Potential Immunotherapy against SARS-CoV-2: Strategy and Status

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Abstract: SARS-CoV-2, the novel coronavirus that was first reported in Wuhan, China in December 2019, has engrossed the world with immense distress. It has shattered the global healthcare system and has inflicted so much pain on humanity. COVID-19, the disease caused by a microscopic enemy, has now spread to almost all the countries in the world affecting millions of people and causing enormous casualties. World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2019. As of June 15, 2020, almost 7.70 million people have already been infected globally with 428,000 reported casualties. In the United States alone, 2.14 million people have been infected and 117,000 people have succumbed to this pandemic. A multipronged approach has been launched towards combating this pandemic with the main focus on exhaustive screening, developing efficacious therapies, and vaccines for long-term immunity. Several pharmaceutical companies in collaboration with various academic institutions and governmental organizations have started investigating new therapeutics and repurposing approved drugs so as to find fast and affordable treatments against this disease. The present communication aims at highlighting the efforts that are currently underway to treat or prevent SARS-CoV-2 infection through immunotherapy. Emphasis has been laid on discussing the approaches and platforms that are being utilized for the speedy development of therapeutic antibodies and preventive vaccines against SARS-CoV-2. The manuscript also presents a detailed discussion regarding strategy, clinical status, and timeline for the development of safe and enduring immunotherapy against SARS-CoV-2. All the details pertaining to the clinical status of each candidate have been last updated on June 15, 2020.

Keywords: COVID-19, SARS-CoV-2, ACE2 receptors, immunotherapy, monoclonal antibodies, Vaccines.

1. INTRODUCTION

Pandemic caused by COVID-19 has shattered the global healthcare system, besides it has deleteriously impacted social, political and economic aspects of life. The causative agent is a betacoronavirus which has genealogy closely related to severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV-1), thus earning the name SARS-CoV-2 [1]. This virus has already been identified and well-characterized [2]. SARS-CoV-2 belongs to the Coronaviridae family, the members of which contain a special glycoprotein that decorates their lipid-protein bilayer, giving them a crown-like appearance as seen under an electron microscope. The family consists of two subfamilies: Letovirinae and Orthocorovirinae, with the latter consisting of four genera, Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Delta-coronavirus [3]. SARS-CoV-2 is a betacoronavirus like its predecessors SARS-CoV-1 and MERS-CoV. Almost all members of this family consist of a large, single-stranded positive-sense RNA genome (30+ kb), the spike protein (S protein) that decorates the lipid-protein bilayer which envelope multiple copies of the nucleocapsid protein (N-protein) bound to the viral genome [4]. S Protein is a class I fusion protein which is responsible for attaching the virus to cell surface receptors, significantly, the angiotensin-converting enzyme-2 (ACE2) receptors [5]. These receptors are mainly attached to lung type II alveolar cells, arterial smooth muscle cells, arterial and venous endothelial cells and enterocytes of the small intestine [6]. ACE2 receptors are also expressed in the cerebral cortex, hypothalamus, brainstem and thus in cortical neurons and glia [7]. This accounts for the fact why COVID-19 patients report serious respiratory and neurological conditions [8,9].

An endosomal uptake followed by proteolytic cleavage of the S protein and fusion of the endosomal and viral membranes leads to the release of viral RNA into the cytosol [10]. Exhaustive replication of the virus inside the host cells and subsequent release of the progeny viruses through secretory vesicles create multiple copies of the virus in the host. Infected carriers are the primary transmission sources shedding viruses into the environment. Droplets from an infected person lead to person-to-person transmission [11]. However, community spread has also been reported in certain geographical regions [12].
2. SYMPTOMS AND PATHOGENESIS

Early symptoms of COVID-19 include persistent fever, breathlessness, chest and muscle pain, cough and chills, etc. Severe conditions include constant chest pain, trouble breathing, bluish lips or face and sudden confusions [13]. The fatality rate is age-dependent with older patients suffering from other conditions at high risk of succumbing to the disease. Less than 20% of the reported cases are severe. The average case fatality rate (CFR) is approximately 1%-3% [14]. The reproductive number (R₀), which represents the number of cases generated directly by one in a 100% susceptible population, is calculated, on an average, at 2-3 [15]. Taking into consideration the severity of the disease and crisis faced globally, immediate and early mitigation mechanisms are needed. Effective therapeutics and vaccines, produced within defined timelines, have become indispensable.

3. VACCINE STRATEGY

Immunotherapy is the most effective first-line defense against any pathogenic disease [16]. While therapeutic antibodies support the defense, vaccines reinvigorate the defense arsenal, keeping it ready for subverting future attack of defined pathogens. Unlike age-old protocols, vaccine technology has significantly evolved over the past few years. With the advent of genomic sequencing techniques, commercial development of several RNA and DNA vaccines, recombinant protein vaccines, vectored vaccines and cell-culture based vaccines, has been highly successful [17]. Analogous to SARS-CoV-1 and MERS-CoV vaccines, S protein is an ideal target for SARS-CoV-2 vaccines [18], owing to the fact that this protein is solely responsible for attachment of the virus to the host receptors. Antibodies targeting the spike protein will limit its binding, thus neutralizing the virus before it enters the host cells. Since the full genome sequencing of SARS-CoV-2 was achieved and made available in record time [2], the high-resolution structure of the spike protein handed us a target antigen that can be exploited and incorporated into advanced vaccine platforms.

In the case of SARS-CoV-1, several vaccine types like recombinant S protein-based vaccines, vectored vaccines and attenuated and whole inactivated vaccines were developed and tested in animal models [19]. However, many of these vaccines posed safety challenges. Exposure to coronaviruses does not induce long-lasting antibody response implying that the survivors can again be at risk of contracting the disease [20]. Thus vaccines against COVID-19 need to be safer with long-lasting effects to protect against endemic and recurrent seasonal epidemics by the virus. Further, as the data indicates now, older people are at a higher risk of developing severe pathology upon SARS-CoV-2 infection [21]. The fact that older people respond low to vaccinations because of immune senescence, vaccines with higher antigen dose amounts or adjuvants, shall be needed for this population segment. Listed below are a series of potential immunotherapies that are currently being investigated at different clinical stages for use against COVID-19. Therapeutic antibodies have been classified on the basis of their target while vaccines candidates have been categorized on the basis of their developmental platforms (Table 1).

4. THERAPEUTIC ANTIBODIES

Several pharmaceutical companies are exploiting different targets for developing therapeutic antibodies against COVID-19. Some of the antibodies are being developed to work against the spike protein of the virus while others aim at targeting the inflammatory cytokines responsible for inducing the fatal cytokine release syndrome (CRS) which leads to organ failure and death. Another strategy is based on using the inactivated convalescent plasma from recovered COVID-19 patients containing apposite antibodies and using the same in patients who are currently afflicted by the virus.

4.1. Anti-inflammatory Therapeutic Antibodies; Clinical Stage: Phase II/III

In response to certain infections, our immune system overproduces certain cytokines resulting in a fatal condition called cytokine response syndrome (CRS) which is characterized by systemic hyperinflammation that damages the patient's tissues leading to organ failure and death. French pharma giant, Sanofi, and American biotech, Regeneron pharmaceuticals, are working on Kevzara (sarilumab, a fully human monoclonal antibody), an approved anti-inflammatory drug that is showing promise in preliminary results against symptoms of COVID-19 [22]. Kevzara is an interleukin-6 (IL-6) receptor antagonist [23] that is being evaluated against COVID-19 alongside similar inhibitors like EUSA Pharma's Sylvant and Roche's Actemra.

Kevzara was approved in 2017, both in the United States and Europe, as a drug for the treatment of rheumatoid arthritis [24-26]. The drug was recently repurposed for use against SARS-CoV-2 and showed promising results in the preclinical and clinical phase I trials. The companies have already started its phase II/III trials in various European countries besides Japan, Canada and Russia [27,28]. The IL-6 inhibitor calms down an overactive immune response in severe COVID-19 patients. The company expects an immediate launch of the drug pending approval and necessary permissions.

4.2. Antibodies Targeting the Viral Spike Protein; Clinical Stage: Phase I

As with pandemic SARS and MERS pathogens, SARS-CoV-2 backs on a surface ‘spike’ protein [29,30] to evade cellular defenses causing severe infection. Stopping this “spike” protein to reach its target, will be the eventual treatment of the disease. Decades ago, Regeneron succeeded in bending the curve of drug development by developing a full human immune system in mice through genetic engineering. This means the genetically engineered mice will produce human antibodies whenever exposed to any foreign agent. Previously, Regeneron has succeeded in transforming these antibodies to several commercial drugs like; Dupixent—a multibillion-dollar eczema drug; Libtayo—recently approved immunotherapy to cancer and REGN-EB3—a cocktail of three monoclonal antibodies against Ebola. With remarkable success in its antibody therapies, Regeneron is now considering its mice for treatment of COVID-19.

The full genome of SARS-CoV-2 has been sequenced to about 30,000 base pairs and that of the protein “spike” on the
Table 1. Overview of various immunotherapy platforms and their clinical progress against SARS-CoV-2.

| Immunotherapy Type | Platform and Type | Target | Developer | Clinical Stage |
|--------------------|-------------------|--------|-----------|---------------|
| Vaccines           | NLP-encapsulated mRNA (mRNA-1273) | S protein | Moderna Therapeutics | Phase II [NCT04283461] |
|                    | DNA (INO-4800)    | S protein | Inovio/Beijing Advanced Biotechnology | Phase I [NCT04336410] |
|                    | mRNA (BNT-162)    | S protein | BioNTech and Pfizer | Phase I |
|                    | STARR-mRNA (LUNAR-CoV19) | S protein | Arcturus/ Singapore Health Sciences Authority | Preclinical |
|                    | Non-replicating viral vector (AD5-nCoV) | S protein | CanSino/ Beijing Institute of Biotechnology | Phase I/II [ChiCTR200030906]/[ChiCTR200031781] |
|                    | Non-replicating viral vector (ChAdoX1 nCoV-19) | S protein | Oxford University | Phase II [NCT04324606] |
|                    | Non-replicating viral vector (Ad26.CoV2-S) | S protein | Janssen Pharmaceutical Co. | Phase I |
|                    | Subunit adjuvanted protein (NVX-CoV2373) | S-protein | Novavax | Phase II |
|                    | Adjuvanted protein | S-protein | GlaxoSmithKline and Sanofi | Preclinical |
|                    | Inactivated virus (CoronaVac) | Whole virion | SinoVac | Phase II |
| Therapeutic antibodies | Monoclonal antibody Kevzara (Sarilumab) | Interleukin-6 (IL-6) inhibition | Sanofi and Regeneron | Phase II/III |
|                    | Genetically engineered pseudovirus (REGN-CoV2) | S-protein | Regeneron | Phase I |
|                    | Monoclonal plasma antibody (LY-CoV555) | S-protein | Eli Lilly and AbCellera | Phase I |

surface of the virus boiling to roughly 10% of the total genome [31,32]. Regeneron has decorated the surface of some otherwise harmless particles with the cloned spike producing code. This generated a pseudovirus with similar spikes that would mimic cell-penetrant biology but would avoid the ability of the virus to replicate and cause illness. Antibodies produced by the genetically engineered mice against this pseudovirus will be eventually scrutinized and studied for human use. Such antibodies are expected to interrupt the virus breaking into the cell. On June 11, 2020, Regeneron announced the start of the first clinical trials of its anti-viral antibody cocktail, REGN-COV2, for the treatment and prevention of covid-19.

4.3. Therapeutic plasma antibodies; Clinical stage: Phase I

Inactivated convalescent plasma from recovered COVID-19 patients containing apposite antibodies can be used as a means of treatment in patients who are currently afflicted by the virus. Identification of the most effective antibodies and their securitization for use against COVID-19 is an interesting immunotherapy approach that requires shorter timelines for mass-production. Eli Lilly, in collaboration with Canadian firm AbCellera, has identified some 500 antibodies from the blood of COVID-19 survivors and is currently looking for the most potent ones which will be securitized and used in human studies [33,34]. On April 13, 2020, Chief Executive of Eli Lilly announced that safety and efficacy profiles are pending, and the company could make its potential therapeutic antibody drug available for emergency human use this fall.

On April 17, 2020, the National Institute of Health (NIH) announced that it will work with twelve reputed governmental and pharmaceutical companies including Eli Lilly towards exploring accelerated and better treatments and vaccines for COVID-19. On June 01, 2020, Eli Lilly started dosing COVID-19 patients in a phase I trial of its AbCellera-partnered antibody, LY-CoV555, which is per-
hap the first drug specifically designed against SARS-CoV-2.

5. VACCINES [35]

As per the available data and the report from the Centre for Disease Control (CDC), USA, less than 25% of confirmed COVID-19 patients need hospitalization. Although alarming, this, however, indicates that in the majority of the infected people, the immune system successfully eliminates the virus on its own. Nevertheless, sometimes the immune system may require extra information in the form of bits of the virus and some irritant that stimulates it to produce a swift and strong immune response which reverses spread of the virus within the body before the onset of symptoms or severe disease. Preventive vaccines provide the necessary training and information to the immune system enabling it to mount a response once the threat is encountered. Specialized T cells and antibody generating B cells are produced to neutralize the virus. Whereas antibodies can bind to the copies of the virus marking them for annihilation; T cells act on the infected cells and eradicate them before the virus can spread to other cells in the body.

There are different approaches and platforms on the basis of which vaccine development against COVID-19 is being pursued. The main approaches are gene (RNA or DNA) based vaccines; vaccines based on the live attenuated virus (adenovirus vector); protein subunit vaccines; and vaccines based on the inactivated virus.

5.1. Gene (RNA or DNA) Based Vaccines

These vaccines are made up of pieces of genetic material, either mRNA or DNA, that encode the instructions for making the protein. The mRNA or DNA then enters cells, which read the instructions and churn out copies of the protein for the immune system to rally against. Most of the coronavirus vaccines that use this method are introducing the gene that encodes a bit of the spike protein. The virus depends on the spike protein to break into cells and replicate. If the immune system is trained to recognize and block that protein, the virus cannot attack cells and continue to spread. Such vaccines are easy to manufacture which is necessary in the case of pandemics, but these are still experimental and no gene-based vaccine has yet been approved for human use.

Moderna therapeutics owned mRNA-1273 [NCT04283461] is a novel lipid nanoparticle (NLP) encapsulated m-RNA based vaccine that encodes for full length of the SARS-CoV-2 spike protein and is currently in phase II clinical trial. Just 42 days after the genome of SARS-CoV-2 was sequenced, Moderna therapeutics started the clinical trials of its vaccine candidate which is based on a synthetic strand of the virus's RNA that convinces cells to produce robust antibody response against the virus [36,37]. Forty-five participants were recruited for evaluating the safety, reactogenicity and immunogenicity of the vaccine formulation. The clinical study was carried out by the US National Institute of Health (NIH), at Kaiser Permanante Washington Health Research Institute at Seattle. Phase II clinical trials of the vaccine have already started and 600 participants aged 18 and above will be enrolled for this study [38]. On April 16, Moderna was awarded a mammoth $483 million fund by federal Biomedical Advanced Research and Development Authority (BARDA) to support the company’s resolve to produce a vaccine in record speed.

Inovio Pharmaceuticals has been working for decades with DNA based stuff aiming at turning DNA into medicine. With grant money from Coalition for Epidemics Preparedness Innovations (CEPI), Inovio is out with a DNA vaccine, INO-4800 [NCT04336410], which, it believes, can generate protective antibodies that can keep patients away from getting the infection. In partnership with a Chinese company, Beijing Advanced Biotechnology, the company is working on clinical studies with its vaccine candidate, INO-4800. As of April 19, 2020, Inovio has already started phase I clinical trial with 40 healthy volunteers participating in 2 trial locations in Philadelphia and Kansas City [39,40]. Preclinical animal studies have shown promising immune responses.

US FDA has accepted the company’s investigational new drug (IND), INO-4800, as the DNA vaccine [41]. DNA vaccines have the potential to be rapidly transformed into usable vaccines and Inovio has promised to manufacture one million doses of its candidate this year once the necessary permissions are granted.

Like other competitors, German company BioNTech and pharma giant Pfizer have started the clinical studies (phase I) of BioNTech’s mRNA based vaccine, BNT162, for the novel coronavirus [42]. This vaccine comprises mRNA strands to produce protective antibodies. Pfizer is considering to present a $748 million grant to BioNTech for a 50% share towards the clinical development, manufacturing and commercialization worldwide [43]. As of May 3, 2020, the clinical trials have started in Germany where twelve study participants have been dosed amongst the 200 healthy subjects included in the study. The company plans to administer doses ranging from 1 µg to 100 µg towards determining the optimal safe dose for optimal immunogenicity of the vaccine [44]. BioNTech has also signed a deal with Shanghai’s Fosun Pharma to market the vaccine in China, if it is eventually approved [45].

Arcturus therapeutics owned LUNAR-COV19 is a low dose, potential single shot (i.m), self-transcribing and replicating (STARR™) mRNA vaccine that is devoid of any viral material or co-adjutants [39]. LUNAR-COV19 has shown promising preclinical in-vitro results generating effective expressions of SARS-CoV-2 virus-like spike proteins, the antigen to which protective antibodies will be formed. As per the company’s protocol, its RNA based drugs are designed to direct the body to manufacture its own medicines. The company has already developed delivery systems and technologies that can deliver RNA directly to cells without being destroyed.

On April 27, 2020, the company reported highly optimistic preclinical data of its vaccine candidate in animal models, which supports the initiation of human clinical trials this summer. As per the data, 100% of animals seroconverted by day 19 at low doses of 2 µg [46]. The results showed STARR™ mRNA induced higher seroconversion relative to conventional mRNA at equivalent doses. Also, higher were the IgG and IgM antibody titers against SARS-CoV-2 (Table 2).
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5.2. Adenovirus Vector Vaccines

A vaccine based on whole, live but heavily weakened virus is one of the best ways to create strong and long-lasting immunity, as in the case of measles and chickenpox. However, the weakening of a virus at the commercial scale is very tough. Scientists make use of another live but already weakened vector virus called adenovirus for generating desired immunity. Adenoviruses carry snippets of the genetic material of other viruses into cells. In the case of COVID-19, the engineered adenovirus dumps a piece of the genetic material of the coronavirus, usually the snippet that encodes for the spike protein, into the cells. The cells then create multiple copies of the protein against which strong immune responses, activated by the live adenovirus, are produced. Adenovirus platforms for vaccine development are chiefly experimental, but, if successful, they are able to produce longer, more robust and more durable immunity, eliminating the requirement of booster doses.

As per the company's timeline for its COVID-19 vaccine, it will employ 76 healthy volunteers for clinical trials with follow-up over several months to evaluate the extent and duration of the immune response [47-49]. The company is coordinating with the Singapore Health Sciences Authority (HSA) which granted around $ 10 million to Arcturus for developing the vaccine [50]. The company has proposed to deliver the first GMP batch in June, 2020; and clinical trials will start early summer.

A German pharma company, Curevac, develops therapies based on man-made mRNA spurred protein production [51]. With working experience in SARS/MERS viruses since 2017, the company has recently been financially supported by European Union with an offer of €80 million to scale up the production and development of vaccine against SARS-CoV-2 in Europe. In collaboration with the coalition for epidemics preparedness innovations (CEPI) and Bill and Malinda Gates Foundation (BMGF), the company has selected its most suitable vaccine candidates for human screening [52,53].

As of April 10, 2020, the company has already identified two primary study centers for clinical trials of the vaccine constructs in coordination with German Paul Ehrlich Institute (PEI), for accelerated clinical development of the vaccine candidate in parallel. Depending on the results of the phase I study, which is set to start early ending June, 2020, the company expects to start its next phase of clinical studies early autumn with a significant number of participants [54]. Germany plans to invest €300m in the private biotech company CureVac, giving Berlin a 23 percent stake in the developer of a potential coronavirus vaccine that uses mRNA technology, which can produce a vaccine more swiftly than traditional methods.

### Table 2. Seroconversion Rate (% of Animals)– STARR™ mRNA vs. Conventional mRNA.

| Single Dose (µg) | LUNAR® Delivery |  |
|------------------|------------------|---|
|                  | STARR™ mRNA (%) | Conventional mRNA (%) |
|                  | Day 10 | Day 19 | Day 10 | Day 19 |
| 0.2              | 40    | 60    | 20    | 20    |
| 2                | 80    | 100   | 20    | 0     |
| 10               | 100   | 100   | 40    | 80    |

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Oxford University adenovirus vaccine, ChAdOx1 nCoV-19 [NCT04324606], is made from a virus (ChAdOx1), which is a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees, that has been genetically changed so that it cannot grow in humans. Genetic material has been added to the ChAdOx1 construct, which is used to make proteins from the COVID-19 virus (SARS-CoV-2) called Spike glycoprotein. Phase I clinical trials on healthy adult volunteers have been completed with more than 1000 immunizations and the follow-up is currently under progress. The phase II part of the clinical study will enroll up to 10,260 adults and children and will involve a number of partner institutions across the country towards assessing the immune response to the vaccine in people of different ages [57].

Johnson & Johnson has responded in the past to virus outbreaks like Zika and Ebola producing rapidly available and affordable treatments. As soon as the SARS-CoV-2 genome sequence became available in January, 2020, Johnson & Johnson in collaboration with Federal Biomedical Advanced Research and Development Authority (BARDA) and with an investment of $ 1 billion, started working on a potential treatment for infected people [58]. This includes working on repurposing its own licensed antiviral drugs against COVID-19. The randomized, double-blind, placebo-controlled Phase 1/2a study is scheduled to commence in July, 2020; and will evaluate the safety, reactogenicity, and
immunogenicity of the investigational SARS-CoV-2 vaccine, Ad26.COV2-S, recombinant in 1045 healthy adults aged 18 to 55 years, as well as adults aged 65 years and older. The study will take place in the U.S. and Belgium [59].

The company relies on its AdVac® and PER.C6® technologies that provide rapid development of new vaccine candidates and enhanced upscale production of the most potent ones. The company has already short selected promising vaccine candidates in collaboration with scientists at multiple academic institutions notably Beth Israel Deaconess Medical centre, part of Harvard Medical school. With the fastest timeline, the company aims at the largest delivery of about 600-800 million coronavirus vaccines early next year, 2021 [60]. For accelerating the program substantially, the additional manufacturing facility is being set up in the United States besides supplementing the company's plant in the Netherlands that can produce up to 300 million doses.

5.3. Protein Subunit Vaccines

In the case of protein subunit vaccines, specific bits of viral protein are directly delivered into the cells to develop antibodies against it. For coronavirus, this is the spike glycoprotein. The vaccines contain copies of the spike protein and immune boosters, called adjuvants. Such vaccines are less likely to trigger side effects. However, limited immunogenicity of these vaccines warrants administering multiple shots of the vaccine. Further, building multiple copies of the protein, exactly similar to the naturally occurring spike protein, is very challenging. Such vaccines are already approved for use against human papilloma virus (HPV).

On May 25, 2020, Novavax, a late-stage biotechnology company developing next-generation vaccines for serious infectious diseases, announced enrollment of the first participants in a Phase I/II clinical trial of its coronavirus vaccine candidate, NVX-CoV2373, a stable, prefusion protein made using its proprietary nanoparticle technology [61]. NVX-CoV2373 includes Novavax’s proprietary Matrix-M™ adjuvant to enhance immune responses and stimulate high levels of neutralizing antibodies. Novavax identified NVX-CoV2373 as its lead SARS-CoV-2 candidate following pre-clinical testing that demonstrated high immunogenicity and high levels of neutralizing antibodies. Preliminary immunogenicity and safety results from the Phase I portion of the trial are expected in July 2020.

GlaxoSmithKline (GSK) and Sanofi, the world's two largest vaccine manufacturers, announced on April 14, 2020, that they will join hands to produce an adjuvanted vaccine against COVID-19 [62]. The vaccine candidates will comprise of adjuvanted proteins that will reduce the amount of antigenic proteins required for effective doses, allowing fast production of more number of vaccine doses to protect people and save lives. Adjuvanted vaccines are especially required during pandemics because of enormous international demand. GSK CEO, Emma Walmsley, announced that the two companies will start the clinical trials in the second half of 2020. Pending success in preclinical studies and subject to regulatory consideration, she said, they aim to complete the development required for mass scale availability of the vaccine by the second half of 2021, at affordable costs.

Sanofi will contribute its S-protein COVID-19 antigen which is based upon recombinant DNA technology producing an exact genetic match to proteins found on the surface of the virus. The DNA sequence encoding this antigen has been combined into the DNA of the baculovirus expression platform, the basis of Sanofi's licensed recombinant influenza product in the US. On the other hand, GSK will provide its proven pandemic adjuvant technology to the collaboration, reducing the amount of the vaccine protein per dose without compromising the immunogenicity.

5.4. Vaccines based on Inactivated Virus

A virus that has been killed using heat or radiation loses the ability to replicate but retains the power to irritate the immune system. Such viruses possess the cell wall, viral capsules and proteins, which can elicit a robust immune response. However, such vaccines are very hard to manufacture and the immunogenicity fades with time, which warrants the need for booster shots.

A handful of Chinese companies are developing coronavirus vaccines using this method. One company, Sinovac Biotech, showed that its vaccine, called CoronaVac, could protect monkeys from COVID-19. CoronaVac uses an inactivated version of the novel coronavirus. On June 14, 2020, Sinovac Biotech announced preliminary study results showing its experimental COVID-19 vaccine generated immune responses in patients and was safe suggesting the vaccine might protect people against infections with the novel coronavirus [63].

The Beijing-based drug maker’s vaccine induced neutralizing antibodies in “above 90%” of people who were tested 14 days after receiving two injections, two weeks apart. There were no severe side effects reported, the company stated. The preliminary results were from a 600-patient, placebo-controlled Phase II study. Sinovac is also conducting a 143-patient, placebo-controlled Phase I study.

6. TIMELINES

Most of the advanced technologies used in vaccine development like vectors, production platforms, precise antigen scissoring, etc. are new and need comprehensive safety evaluation before being used in the vaccine development [64]. As there are no approved vaccines against human coronavirus and no sufficient data on the production process is available, the clinical development has to start ab-initio. Proper animal models expressing human ACE2 receptors need to be identified. Assessment of induced complications, safety and toxicity studies need to be evaluated. The clinical development ladder (Fig. 1) starting from current Good Manufacturing Practice (cGMP) production through clinical trials to licensure, large scale production, marketing, administration and evaluation of the immunity generated by the vaccine, is typically a long-lasting process. The nearest possible timeline, even when strong cohesive and coordinated efforts among production companies, governmental agencies, regulatory authorities and the World Health Organization are invoked, would still be 6-18 months from now. This implies that we may be unable to mitigate the effects of the present pandemic wave. However, we will be ready for future waves of the virus.
CONCLUSION

COVID-19 has inflicted unimaginable distress on the healthcare system worldwide. The microscopic enemy has brought civilization to a standstill. As of June 15, 2020, almost 7.70 million people have already been infected globally with 428,000 reported casualties. Immediate corrective actions to control and subsequently overcome this global life and health crisis would need stringent measures to investigate new therapies, potentially, immunotherapy. New vaccines for long-term immunity become imperative for rapid containment and preventing the subsequent onset of the disease. A detailed clinical status of potential therapeutic efforts that are currently underway has become essential for researchers and clinicians alike. A multifaceted and cross-institutional collaborative approach towards finding better solutions to this pandemic is the immediate requirement. This may involve speeding up the collaborative efforts between governmental organizations, academic and research institutions and pharmaceutical companies for the timely development of safe and effective treatments against COVID-19. Further, advanced vaccine development technologies need to be exploited for the mass-production of fast and affordable immunotherapy against this virulent disease.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF, Garry RF. The proximal origin of SARS-CoV-2. Nat Med 2020; 26(4): 450-2. http://dx.doi.org/10.1038/s41591-020-0820-9 PMID: 32284615

[2] Wang H, Li X, Li T, et al. The genetic sequence, origin, and diagnosis of SARS-CoV-2. Eur J Clin Microbiol Infect Dis 2020; 4: 1-7. PMID: 32333222

[3] Boni MF, Lemey P, Jiang X, et al. Evolutionary origins of the SARS-CoV-2 sarbecovirus lineage responsible for the COVID-19 pandemic. bioRxiv 2020.

[4] Amanat F, Krammer F. SARS-CoV-2 Vaccines: Status Report. Immunity 2020; 52(4): 583-9. http://dx.doi.org/10.1016/j.immuni.2020.03.007 PMID: 32259480

[5] Ou X, Liu Y, Lei X, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun 2020; 11(1): 1620. http://dx.doi.org/10.1038/s41467-020-15562-9 PMID: 32221306

Fig. (1). Clinical development ladder of new vaccines against COVID-19.
[9] Xia H, Lazartigues E. Angiotensin-converting enzyme 2 in the brain: properties and future directions. J Neurochem 2008; 107(6): 1482-94. http://dx.doi.org/10.1111/j.1471-4159.2008.05723.x PMID: 19014390

[10] Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. CNS Neurosci Ther 2020; 26(5): 499-501. http://dx.doi.org/10.1111/cns.13372 PMID: 32266761

[11] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 2020; 11(7): 995-8. http://dx.doi.org/10.1021/acschemneuro.0c00122 PMID: 32167747

[12] Burkard C, Verheije MH, Wicht O, et al. Coronavirus cell entry occurs through the endo-/lysosomal pathway in a proteolysis-dependent manner. PLoS Pathog 2014; 10(11): e1004502. http://dx.doi.org/10.1371/journal.ppat.1004502

[13] Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations.

[14] Insight into Community Transmission of COVID-19. https://www.infectioncontroltoday.com/covid-19/insight-community-transmission-covid-19-note-hospitals-are-communities

[15] Symptoms of Coronavirus (COVID-19) https://www.cdc.gov/coronavirus/2019-ncov/downloads/COVID19-symptoms.pdf

[17] Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect Dis 2020; S1473-3099(20): 30195-X PMID: 32171390

[19] Li Q, Guan X, Wu P, et al. Early Transmission dynamics in wuhan, china, of novel coronavirus-infected pneumonia. N Engl J Med 2020; 382(13): 1199-207. http://dx.doi.org/10.1056/NEJMoa2001316 PMID: 31995857

[20] Naran K, Kundallah T, Chetty S, Barth S. Principles of Immunotherapy: Implications for Treatment Strategies in Cancer and Infectious Diseases. Front Immunother 2020; 8: 3158-3324

[21] Seib KL, Dougan G, Rappuoli R. The key role of genomics in the molecular bridge between epidemiologic and clinical features of infectious diseases. Nat Rev Genet 2009; 10(10): e1000612. http://dx.doi.org/10.1038/nrn2220 PMID: 19198616

[23] Jiang S, He Y, Liu S. SARS vaccine development. Emerg Infect Dis 2005; 11(7): 1016-20. http://dx.doi.org/10.3201/110705219 PMID: 16022774

[24] Gabriela, di.M.; Cristina, S.; Concetta, R.; Francesco, R.; Annalisa, C. SARS-CoV-2 infection: Response of human immune system and possible implications for the rapid test and treatment. Int Immunopharmacol 2020; 84: 106519-21. http://dx.doi.org/10.1016/j.intimp.2020.106519

[25] People Who Are at Higher Risk For Severe Illness. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html.

[26] In the race to develop a coronavirus treatment, regeneneron thinks it has the inside track https://www.statnews.com/2020/02/05/in-the-inside-track/

[27] Kevzara (Sarilumab). A Novel IL-6 Receptor Antagonist for Rheumatoid Arthritis https://www.ahdbonline.com/supplements/2438-kevzara-sarilumab-a-novel-il-6-receptor-antagonist-for-rheumatoid-arthritis

[28] Lamb YN, Deeks ED. Sarilumab: A Review in Moderate to Severe Rheumatoid Arthritis. Drugs 2018; 78(9): 929-40. http://dx.doi.org/10.1007/s40265-018-0929-z PMID: 29931592

[29] FDA Approves Sarilumab for Adults With Rheumatoid Arthritis https://www.medscape.com/viewarticle/880473

[30] Baig AM, Oberste MS, Monroe S, et al. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. Science 2003; 300(5624): 1394-9. http://dx.doi.org/10.1126/science.1085952 PMID: 12730500

[31] Li Q, Guan X, Wu P, et al. Early Transmission dynamics in wuhan, china, of novel coronavirus-infected pneumonia. N Engl J Med 2020; 382(13): 1199-207. http://dx.doi.org/10.1056/NEJMoa2001316 PMID: 31995857

[32] Thiel V, Ivanov KA, Puthia A, et al. Mechanisms and enzymes involved in SARS coronavirus genome expression. J Gen Virol 2003; 84(Pt 9): 2305-15. http://dx.doi.org/10.1099/vir.0.19424-0 PMID: 12917450

[33] ABCellera and Lilly to Co-develop Antibody Therapies for the Treatment of COVID-19. https://investor.lilly.com/news-releases/news-release-details/abcellera-and-lillys-co-develop-antibody-therapies-treatment2020.

[34] Lilly to Start Testing Experimental Drug in Coronavirus Patients Soon https://www.wsj.com/articles/lilly-to-start-testing-experimental-drug-in-coronavirus-patients-soon-1158766027

[35] Pfizer announce completion of dosing for first cohort of phase 1/2 trial of covid-19 vaccine candidates in Germany https://www.infectioncontroltoday.com/covid-19/insight-vaccine-tracking/

[36] COVID-19 vaccine tracker https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

[38] Moderna starts dosing in Phase II Covid-19 vaccine trial https://www.clinicaltrialsarena.com/news/moderna-phaseii-vaccine-trial

[39] COVID-19 vaccine tracker https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

[40] PFIZER, BioNTech to co-develop potential coronavirus vaccine https://www.investor.lilly.com/news-releases/news-release-details/abcellera-and-lillys-co-develop-antibody-therapies-treatment2020.

[41] Moderna Initiates Phase 1 Clinical Trial Of Its COVID-19 Vaccine And Plans First Dose Today http://ir.inovio.com/news-and-media/news/pfizer-biontech-to-co-develop-potential-coronavirus-vaccine/article.detail/pfizer-and-biontech-announce-further-details-collaboration.

[42] Pfizer, BioNTech to co-develop potential coronavirus vaccine https://www.europeanpharmaceuticalreview.com/news/62816/eu-approval-kevzara/

[43] Moderna and NIAID Partner on Planned Trial of Coronavirus mRNA Vaccine https://www.genengnews.com/news/moderna-niaid-partner-on-planned-trial-of-coronavirus-mrna-vaccine/

[44] Moderna Initiates Phase 1 Clinical Trial Of Its COVID-19 Vaccine And Plans First Dose Today http://ir.inovio.com/news-and-media/news/pfizer-biontech-to-co-develop-potential-coronavirus-vaccine/article.detail/pfizer-and-biontech-announce-further-details-collaboration.

[45] Pfizer, BioNTech to co-develop potential coronavirus vaccine https://www.clinicaltrialsarena.com/news/moderna-phaseii-vaccine-trial

[46] Pfizer, BioNTech to co-develop potential coronavirus vaccine https://www.economictimes.indiatimes.com/industry/healthcare/biotech/pfizer-biontech-to-co-develop-potential-coronavirus-vaccine/articleshow/74668162.cms?from=mdr

[47] Pfizer, BioNTech to co-develop potential coronavirus vaccine https://www.clinicaltrialsarena.com/news/moderna-phaseii-vaccine-trial
BioNTech in China alliance with Fosun over potential coronavirus vaccine https://in.reuters.com/article/us-biontech-fosunpharma-vaccine-collaboration-china-bioNTech-idUSKBN213005.

Arcturus Reports Positive Preclinical Data for its COVID-19 Vaccine Candidate https://ir.arcturusrx.com/news-releases/news-release-details/arcturus-reports-positive-preclinical-data-its-covid-19-vaccine.

Arcturus Announces Summer COVID-19 Vaccine Trial http://sdbj.com/news/2020/apr/19/arcturus-announces-summer-covid-19-vaccine-trial/.

BioNTech and Pfizer announce completion of dosing for first cohort of Phase 1/2 trial of COVID-19 vaccine candidates in Germany/default.aspx.

BioNTech in China alliance with Fosun over potential coronavirus vaccine https://in.reuters.com/article/us-biontech-fosunpharma-vaccine-collaboration-biontech-in-china-alliance-with-fosun-over-potential-coronavirus-vaccine-idUSKBN213005.

Arcturus Reports Positive Preclinical Data for its COVID-19 Vaccine Candidate https://ir.arcturusrx.com/news-releases/news-release-details/arcturus-reports-positive-preclinical-data-its-covid-19-vaccine.

Arcturus Announces Summer COVID-19 Vaccine Trial http://sdbj.com/news/2020/apr/19/arcturus-announces-summer-covid-19-vaccine-trial/.

Biopharma Update on the Novel Coronavirus. https://www.biospace.com/article/biopharma-update-on-the-novel-coronavirus-april-9/.

Arcturus Therapeutics Announces Clinical Trial Timeline for its COVID-19 Vaccine https://www.biospace.com/article/releases/arcturus-therapeutics-announces-clinical-trial-timeline-for-its-covid-19-vaccine/.

San Diego’s Arcturus Therapeutics will get up to $10M from Singapore for coronavirus vaccine https://www.sandiegouniontribune.com/business/biotech/story/2020-03-05/arcturus-therapeutics-nets-up-to-10-million-in-funding-from-singapore-for-covid-19-vaccine.

About CureVac’s activities regarding an mRNA based vaccine against COVID-19 https://www.curevac.com/covid-19/

CureVac and CEPI extend their Cooperation to Develop a Vaccine against Coronavirus nCoV-2019 https://centerforvaccineethicsandpolicy.net/2020/02/02/announcements-142/.

Is mRNA the Key to a Coronavirus Vaccine? https://www.fool.com/investing/2020/04/09/is-mrna-the-key-to-a-coronavirus-vaccine.aspx.

CureVac focuses on the development of mRNA-based coronavirus vaccine to protect people worldwide https://www.curevac.com/news/curevac-focuses-on-the-development-of-mrna-based-coronavirus-vaccine-to-protect-people-worldwide.

China's CanSino pushes coronavirus vaccine into clinical testing as Moderna kicks off trial https://www.businesswire.com/news/home/20200316005666/en/Moderna-Announces-Participant-Dosed-NIH-led-Phase-1.

A Phase II Clinical Trial to Evaluate the Recombinant Vaccine for COVID-19 (Adenovirus Vector) (CTII-nCoV) https://clinicaltrials.gov/ct2/show/NCT04341389.

Oxford COVID-19 vaccine to begin phase II/III human trials http://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiii-human-trials.

Johnson Johnson Announces a Lead Vaccine Candidate for COVID-19; Landmark New Partnership with US Department of Health Human Services; and Commitment to Supply One Billion Vaccines Worldwide for Emergency Pandemic Use https://www.jnj.com/johnson-johnson-announces-a-lead-vaccine-candidate-for-covid-19-landmark-new-partnership-with-u-s-department-of-health-human-services-and-commitment-to-supply-one-billion-vaccines-worldwide-for-emergency-pandemic-use.

Johnson Johnson Announces Acceleration of its COVID-19 Vaccine Candidate; Phase 1/2a Clinical Trial to Begin in Second Half of July https://www.jnj.com/johnson-johnson-announces-acceleration-of-its-covid-19-vaccine-candidate-phase-1-2a-clinical-trial-to-begin-in-second-half-of-july.

Johnson Johnson will have 600-800 million coronavirus vaccines by 2021 2021. https://nypost.com/2020/04/15/johnson-johnson-eyes-600-million-coronavirus-vaccines-by-early-2021/.

Novavax Initiates Phase 1/2 Clinical Trial of COVID-19 Vaccine https://ir.novavax.com/news-releases/news-release-details/novavax-initiates-phase-12-clinical-trial-covid-19-vaccine.

Sanofi and GSK to join forces in unprecedented vaccine collaboration to fight COVID-19 https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-13-13-00-00.

Sinovac says early data show its Covid-19 vaccine generated immune responses https://www.statnews.com/2020/06/14/sinovac-early-data-covid19-vaccine-generated-immune-responses/.

Brennan FR, Dougan G. Non-clinical safety evaluation of novel vaccines and adjuvants: new products, new strategies. Vaccine 2005; 23(24): 3210-22.

http://dx.doi.org/10.1016/j.vaccine.2004.11.072 PMID: 15837222