Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Potential Repurposed Therapeutics and New Vaccines against COVID-19 and Their Clinical Status

Abid H. Banday[1,2], Shameem A. Shameem[2], and Sheikh J. Ajaz[3]

Abstract

SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), was first reported in Wuhan, China, in December 2019. Since then, the virus has stretched its grip to almost all the countries in the world, affecting millions of people and causing enormous casualties. The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2019. As of June 12, 2020, almost 7.30 million people have already been infected globally, with 413,000 reported casualties. In the United States alone, 2.06 million people have been infected and 115,000 have succumbed to this pandemic. A multipronged approach has been launched toward 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 is aimed at highlighting the efforts that are currently underway to treat or prevent SARS-CoV-2 infection, with details on the science, clinical status, and timeline for selected investigational drugs and vaccines. This article is going to be of immense help to the scientific community and researchers as it brings forth all the necessary clinical information of the most-talked-about therapeutics against SARS-CoV-2. All the details pertaining to the clinical status of each therapeutic candidate have been updated as of June 12, 2020.

Keywords

COVID-19, SARS-CoV-2, repurposed therapeutics, monoclonal antibodies, vaccines

Introduction

SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), was first reported in Wuhan, China, in December 2019 and spread rapidly to almost all the countries globally. The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020, implying that the virus has the ability to cause a rapid global health emergency and strenuous efforts are required to immediately put all the available resources and measures in place to thwart the pandemic.[1] The most effective measures would include reliable diagnostic tests, efficacious therapeutics, and vaccines for long-term protection. The director general of the WHO, Tedros Adhanon Ghebreyesus, declared on March 18, 2020, that the WHO would launch a multifaceted campaign to look for therapies that would prevent SARS-CoV-2 from infecting people and save the lives of those infected.[2] The WHO would also fund trials for repurposing some drugs that need concrete testing for evaluating their efficacy against the novel coronavirus. Instead of multiple small trials involving diverse approaches, concrete simpler trial methods would have a focused objective of finding whether or not a candidate drug reduces mortality or hospitalization time. The main reason for testing known antiviral drugs/drug combinations or repurposing some drugs is that such drugs and formulations are approved and licensed with documented safety protocols and synthetic strategies that become very important to combat pandemics given the enormous and urgent international demand. Since then, pharmaceutical companies worldwide have pooled their resources and are trying to advance their best ideas to

[1]Department of Chemistry and Biochemistry, Auburn University, Auburn, Alabama, USA
[2]Department of Chemistry, Islamia College of Science and Commerce, Srinagar, Jammu and Kashmir, India
[3]Government Medical College, Karan Nagar, Srinagar, Jammu and Kashmir, India

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Corresponding Author:
Abid H. Banday, Department of Chemistry, Islamia College of Science and Commerce, Srinagar-India, 190002, India.
Email: abidrrl@gmail.com

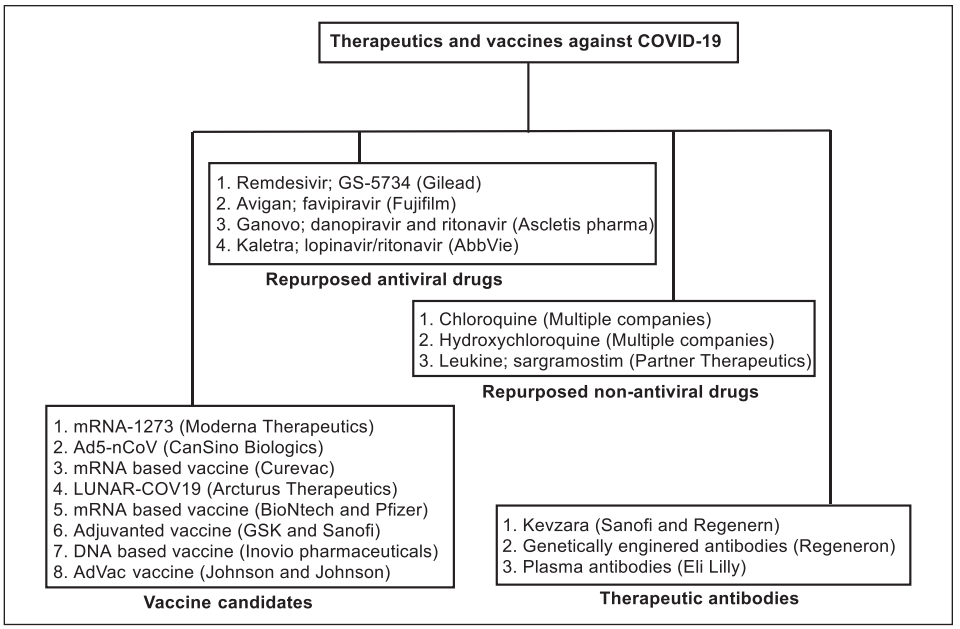

Figure 1. Schematic representation of potential therapeutics and vaccines against COVID-19.

prevent this pandemic. Some of the drug makers are backing older antiviral drugs, while others are striving hard to investigate novel targets and approaches toward affordable medicines against this dreadful disease. The present communication aims to highlight the efforts that are currently underway to treat or prevent SARS-CoV-2 infection with details on the science, clinical status, and timeline for selected investigational drugs and vaccines. All the investigational therapeutics have been classified into four categories—repurposed antiviral drugs, therapeutic antibodies, vaccines, and repurposed non-antiviral drugs—with detailed discussion on the composition and mechanism of action of each individual candidate (**Fig. 1**).

During pandemics and other health emergency situations, routine regulatory and statutory approvals for the use of various drugs or devices may be relaxed owing to the constraints of time, manpower, and resources. The repurposing of approved drugs becomes a necessity because of their known safety and efficacy parameters. Further, the routine institutional review board (IRB) approvals may be exempted for the emergency use of a drug or device on a human subject in a life-threatening or severely debilitating situation in which no standard treatment is available. The exemption under U.S. Food and Drug Administration (FDA) regulations (21 CFR 56.104(c)) allows for single emergency use of a test article, and any subsequent use of the product at the institutional level must have the necessary IRB review and approval. Further, the FDA also recognizes the use of an investigational product (drug or device) for patients facing serious but not life-threatening, disease or conditions, if the physicians believe that it may benefit treating and/or diagnosing the disease or condition. Such use of a product for individual patients or a small group of patients is called compassionate use.

Survey of Small and Large Molecules Being Tested against SARS-CoV-2

All the potential repurposed antiviral and non-antiviral drugs, monoclonal antibodies, and new vaccines that are currently being tested against SARS-CoV-2 are at different stages of clinical development (**Fig. 2**) and have been listed company-wise in descending order of their clinical progress/trial stage (**Table 1**).

I. Repurposed Antiviral Drugs

a. Gilead Sciences: Remdesivir (GS-5734); Clinical Stage: Phase III (NCT04292730)

Remdesivir (GS-5734) is an adenosine analog that inhibits viral replication through rapid premature termination of viral RNA transcription after insertion into its chains. Gilead has studied this candidate against COVID-19 in five different clinical trials aimed at reducing the intensity and duration of the infection.[3] The company recruited 1000 COVID-19-positive patients in China for evaluating whether the drug can reverse the infection, reduce fever, and help minimize hospitalization to less than 2 weeks to ease the burden on the health system globally. Though remdesivir was earlier used against SARS-CoV and MERS-CoV, the company was always keen to pursue the approval of this drug for a different kind of infection: Ebola.[4] Soon after the onset of COVID-19, studies showed an impressive recovery

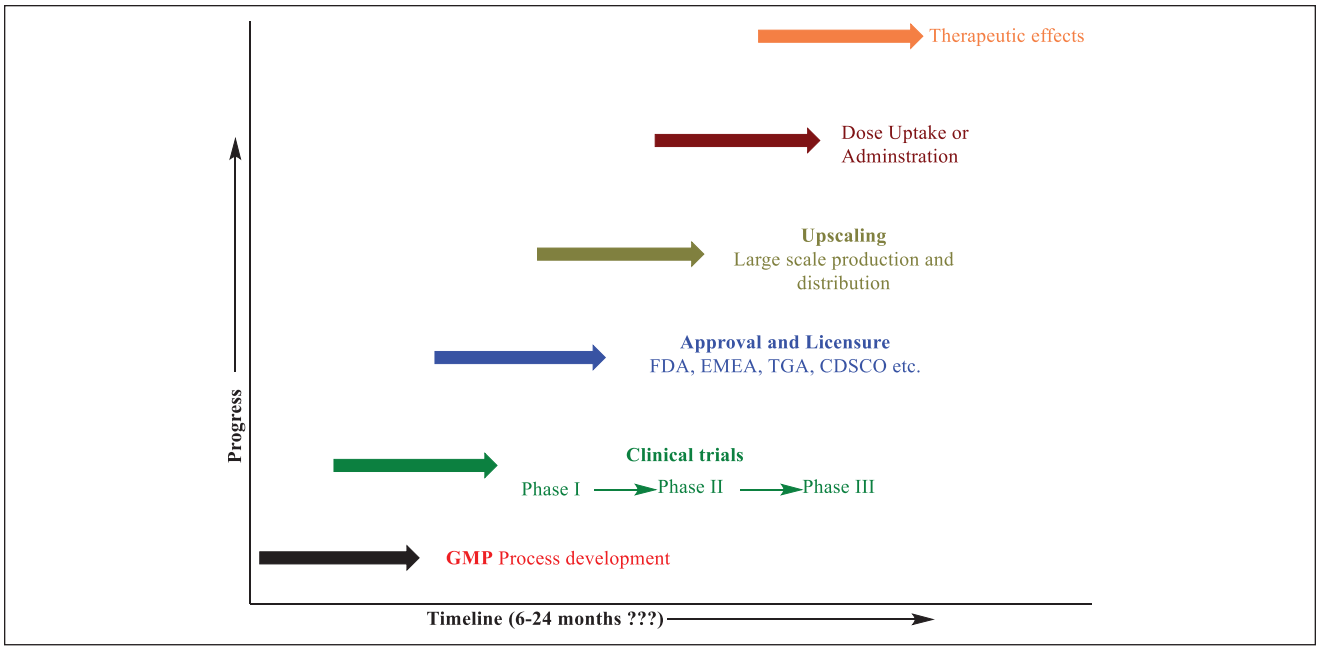

Figure 2. Clinical development ladder of repurposed drugs and new vaccines against COVID-19.

and survival benefit.[5,6] Based on optimistic results, remdesivir was approved by the FDA in a compassionate program[7] to treat the first COVID-19 patient in the United States who had visited China and returned to Washington to be admitted to Providence Regional Medical Center in Everett, Washington, on January 20, 2020. The WHO updated some results of a clinical trial in China on April 23, 2020, which showed no benefit of the drug to COVID-19 patients. However, the results were inadvertently posted and were soon taken off the website. On June 1, 2020, Gilead announced the open-label results from a phase III clinical trial of remdesivir in patients with moderate COVID-19 symptoms. The results showed significant improvement in the patients on day 11 of admission compared with those of patients who received standard treatment alone. Remdesivir is currently approved for use against COVID-19 only in Japan. Outside Japan, remdesivir is an investigational, unapproved drug. The U.S. FDA granted remdesivir a temporary Emergency Use Authorization for the treatment of hospitalized patients with severe COVID-19.

b. Fujifilm: Avigan (Favipiravir, T-705); Clinical Stage: Phase II/III (NCT04336904)

Favipiravir is a broad-spectrum antiviral drug that has been approved in Japan since 2017 against influenza and is also effective against the West Nile virus, foot-and-mouth disease, yellow fever, and many other viruses.[8] Like remdesivir of Gilead Sciences, favipiravir is a selective inhibitor of RNA polymerase, the enzyme involved in viral replication.[9–11] Currently, favipiravir, marketed as Avigan, is under phase III clinical trials in Japan, while phase II clinical trials are in progress in the United States.[12] The Japanese government has already ordered 2 million tablets of Avigan.

c. Ascletis Pharma: Ganovo (Danoprevir) with (Ritonavir); Clinical Stage: Phase I (NCT04291729)

The China-based Ascletis Pharma's Ganovo (danoprevir) is an orally available approved drug against hepatitis C virus (HCV) genotypes 1–6 and its key mutants.[13] Chemically, the drug is a 15-membered macrocyclic peptidomemitic inhibitor of NS3/4A HCV protease.[14] Ritonavir, on the other hand, is an L-valine derivative antiretroviral drug belonging to the protease inhibitor family and is approved against HIV.[15]

On March 25, 2020, results from the first clinical study, in which 11 naive and experienced patients were treated with danoprevir and ritonavir cocktail, showed that the combination therapy is safe and well tolerated.[16,17] Per the study, all 11 patients were discharged after 4–12 days of admission as they met all four standard recovery conditions, that is, normal body temperature for 3 days, significantly improved respiratory system, obvious absorption and recovery of acute exudative lesion revealed by lung imaging, and two consecutive reverse transcription (RT) PCR-negative results of SARS-CoV-2 nucleic acid.

Table 1. Potential Drugs and Vaccines under Clinical Investigation against COVID-19.

S. No.	Company	Product Name and Candidate	Description	Originally Licensed Against	Current Clinical Status
1	Gilead Sciences	Remdesivir	Adenosine analog RNA polymerase inhibitor	Not yet approved for any use	Phase III
2	Fujifilm	Avigan (favipiravir)	RNA polymerase inhibitor	Influenza	Phase III
3	Ascletis Pharma	Ganovo (danoprevir)	Peptidomemetic macrocycle Protease inhibitor	HCV	Phase I
		(ritonavir)	L-valine derivative Protease inhibitor (antiretroviral)	HIV	
4	Abbvie	Kaletra or Aluvia (lopinavir)	Protease inhibitor (antiretroviral)	HIV	Preclinical
		(ritonavir)	L-valine derivative Protease inhibitor (antiretroviral)		
5	Chloroquine	Belongs to 4-aminoquinoline class of drugs	Antiparasital and immunosuppressant	Malaria, immunosuppression	Phase I
6	Hydroxychloquine	Belongs to 4-aminoquinoline class of drugs	Antiparasital and immunosuppressant	Malaria, immunosuppression	Phase I
7	Partner Therapeutics	Leukine (sargamostin, rhu-GM-CSF)	GM-CSF glycoprotein	Immunomodulation	Phase I
8	Sanofi and Regenron	Kevzara (sarilumab)	Human monoclonal antibody IL-6 inhibitor	Rheumatoid arthritis	Phase II/III
9	Regeneron	Monoclonal antibodies	Human antibodies from genetically engineered mice	Not yet approved	Phase I
10	Eli Lilly	Therapeutic antibodies	Antibodies from the blood of COVID-19 survivors	Not yet approved	Phase I
11	Moderna Therapeutics	mRNA-1273	Lipid nanoparticle encapsulated mRNA vaccine	Not yet approved	Phase I
12	CanSino Biologics	AD5-nCoV	Adenovirus 5 vector-based recombinant COVID-19 vaccine	Not yet approved	Phase I
13	Inovio Pharmaceuticals	INO-4800 (DNA vaccine)	Protective antibodies for long-term immunity	Not yet approved	Phase I
14	Arcturus Therapeutics	LUNAR-COV19 nonadjuvanted mRNA vaccine	Spike (S) protein antigen-targeted immunotherapy	Not yet approved	Preclinical
15	BioNTech and Pfizer	mRNA vaccine	Snippet mRNA-based antibody immunotherapy	Not yet approved	Preclinical
16	GlaxoSmithKline and Sanofi	Subunit adjuvanted protein vaccine	Adjuvant-enhanced low-antigen-dose immunotherapy	Not yet approved	Preclinical
17	CureVac	Synthetic mRNA vaccine	Spike (S) protein antigen-targeted immunotherapy	Not yet approved	Preclinical
18	Johnson & Johnson	AdVac and PER.C6 technology-based vaccines	Protective antibodies for long-term immunity	Not yet approved	Preclinical

d. AbbVie: Kaletra or Aluvia (Lopinavir and Ritonavir); Clinical Stage: Preclinical

AbbVie's Kaletra, also marketed as Aluvia, is a combined formulation of lopinavir and ritonavir. Lopinavir and ritonavir are both protease inhibitor antiretroviral drugs widely used for the treatment of HIV.

The SARS-CoV-2 virus, like its predecessors SARS-CoV and MERS-CoV, is a single-stranded RNA beta coronavirus.[18–20] It replicates within the host cells using its machinery and produces multiple copies of the genetic material that accumulates near the periphery of the host cells, ready for cleavage, packaging, and release. A crucial role is played by the enzyme 3-chymotrypsin like-protease (3-CL^{PRO}) in processing the virus polyproteins. Recent studies have shown that lopinavir has promising in vitro antiviral activity against SARS-CoV-2, indicating that it probably has something to do with the inhibition of 3-CL^{PRO}.[21] Ritonavir, on the other hand, inhibits the metabolizing enzyme cytochrome P450 3A, thereby increasing the half-life of lopinovir in a synergistic formulation called Kaletra.[22]

As of April 15, 2020, formal clinical trials of Kaletra are yet to start, and so far there are limited preliminary reports from China where the results of a few COVID-19-positive patients had turned negative after taking this drug, but with more randomized trials results were not encouraging.[23,24]

II. Repurposed Non-Antiviral Therapeutics

a. Chloroquine/Hydroxychloquine (Antimalarial/ Anti-Inflammatory Drugs); Clinical Stage: Phase I (ISRCTN83971151)

Chloroquine and hydroxychloroquine are known antimalarial and anti-inflammatory drugs.[25] Both drugs are under investigations in Solidarity clinical phase I trials for pre- or postexposure prophylaxis of SARS-CoV-2 infection.[26] There are many clinical studies from China and France, where the drugs have been found to be effective in treating patients with mild, moderate, and severe COVID-19. Recently, the FDA issued an Emergency Use Authorization for both drugs for the treatment of COVID-19 patients.[27,28] On May 25, 2020, the WHO suspended the clinical trials of hydroxychloroquine because of concerns over its safety. However, the Solidarity trials of the malaria drug were resumed on June 3, 2020, after no apparent safety concerns were observed by the competent authority set by the WHO.

b. Partner Therapeutics: Leukine (Sargamostin, rhu-GM-CSF); Clinical Stage: Phase I

Partner Therapeutics started clinical trials of Leukine (sargamostin, rhu-GM-CSF) on March 24, 2020, toward testing patients with COVID-19-associated respiratory illness.[29] Patients with severe COVID-19 with acute hypoxic respiratory failure do not have many treatment options available, which further decreases the survival chances of such patients. Leukine is a granulocyte–macrophage colony-stimulating factor (GM-CSF) glycoprotein, which is an immunomodulator,[30] playing a critical role in the body's defense against pathogens primarily because of its importance in the differentiation and functioning of alveolar macrophages in lungs.[31] Leukine has effective antiviral immunity leading to lung repair by restoring immune homeostasis in lungs and has already shown promising effects in patients with viral lung pneumonia in preclinical trials.[32,33] Partner Therapeutics is collaborating with several academic and governmental agencies for investigating Leukine in COVID-19 patients and the studies are under phase I clinical trial.[34]

III. Therapeutic/Monoclonal Antibodies

a. Sanofi and Regeneron: Kevzara (Sarilumab); Clinical Stage: Phase II/III

The French pharma giant Sanofi and the American biotech company 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.[35] Kevzara is an interleukin-6 (IL-6) receptor antagonist[36] that is being evaluated against COVID-19 alongside similar inhibitors like EUSA Pharma's Sylvant and Roche's Actemra.

Kevzara was approved in 2017, in both the United States and Europe, as a drug for the treatment of rheumatoid arthritis.[37–39] The drug was recently repurposed for use against SARS-CoV-2 and showed promising results in preclinical and clinical phase I trials. The companies have already started phase II/III trials in various European countries, as well as Japan, Canada, and Russia.[40,41] 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.

b. Regeneron Antibodies from Genetically Engineered Mice; Clinical Stage: Phase I

Decades ago, Regeneron succeeded in bending the curve of drug development by developing a fully 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 the following:

i. Dupiant—a multi-billion-dollar eczema drug
ii. Libtayo—a recently approved immunotherapy to cancer
iii. REGN-EB3—a cocktail of three monoclonal antibodies against Ebola

With remarkable success in its antibody therapies, Regeneron is now betting its mice for the treatment of COVID-19. As with pandemic SARS and MERS pathogens, SARS-CoV-2 backs on a surface "spike" (S) protein[42,43] that has a receptor-binding domain (RBD) located in the S1 subunit of the virus that facilitates entry of the virus into the host cell by binding to its receptors. Stopping this S protein from reaching its target will be the eventual treatment of the disease.

The full genome of SARS-CoV-2 has been sequenced to about 30,000 base pairs, and that of the protein "spike" on the surface of the virus is roughly 10% of the total genome.[44,45] Regeneron has decorated the surface of some otherwise harmless particles with a cloned spike producing code. This has generated a pseudovirus with similar spikes that would mimic cell-penetrant biology but avoid the ability of the virus to replicate and cause illness. Antibodies produced by the genetically engineered mice against this pseudovirus will eventually be 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 antiviral antibody cocktail REGN-COV2 for the treatment and prevention of COVID-19.

c. Eli Lilly: Therapeutic Plasma Antibodies; Clinical Stage: Phase I

Eli Lilly, in collaboration with the Canadian firm AbCellera, is working on an antibody treatment for COVID-19 patients.[46] The combo has identified some 500 antibodies from the blood of COVID-19 survivors and is currently looking for the most potent ones, which will be secured and moved into human studies.[47]

On April 13, 2020, the chief executive of Eli Lilly announced that pending safety and efficacy profiles, the company could make its potential therapeutic antibody drug available for emergency human use this fall. On April 17, 2020, the National Institutes of Health (NIH) announced that it will work with 12 reputed governmental and pharmaceutical companies, including Eli Lilly, toward exploring accelerated and better treatments and vaccines for COVID-19.[48] On June 1, 2020, Eli Lilly started dosing COVID-19 patients in a phase I trial of its AbCellera-partnered antibody, LY-CoV555, which is perhaps the first drug specifically designed against SARS-CoV-2.

IV. Vaccines[49]

a. Moderna Therapeutics: mRNA-1273; Clinical Stage: Phase I (NCT04283461)

Moderna Therapeutics owns mRNA-1273, a novel lipid nanoparticle (NLP)-encapsulated, mRNA-based vaccine that encodes for the full length of the SARS-CoV-2 S protein. 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 a robust antibody response against the virus.[50,51] Forty-five participants were recruited for evaluating the safety, reactogenicity, and immunogenicity of the vaccine formulation. The clinical study is being carried out by the U.S. NIH, at the Kaiser Permanente Washington Health Research Institute in Seattle. The study will involve dosing the patients twice with the vaccine after a 28-day gap and follow-up for 1 year. On March 27, 2020, a batch of 17 participants at Emory University, Atlanta, were selected for a second set of clinical trials.[52] Phase II clinical trials of the vaccine are expected to be launched in the summer of this year.[53]

b. CanSino Biologics: AD5-nCoV; Clinical Stage: Phase I (ChiCTR2000030906)

The Chinese pharma company CanSino Biologics, which already markets a vaccine for Ebola in China, has recently completed phase I clinical trials of its vaccine, named AD5-nCoV, against SARS-CoV-2.[54] The vaccine consists of a snippet of SARS-CoV-2 genetic code, entwining it with a harmless virus. After injecting the vaccine in healthy volunteers, antibodies start spurring. As of April 10, the company has already been granted approval by Chinese authorities for a phase II clinical trial of the investigational adenovirus 5 vector-based recombinant COVID-19 vaccine, AD5-nCoV, in collaboration with researchers at the Academy of Military Medical Sciences, Institute of Biotechnology, China.[55] The decision to start immediate phase II clinical trials was based on optimistic results and safety data obtained from phase I studies.[56]

c. Inovio Pharmaceuticals: INO-4800 (DNA Vaccine); Clinical Stage: Phase I (NCT04336410)

Inovio Pharmaceuticals has been working for decades with DNA-based stuff aimed at turning DNA into medicine. With grant money from the Coalition for Epidemic Preparedness Innovations (CEPI), Inovio has come up with a DNA vaccine that it believes can generate protective

antibodies that can keep patients from getting infection. In partnership with a Chinese company, Beijing Advanced Biotechnology, the company is working on clinical studies with a candidate called INO-4800. As of April 19, 2020, Inovio has already started the phase I clinical trial with 40 healthy volunteers participating at two trial locations, Philadelphia and Kansas City.[56,57] Preclinical animal studies have shown promising immune responses.

The U.S. FDA has accepted company's investigational new drug (IND), INO-4800, as the DNA vaccine.[58] DNA vaccines have the potential to be rapidly transformed into usable vaccines, and Inovio has promised to manufacture 1 million doses of its candidate this year pending the necessary permissions.

d. Arcturus Therapeutics: LUNAR-COV19 (mRNA Vaccine); Clinical Stage: Preclinical

LUNAR-COV19 is a low-dose, potential single-shot (intramuscular), self-replicating, mRNA vaccine that is devoid of any viral material or co-adjuvants.[56] LUNAR-COV19 has shown promising preclinical in vitro results generating effective expressions of SARS-CoV-2 virus-like S 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.

As per the company's timeline for its COVID-19 vaccine, it will employ 76 healthy volunteers for clinical trials with a follow-up over several months to evaluate the extent and duration of the immune response.[59–61] The company is coordinating with Singapore's Health Sciences Authority (HSA), which granted around $10 million to Arcturus for developing the vaccine.[62] The company has proposed to deliver the first Good Manufacturing Practice (GMP) batch in June 2020, and clinical trials will start in early summer.

e. BioNTech: mRNA Vaccine; Clinical Stage: Preclinical

Like other competitors, the German company BioNTech and pharma giant Pfizer are all set to start clinical studies of BioNTech's mRNA-based vaccine for the novel coronavirus.[63] This vaccine comprises mRNA strands to produce protective antibodies. Pfizer is considering a $748 million grant to BioNTech for a 50% share toward the clinical development, manufacturing, and commercialization worldwide.[64] As of May 5, 2020, the clinical trials have started in Germany where twelve study participants have been dosed amongst the 200 healthy subjects included in the study. BioNtech and Pfizer have also started clinical trials in United States and other locations across Europe.

BioNTech has also signed a deal with Shanghai's Fosun Pharma to market the vaccine in China if it is eventually approved.[65]

f. GlaxoSmithKline and Sanofi: Adjuvanted Protein Vaccine; Clinical Stage: Preclinical

The world's two largest vaccine manufacturers, GlaxoSmithKline (GSK) and Sanofi, announced on April 14, 2020, that they will join forces to produce an adjuvanted vaccine against COVID-19.[66] The vaccine candidates will be composed of adjuvanted proteins that will reduce the amount of antigenic proteins required for the effective doses and allow fast production of more vaccine doses to protect people and save lives. Adjuvanted vaccines are especially required during pandemics because of the 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 that they aim to complete the development required for mass scale availability of the vaccine by the second half of 2021 at an affordable cost.

Sanofi will contribute its S protein COVID-19 antigen, which is based on recombinant DNA technology producing an exact genetic match to the protein 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 United States. On the other hand, GSK will provide its proven pandemic adjuvant technology to the collaboration, reducing the amount of vaccine protein per dose without compromising the immunogenicity.

g. Curevac: Synthetic mRNA Vaccine; Clinical Stage: Preclinical

The German pharma company Curevac develops therapies based on man-made mRNA-spurred protein production.[67] With working experience on SARS/MERS viruses since 2017, the company has been financially supported by the European Union with an offer of €80 million to scale up the production and development of a vaccine against SARS-CoV-2 in Europe. In collaboration with the CEPI and the Bill and Malinda Gates Foundation (BMGF), the company has selected its most suitable vaccine candidates for human screening.[68,69]

As of April 10, 2020, the company has already identified two primary study centers for clinical trials of the vaccine constructs, in coordination with the 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 in Germany and Belgium by the end of July, 2020, the company expects to start its next phase of clinical studies in early autumn with a significant number of participants.[70]

h. Johnson & Johnson: Vaccine Based on AdVac and PER.C6 Technologies; Clinical Stage: Preclinical

Johnson & Johnson has responded in the past to virus outbreaks like Zika and Ebola by 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 the federal Biomedical Advanced Research and Development Authority (BARDA) and with an investment of $1 billion, started working on potential treatment for infected people.[71] This includes working on repurposing its own licensed antiviral drugs against COVID-19.

The company relies on its AdVac and PER.C6 technologies, which 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 Center, part of Harvard Medical School. With a fast timeline, the company aims to deliver 600–800 million coronavirus vaccines in early 2021.[72] The company also expects its antiviral drug to be approved by the U.S. FDA by the same time, human testing for which is expected to start this September. For accelerating the program substantially, an additional manufacturing facility is being set up in the United States, to supplement the company's plant in the Netherlands, which can produce up to 300 million doses.

Discussion

SARS-CoV-2 is a beta coronavirus 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, the S protein that decorates the lipid–protein bilayer, which envelopes multiple copies of the nucleocapsid protein (N protein) bound to the viral genome.[73] The S protein is a class I fusion protein that is responsible for attaching the virus to cell surface receptors, significantly, the angiotensin-converting enzyme 2 (ACE2) receptors.[74] 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.[75] Exhaustive replication of the virus inside the host cells, and subsequent release of the progeny viruses through secretory vesicles, creates 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.[76] However, community spread has also been reported in certain geographical regions.[77]

Various strategies for the effective development of therapeutics and vaccines against COVID-19 by several pharmaceutical companies have already been discussed. However, the clinical development of therapeutics and vaccines (**Fig. 2**), starting from GMP production through clinical trials to the licensure, large-scale production, marketing, administration, and evaluation of the therapeutic effects, is typically a long-lasting process. The nearest possible timeline for the commercial availability of therapeutics or vaccines would still be 6–18 months from now. This implies that we may be unable to alleviate the effects of the present pandemic wave. However, we will be ready for future waves of the virus.

Conclusion

COVID-19 has created unimaginable distress to healthcare systems worldwide. Almost 7.30 million people have been infected globally and nearly 413,000 people have lost their lives as of June 12, 2020. Immediate corrective measures to control and subsequently overcome this global life and health crisis would need stringent measures to investigate already approved and licensed drugs against COVID-19. Repurposing older drugs and investigating new vaccines for long-term immunity has become imperative for rapid containment and preventing subsequent onset of the disease. A detailed clinical status of potential therapeutic efforts that are currently underway is essential for researchers and clinicians alike. A multifaceted and cross-institutional collaborative approach toward finding better solutions to this pandemic is the immediate requirement. All collaborative efforts involving governmental organizations, academic and research institutions, and pharma companies need to be made available to the masses so that focused efforts lead to better achievable outcomes.

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