together with the plasminogen activator signal peptide gene, an optimized full-length gene of the S protein in the Ad5 vector devoid of genes E1 and E3 [29]. The vaccine was constructed from the Microbix Biosystem using the Admax system. A positive antibody reaction or seroconversion of immunization was identified in phase I clinical trials and peaked at day 28, post-vaccination. Also, the response of CD4+T cells and CD8+T cells peaked at day 14 post-vaccination. However, the pre-existing anti-Ad5 immunity has partially restricted the reaction of both the antibody and the T cell [51]. The study would further assess the antibody response in recipients between 18 and 60 years of age who received one of three doses in the study, with follow-up at 3- and 6-months post-vaccination [29].

Coroflu (University of Wisconsin-Madison, FluGen, Bharat Biotech)

M2SR, a self-limiting variant of the influenza virus that is modified by spike protein sequence insertion of the SARS-CoV-2 gene. Besides, the vaccine expresses the influenza virus' hemagglutinin protein, thereby triggering an immune response to both viruses [52]. The M2SR is self-limiting and, since it lacks the M2 gene, does not undergo replication. It is capable of entering the cell, thereby causing immunity to the virus [32]. It is delivered intra-nasally, mimicking the normal viral infection pathway. Compared to intramuscular injections, this route stimulates many immune system modes and has higher immunogenicity [52].

LV-SMENP-DC (Shenzhen Geno-Immune Medical Institute)

By using SMENP minigenes to engineer dendritic cells (DC) with a lentiviral vector expressing the conserved domains of the structural proteins SARS-CoV-2 and protease [29], the LV-SMENP-DC vaccine is prepared. Subcutaneous vaccine inoculation introduces antigen-presenting cell antigens, which eventually cause cytotoxic T cells and produce an immune response [48].

ChAdOx1 (University of Oxford)

The recombinant adenovirus vaccine ChAdOx1 was developed using codon-optimized S glycoprotein and synthesized at the 5 ends with the leading tissue plasminogen activator (tPA) sequence [50]. The SARS-CoV-2 amino acid coding sequence (2 to 1273) and the tPA leader have been propagated in the shuttle plasmid. This shuttle plasmid is responsible for the coding between the Gateway recombination cloning site of the main immediate-early genes of the human cytomegalovirus (IE CMV) along with tetracycline operator sites and polyadenylation signal from bovine growth hormone (BGH) [29]. In the bacterial artificial chromosome, the adenovirus vector genome is built by inserting the SARS-CoV-2 S gene into the ChAdOx1 adenovirus genome's E1 locus. In the T-Rex human embryonic kidney 293 (HEK-293) cell lines, the virus was then allowed to replicate and purified by ultracentrifugation of the CsCl gradient [53]. The absence of any subgenomic RNA from preclinical trials in intra-muscularly vaccinated animals is suggestive of improved immunity to the virus [50]. Previous studies have proposed that the immune response should be marshalled by a single shot [53]. In Table 2, potential viral vector-based vaccine candidates are listed below for COVID-19 which are in the clinical development phase and registered globally [45,54-61].

Protein Subunit-Based Vaccines

Subunit vaccines, safer and more straightforward to manufacture, present a host with high immunogenicity with one or few antigens, but need adjuvants to evoke a strong defensive immune response [62]. A subunit vaccine is a synthetic peptide or recombinant antigenic protein-dependent vaccine which is essential for long-term protection and a therapeutic invigoration of the immune response [63]. The subunit vaccine exhibits low immunogenicity and requires an adjuvant's additional assistance to potentiate the vaccine-induced immune responses. An adjuvant may improve the biological

Table 2. Potential viral vector-based vaccine candidates for COVID-19 in the clinical development pipeline

No.	Title	Description	Vaccine candidate	Phase trial	Sponsor and collaboration	Reference
1	Clinical trial to evaluate the safety and immunogenicity of the COVID-19 vaccine (COVID-19-101)	This is a randomized, placebo-controlled, two-center, trial in healthy adult volunteers to investigate the safety, tolerability, and immunogenicity of a novel measles-vector-based vaccine candidate against SARS-CoV-2 infection (TMV-083).	Measles-vector based	Phase 1	Sponsor: Institute Pasteur Collaborator: Themis Bioscience GmbH, Coalition for Epidemic Preparedness Innovations	NCT04497298 [54]
2	A phase I clinical trial of influenza virus vector COVID-19 vaccine for intranasal spray (DelNS1-2019-nCoV-RBD-OPT1)	The effect of pre-existing antibodies against influenza A (H1N1) virus on the immunogenicity of Influenza virus vector COVID-19 vaccine for intranasal spray (DelNS1-2019-nCoV-RBD-OPT1) in a healthy population for safety.	Intranasal flu-based-RBD	Phase 1	Sponsor: Beijing Wantai Biological Pharmacy Collaborator: Xiamen University	ChiCTR2000037782 [45]
3	A phase I/II study to determine efficacy, safety, and immunogenicity of the candidate coronavirus disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers	To assess the efficacy of ChAdOx1 nCoV-19 against COVID-19. To assess the safety of the candidate vaccine ChAdOx1 nCoV.	ChAdOx1-S	Phase 1/2	Sponsor: University of Oxford Collaborator: AstraZeneca	2020-001072-15 [55]
4	A phase III study to investigate a vaccine against COVID-19	This study aims to assess whether healthy people in Brazil can be protected from COVID-19 with a new vaccine called ChAdOx1 nCoV-19.	ChAdOx1-S	Phase 3	Sponsor: University of Oxford Collaborator: AstraZeneca	ISRCTN89951424 [56]
5	Study of AZD1222 for the prevention of COVID-19 in Japan	A safe and effective vaccine for COVID-19 prevention would have a significant global public health impact because currently, there are no licensed preventions available against COVID-19.	AZD1222	Phase 1/2	Sponsor: AstraZeneca Collaborator: Iqvia Pty. Ltd.	NCT04568031 [57]
6	Phase III double-blind, placebo-controlled study of AZD1222 for the prevention of COVID-19 in adults	The study aims to assess the safety, efficacy, and immunogenicity of AZD1222 for the prevention of COVID-19.	AZD1222	Phase 3	Sponsor: AstraZeneca Collaborator: Iqvia Pty. Ltd.	NCT04516746 [57]
7	Replication defective simian adenovirus (GRAd) encoding S	RT-CoV-2 is an open-label, dose-escalation multicenter clinical trial to assess the safety and immunogenicity of the candidate COVID-19 vaccine GRAd-CoV-2 in healthy Italian volunteers aged 18–55 years and 65–85 years inclusive.	Replication defective simian adenovirus (GRAd) encoding S	Phase 1	Sponsor: ReiThera Srl Collaborator: Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani	NCT04528641 [58]
8	A clinical trial of a recombinant adenovirus 5 vectored COVID-19 vaccine (Ad5-nCoV) with two doses in healthy adults	This is a clinical trial to evaluate the safety and immunogenicity of a recombinant Ad5-nCoV with two doses and with different administration routes in healthy adults aged 18 years and older.	Ad5-nCoV	Phase 1	Sponsor: Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China Collaborator: Zhongnan Hospital	NCT04552366 [59]
9	Safety and immunogenicity trial of an oral SARS-CoV-2 vaccine (VXA-CoV2-1) for prevention of COVID-19 in healthy adults	VXA-CoV2-1 is a non-replicating Ad5 vector adjuvanted tableted vaccine being developed to prevent COVID-19.	Ad5 adjuvanted oral vaccine platform	Phase 1	Vaxart	NCT04563702 [60]
10	Safety, tolerability, and immunogenicity of the candidate vaccine MVA-SARS-2-S against COVID-19	In this clinical trial, healthy volunteers in two different dose cohorts will be vaccinated twice with the candidate vaccine MVA-SARS-2-S.	MVA-SARS-2-S	Phase 1	Sponsor: Universitätsklinikum Hamburg-Eppendorf Collaborator: German Center for Infection Research, Philipps University Marburg Medical Center, Ludwig-Maximilians–University of Munich	NCT04569383 [61]

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RBD, receptor-binding domain; MVA, modified vaccinia Ankara.

half-life of the antigenic material, or the immunomodulatory cytokine response may be improved. The use of an adjuvant, therefore, helps to overcome the shortcomings of the protein subunit vaccines [64]. Subunit vaccines may be designed to concentrate the immune response on the neutralization of epitopes, thus preventing the development of non-neutralizing antibodies that may encourage disease-related antibody-dependent enhancement [65]. Antigenic proteins thought to cause a defensive immune response are used in protein subunit vaccines. The S protein of SARS-CoV-2 is the most appropriate antigen to induce neutralizing antibodies against the pathogen [13]. The S protein is comprised of two subunits. In the S1 subunit, the N-terminal domain, RBD, and receptor-binding motif (RBM) domains are found, while the S2 subunit consists of FP, HR 1, and 2 [62]. The virus reaches the cell by endocytosis using S-protein mediated binding to the human angiotensin-converting enzyme 2 (hACE2) receptor. Therefore, S-protein and its antigenic fragments are key objectives for the establishment of a subunit vaccine [63]. A complex protein with two conformation states, i.e., a pre-fusion and post-fusion state, is the S glycoprotein [62]. Therefore, the antigen must maintain its surface chemistry and the profile of the initial pre-fusion spike protein to retain the epitopes for igniting good quality antibody responses. Also, targeting the masked RBM as an antigen, it will increase the neutralizing antibody response and enhance the overall efficacy of the vaccine [66].

NVX-CoV2373 (Novavax Inc., Emergent BioSolutions)

NVX-CoV2373 is a nano-particle-mediated immunogenic vaccine-mediated on coronavirus S-protein, the recombinant expression of stable pre-fusion [67]. In the baculovirus system, the protein has been stably expressed. By inducing high levels of neutralizing antibodies, the company aims to use the matrix-M adjuvant to strengthen the immune response against the SARS-CoV-2 spike protein [35]. A single immunization in animal models resulted in a high level of anti-spike protein antibodies that blocked the binding domain of the hACE2 receptor and could elicit SARS-CoV-2 wild-type virus-neutralizing antibodies [68].

Molecular clamp stabilized spike protein vaccine candidate

It is being developed in partnership with GSK and Dynavax by the University of Queensland [29]. The University will have access to the vaccine adjuvant (AS03 Adjuvant) platform technology, which is believed to enhance the response of the vac-cine and reduce the amount of vaccine needed per dose [69]. The University is developing a stabilized pre-fusion, recombinant viral protein subunit vaccine based on the molecular clamp technology. It has been established that this technology induces the development of neutralizing antibodies [34].

PittCoVacc (University of Pittsburgh)

It is a recombinant SARS-CoV-2 vaccine based on the microneedle array (MNA) that involves administering rSARS-CoV-2 S1 and rSARS-CoV-2-S1fRS09 (recombinant immunogens) [70]. A significant increase in statistically significant antigen-specific antibodies was found in the mice models in preclinical studies at the end of 2 weeks [29]. Furthermore, even after sterilization using gamma rays, the immunogenicity of the vaccine was maintained. Statistically, relevant antibody titers confirm the feasibility of the MNA-SARS-CoV-2 vaccine at the early stage and even before boosting [70].

Triple antigen vaccine (Premas Biotech, India)

It is a multi-antigenic VLP vaccine prototype in which an engineered Saccharomyces cerevisiae expression platform (D-CryptTM) co-expresses the recombinant spike, membrane, and envelope protein of SARS-CoV-2 [71]. The proteins then, like the VLP, undergo self-assembly. The biophysical characterization of the VLP was simultaneously given by the transmission electron microscopy and allied analytical data [29]. After more research and development, this prototype has the potential to engage in preclinical trials as a vaccine candidate. Besides, cost-effectively, it is assumed to be safe and easy to produce on a mass scale [71]. In Table 3, potential protein subunit-based vaccine candidates are listed below for COVID-19 which are in the clinical development phase and registered globally [45,72-83].

DNA-Based Vaccines

A typical DNA vaccine is a plasmid DNA molecule that codes for the host immune system to be presented with one or more antigens [62]. They have the advantages of stability and successful delivery over mRNA vaccines [84]. Still, since they are needed to reach the nucleus, they have the risk of vector mutations and incorporation into the host genome [85]. DNA vaccines reflect a revolutionary approach, followed by a wide variety of immune responses, by the direct injection of plasmids encoding antigens [86]. The most groundbreaking approach to vaccination is the introduction of the DNA vaccine

Table 3. Potential protein subunit-based vaccine candidates for COVID-19 in the clinical development pipeline

No.	Title	Description	Vaccine candidate	Phase trial	Sponsor and collaboration	Reference
1	Evaluation of the safety and immunogenicity of a SARS-CoV-2 rS nanoparticle vaccine with/without matrix-M adjuvant	The study is designed to evaluate the safety and immunogenicity in 131 healthy participants ≥18 to 59 (inclusive) years of age at two sites in Australia.	Full-length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with matrix M	Phase 1/2	Sponsor: Novavax Collaborator: Coalition for Epidemic Preparedness Innovations	NCT04368988 [72]
2	A study looking at the effectiveness and safety of a COVID-19 vaccine in South African adults	This is a study to evaluate the effectiveness and safety of healthy HIV-negative (HIV-) adult participants and in medically stable HIV-positive (HIV+) adult participants in up to 10 sites across South Africa.	Full-length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with matrix M	Phase 2	Novavax	NCT04533399 [73]
3	Phase I clinical study of recombinant novel coronavirus vaccine	In this trial, a total of 50 subjects were recruited; the test vaccines were divided into three groups, low-dose, high-dose vaccine groups, and placebo groups.	Adjuvanted recombinant protein (RBD-Dimer)	Phase 1	Sponsor: Anhui Zhifei Longcom Biologic Pharmacy Co. Ltd. Collaborator: Beijing Chao Yang Hospital	NCT04445194 [74]
4	Recombinant new coronavirus vaccine (CHO cells) to prevent SARS-CoV-2 phase i clinical trial (≥60 years old)	To evaluate the safety and tolerability of recombinant new coronavirus vaccine (CHO cells) to explore the immunogenicity and durability of different doses.	Adjuvanted recombinant protein (RBD-Dimer)	Phase 1/2	Anhui Zhifei Longcom Biologic Pharmacy Co. Ltd.	NCT04550351 [75]
5	KBP-201 COVID-19 vaccine trial in healthy volunteers	This is a FIH, observer-blinded, randomized, placebo-controlled, parallel-group study to evaluate the safety and immunogenicity of the KBP-COVID-19 vaccine.	RNA-based protein subunit	Phase 1/2	Kentucky Bioprocessing Inc.	NCT04473690 [76]
6	Study of recombinant protein vaccine formulations against COVID-19 in healthy adults 18 years of age and older	The objective of the study is to describe the neutralizing antibody profile and safety profile of all participants in each group up to 12 months post-last injection.	S protein (baculovirus production)	Phase 1/2	Sponsor: Sanofi Pasteur, a Sanofi Company Collaborator: GlaxoSmithKline	NCT04537208 [77]
7	A study to evaluate the safety, tolerability, and immunogenicity of UB-612 COVID-19 vaccine	This is an open-label, dose-escalation clinical study of 3 ascending doses of UB-612 COVID-19 vaccine in healthy adults, aged from 20 to 55 years old.	S1-RBD-protein	Phase 1	Sponsor: United Biomedical Inc., Asia Collaborator: COVAXX	NCT04545749 [78]
8	SCB-2019 as COVID-19 vaccine	This is a randomized, double-blind, placebo-controlled, FIH study to assess safety, reactogenicity, and immunogenicity of SCB-2019 at multiple dose levels.	Native like trimeric subunit spike protein vaccine	Phase 1	Clover Biopharmaceuticals AUS Pty. Ltd.	NCT04405908 [79]
9	Monovalent recombinant COVID19 vaccine (COVAX19)	This is a study to test a new vaccine (Covax-19) against COVID-19	Recombinant spike protein with Advax adjuvant	Phase 1	Sponsor: Vaxine Pty. Ltd. Collaborator: Central Adelaide Local Health Network Incorporated	NCT04453852 [80]
10	An interventional study to evaluate the safety and immune response of a vaccine against SARS-CoV-2, when given to healthy adult participants	To assess the safety and tolerability of SARS-CoV-2 Sclamp vaccine compared to placebo by evaluating solicited local adverse events will be evaluated by severity score, frequency, duration, and intensity by FDA toxicity scoring.	Molecular clamp stabilized spike protein with MF59 adjuvant	Phase 1	University of Queensland, CSL, Seqirus	ACTRN12620000674932 [81]

(Continued on next page)

Table 3. Continued

No.	Title	Description	Vaccine candidate	Phase trial	Sponsor and collaboration	Reference
11	A study to evaluate the safety and immunogenicity of MVC-COV1901 against COVID-19	This is a prospective, open-labelled, single-center study to evaluate the safety and immunogenicity of MVC-COV1901.	S-2P protein+CpG 1018	Phase 1	Medigen Vaccine Biologics Corp.	NCT04487210 [78]
12	Study of the safety, reactogenicity, and immunogenicity of "EpiVacCorona" vaccine for the prevention of COVID-19 (EpiVacCorona)	The research tasks are to evaluate the safety, reactogenicity of the EpiVacCorona vaccine when administered twice intramuscularly and to identify the development of adverse.	Peptide	Phase 1	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	NCT04527575 [82]
13	A randomized, double-blind, placebo-controlled phase I trial for anti-novel coronavirus pneumonia (COVID-19) recombinant vaccine (Sf9)	The aim is to evaluate the safety, tolerability, and immunogenicity of a recombinant SARS-CoV-2 vaccine (Sf9 cell) in a healthy Chinese population aged 18 years and older.	RBD (baculovirus production expressed in Sf9 cells)	Phase 1	West China Hospital, Sichuan University	ChiCTR2000037518[45]
14	Safety and immunogenicity trial of multi-peptide vaccination to prevent COVID-19 infection in adults (pVAC)	To evaluate the safety and immunogenicity of a single use of a SARS-CoV-2-derived multi-peptide vaccine in combination with the toll-like receptor 1/2 ligand XS15 in adults.	SARS-CoV-2 HLA-DR peptides	Phase 1	University Hospital Tuebingen	NCT04546841 [83]

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HIV, human immunodeficiency virus; RBD, receptor-binding domain; FIH, first-in-human; FDA, U.S. Food and Drug Administration.

that codes for the antigen and an adjuvant that stimulates the adaptive immune response [87]. The transfected cells express the transgene, which gives a steady supply of transgene-specific proteins very similar to the live virus [84]. Also, immature DCs, which eventually present the antigen on the cell surface to the CD4 + and CD8 + T cells in combination with the major histocompatibility complex (MHC) 2 and MHC 1 antigens, endocytose the antigen material, thereby stimulating both successful humoral and cell-mediated immune systems [87]. DNA vaccines are considered safe and stable and can be developed easily, but their immunogenicity and immune response efficiency in humans have not yet been demonstrated [21].

INO-4800 (Inovio Pharmaceuticals)
It is an anti-SARS-CoV-2 prophylactic DNA vaccine. It uses the SARS-CoV-2 codon-optimized S protein sequence to which an immunoglobulin E (IgE) leader sequence is attached [29]. Using BamHI and XhoI, the SARS-CoV-2 IgE-spike sequence was synthesized and digested. Under the management of IE CMV, and BGH polyadenylation signal, the digest-

ed DNA was incorporated into the expression plasmid pGX0001 [85]. In preclinical studies, the existence of functional antibodies and the response of T cells indicate that the vaccine will produce an efficient immune response within seven days after vaccination [88]. The vaccine has entered phase I clinical trials (phase I: NCT04336410) and it is anticipated that this phase of clinical trials will be completed by July, with participants receiving 1.0 mg of INO-4800 by electroporation with CELLECTRA 2000 per dosing visit. The research will assess the immunological profile, efficacy, and tolerability of the candidate vaccine in healthy human adults upon intradermal injection and electroporation [29]. INO-4800 and the previous Inovio vaccine INO-4700 express either SARS-CoV-2-S or MERS-CoV-S inside the same DNA vector, respectively [85]. The vaccine is delivered by intramuscular injection, accompanied by injection site electroporation. The need for electroporation could restrict INO-4800's ability to be expanded to the scales necessary for a global pandemic and may be difficult to handle globally [13].

Table 4. Potential DNA-based vaccine candidates for COVID-19 in the clinical development pipeline

No.	Title	Description	Vaccine candidate	Phase trial	Sponsor and collaboration	Reference
1	Safety, tolerability, and immunogenicity of INO-4800 followed by electroporation in healthy volunteers for COVID-19	INO-4800 was administered by intradermal injection followed by electroporation using the CELLECTRA 2000 device in healthy adults aged 19 to 64 years of Korea.	DNA plasmid vaccine with electroporation	Phase 1/2	Sponsor: International Vaccine Institute Collaborator: Inovio Pharmaceuticals	NCT04447781 [89]
2	Safety, tolerability, and immunogenicity of INO-4800 for COVID-19 in healthy volunteers	This is an open-label trial of INO-4800 which contains the plasmid pGX9501, which encodes for the full length of the Spike glycoprotein of SARS-CoV-2.	DNA plasmid vaccine with electroporation	Phase 1	Sponsor: Inovio Pharmaceuticals Collaborator: Coalition for Epidemic Preparedness Innovations	NCT04336410 [90]
3	Study of COVID-19 DNA vaccine (AG0301-COVID19)	This is a single-center, non-randomized, open-label, non-controlled trial. 30 healthy volunteers aged 20–65, will be enrolled for low and high dose group.	DNA plasmid vaccine+ adjuvant	Phase 1/2	Sponsor: AnGes Inc. Collaborator: Japan Agency for Medical Research and Development	NCT04463472 [91]
4	Study of COVID-19 DNA vaccine (AG0302-COVID19)	This study will assess the safety and immunogenicity of AG0302-COVID19 in healthy adult volunteers.	DNA plasmid vaccine+ adjuvant 2	Phase 1/2	AnGes Inc.	NCT04527081 [92]
5	Novel corona virus-2019-nCov vaccine by intradermal route in healthy subjects	A prospective, randomized, adaptive clinical study to evaluate the safety and immunogenicity of novel corona virus-2019-nCov vaccine candidate.	DNA plasmid vaccine	Phase 1/2	Cadila Healthcare Limited	CTRI/2020/07/026352 [93]
6	Safety and immunogenicity study of GX-19, a COVID-19 preventive DNA vaccine in healthy adults	This clinical study is to evaluate the safety, tolerability, and immunogenicity of the COVID-19 preventive vaccine by intramuscular administration in healthy volunteers.	DNA Vaccine (GX-19)	Phase 1/2	Genexine Inc.	NCT04445389 [94]

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

bacTRL (Symvivo Corporation)

Symvivo Corporation's bacTRL platform uses the engineered probiotic *Bifidobacterium* longum to deliver a SARS-CoV-2-S expressing DNA vaccine into intestinal cells. The first-in-man study of the bacTRL platform will also be a phase I study of the COVID-19 vaccine, so no prior immunological results are available [13]. In Table 4, DNA-based vaccine candidates are listed below for COVID-19 which are in the clinical development phase and registered globally [89-94].

Virus-Like Particles Vaccine

VLPs are particles that form spontaneously, consisting of many co-expressed or mixed structural viral proteins. Several commercial vaccines are based on VLPs, such as hepatitis B and human papillomavirus vaccines [95]. Without the need for adjuvants, these vaccines can be constructed and used. Only when antigens with neutralizing epitopes are extensively investigated is the production of such vaccines possible [22]. A VLP is a self-assembled nanostructure incorporating essential viral structural proteins. VLP is similar to true viruses' molecular and morphological features but is non-infectious and non-replicating due to the absence of genetic materials [26]. Successful applications of VLP have been proved by vaccinological and virological study [95]. In the ongoing battle against the COVID-19 pandemic, the development of SARS-CoV-2 VLPs is highly in demand as an accessibly safe and relevant substitute for naturally pathogenic viruses [26]. A study suggested the possible use of plant biotechnology for the development of low-cost COVID-19 vaccines and plant-made antibodies for diagnosis, prophylaxis, and therapy [22].

In the current research, we have established SARS-CoV-2 VLPs effectively, using the mammalian expression system [47], which helps maintain specific patterns of protein glycosylation [22]. For the efficient formation and release of SARS-CoV2 VLPs among the four SARS-CoV-2 structural proteins, we have shown that membrane protein (M) expression and small envelope protein (E) are essential [47]. Also, the corona-like structure presented in SARS-CoV-2 VLPs from Vero E6 cells is more stable and unified in comparison with those

Table 5. Potential VLPs-based vaccine candidates for COVID-19 in the clinical development pipeline

No.	Title	Description	Vaccine candidate	Phase trial	Sponsor and collaboration	Reference
1	A phase 1/2 randomized, placebo-controlled, multicentre study to evaluate the safety and immunogenicity of COVID-19 vaccine in healthy adults	RBD SARS-CoV-2 HBsAg VLP vaccine, administered at two dose amounts 5 mcg and 25 mcg, by intramuscular injection by investigators during an in-clinic visit.	RBD-HBsAg VLPs	Phase 1/2	Sponsor: SpyBiotech Collaborator: Serum Institute of India	ACTRN12620000817943 [81]
2	Safety, tolerability, and immunogenicity of a coronavirus-like particle COVID-19 vaccine in adults aged 18–55 years	The study will be a randomized, partially-blinded, prime-boost, staggered dose-escalation study at three dose levels (3.75 µg, 7.5 µg, and 15 µg VLP).	Plant-derived VLP was adjuvanted with GSK or Dynavax adjs.	Phase 1	Medicago	NCT04450004 [99]

VLP, virus-like particle; COVID-19, coronavirus disease 2019; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HBsAg, Hepatitis B surface antigen.

from HEK-293 T cells. Our data show that the molecular and morphological characteristics of native virion particles in SARS-CoV-2 VLPs make SARS-CoV-2 VLPs a promising candidate vaccine and a powerful tool for research into SARS-CoV-2 [96]. The immunogenic composition composed of MERS-CoV nanoparticle VLPs containing at least one trimer of S protein formed by baculovirus overexpression in Sf9 cells was disclosed in patent application WO2015042373 by Novavax in 2015 [35]. When administered along with their patented adjuvant Matrix M, this VLP preparation induced a neutralizing antibody response in mice and transgenic cattle. Sera preparations from vaccinated cattle (SAB-300 or SAB-301) were also injected into Ad5-hDPP4 transduced BALB/c mice before the MERS-CoV challenge [22]. With a single prophylactic injection, both SAB-300 and SAB-301 were able to protect these mice from MERS-CoV infection [96]. On 26 February, Novavax announced that due to their prior experience dealing with other coronaviruses, including both MERS and SARS, animal testing of possible COVID-19 vaccine candidates had begun. Using their recombinant nanoparticle vaccine technology along with their proprietary adjuvant matrix-M, their COVID-19 candidate vaccines targeting the S protein of SARS-CoV-2 were created [35].

UMass Medical School researchers have developed a framework to create vaccines using VLPs, which one scientist claims may be a successful and safer alternative to a COVID-19 vaccine. Trudy Morrison, Ph.D., professor of Microbiology & Physiological Systems, said her work on a VLP-based respiratory syncytial virus vaccine that can be modified to COVID-19 causes severe lower respiratory tract disease in young children and the elderly. And some of the problems inherent in the production of vaccines from inactivated or live viruses will be avoided [97].

Medicago, a biopharmaceutical company, headquartered in Quebec City, announced the successful development of a coronavirus VLP only 20 days after the SARS-CoV-2 (COVID-19 disease virus) gene was obtained [29]. The manufacturing of VLP is the first step in the development of the COVID-19 vaccine, which will now undergo preclinical protection and efficacy testing. They plan to negotiate clinical testing of the vaccine with the relevant health authorities by summer (July/August) 2020 once this is done. Medicago uses its technology platform to create antibodies against SARS-CoV-2. These antibodies to SARS-CoV-2 might theoretically be used to treat people who are infected by the virus. In part, this study is sponsored by the Canadian Institutes for Health Research [98]. In Table 5, potential VLPs-based vaccine candidates are listed below for COVID-19 which are in the clinical development phase and registered globally [81,99].

Current Updates

To bring this pandemic to an end, a large share of the world needs to be immune to the virus. The safest way to achieve this is with a vaccine. Vaccines are a technology that humanity has often relied on in the past to bring down the death toll of infectious diseases. Within less than 12 months after the beginning of the COVID-19 pandemic, several research teams rose to the challenge and developed vaccines that protect from SARS-CoV-2, the virus that causes COVID-19. Now the challenge is to make these vaccines available to people around the world.

Conclusion

To resume a normal lifestyle, free from government lockdowns, and fear of continuing pandemic waves over the coming months, the world is anxiously awaiting a safe, successful vaccine to protect against COVID-19. Innovative ties with both pharmaceutical companies and medical start-ups are joining hands with scientists across the continents to repurpose medications, create vaccines, and devices to hinder the progress of this overwhelming pandemic. A large number of vaccine candidates for COVID-19 based on different platforms have already been identified. Current review shows preclinical as well as in clinical development of vaccine candidates, wherein, five major vaccine platforms for COVID-19 namely RNA, DNA, viral vector, protein subunit, and VLP which constitutes 10, 2, 10, 14, and 2 vaccine candidates globally in clinical development as of 15 October 2020. Among all the vaccine platforms, extensive research and development are going on protein subunit-based vaccine which has the maximum candidates in the clinical development.

A significant amount of hindrance to the rapid production of vaccines is the length of clinical trials. With several phases, including the preclinical stage and clinical development, which is a three-phase process, the vaccine development process is very laborious. However, if adequate data is already available, it has been proposed that a few stages be skipped to accelerate the achievement of a vaccine faster with a rapid regulatory review, approval, development, and quality control. By looking towards pandemic conditions, the scientific fraternity will be ready for any harmful situation to overwhelmed opportunities. Therefore, the current situation has given the world a new perspective to facilitate research in the worst circumstances and hasten the drug development process.

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