CHAPTER 2

Applications of nanoengineered therapeutics and vaccines: special emphasis on COVID-19*

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2.1 Coronavirus disease-2019

Coronavirus disease–2019 (COVID-19) is a rapidly spreading disease in all of the six continents since it first appeared in Wuhan, China, in December 2019, leading to a pandemic, reporting 1,38,76,441 confirmed cases and 5,93,087 confirmed deaths to date, according to the World Health Organization (WHO) (Coronavirus Disease COVID-19 Pandemic, 2021). It is caused by the newly evolved strain of coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), according to the international virus classification commission (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020). SARS-CoV-2 is highly contagious, probably due to spreading via asymptomatic-infected individuals and the long incubation periods of up to 24 days (Chan et al., 2020; Rothe et al., 2020). Previous severe outbreaks induced by other members of the same corona family were associated with SARS in China in 2003, which was caused by the severe acute respiratory syndrome coronavirus (SARS-CoV), and middle east

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* Information regarding diagnosis and therapeutic protocols for the management of COVID-19 are continuously changing. Details included in this chapter are updated based on the information available at the time of writing the chapter, but may not present the current situation.

respiratory syndrome (MERS) infection in Saudi Arabia in 2012, which was triggered by the MERS-coronavirus (CoV) (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020).

2.2 Morphological structure and genome

SARS-CoV-2 belongs to the Coronaviridae family that comprises enveloped viruses encapsulating positive-sense, single-stranded RNA. The genome of the SARS-CoV-2 is c. 30 kb in size (Fig. 2.1) (Chan et al., 2020; Aust, 2019). Nonstructural proteins 1−16 are encoded by open
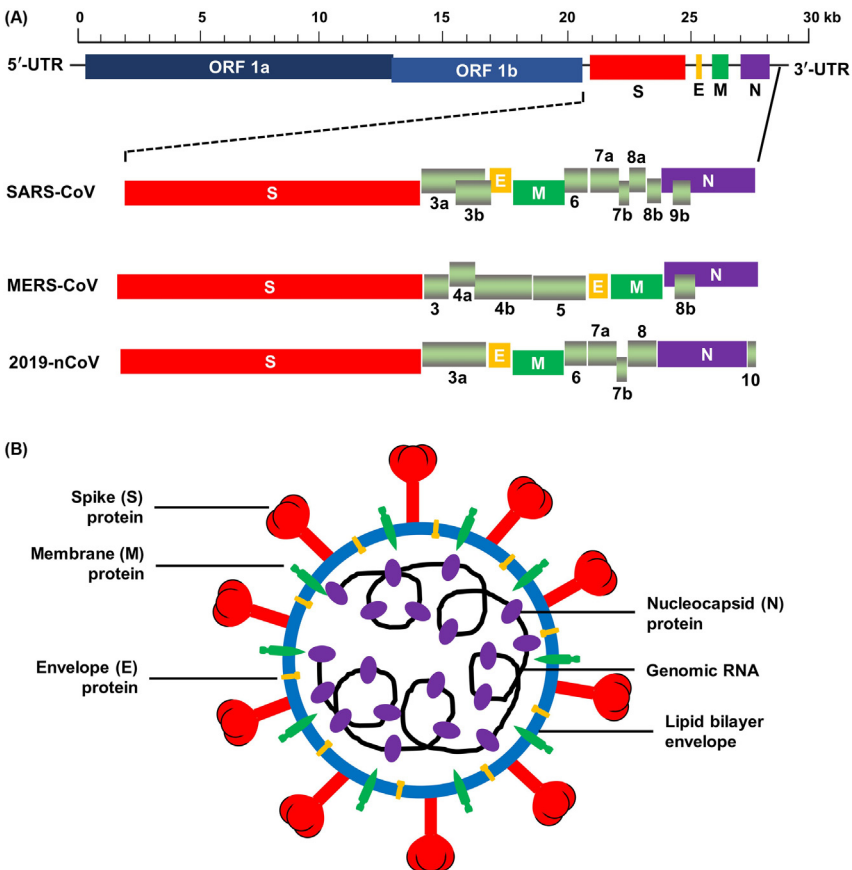

Figure 2.1 SARS-CoV-2 virus. Schematic diagram of genomic organization (A) and virion structure (B) of SARS-CoV, MERS-CoV, and SARS-CoV-2, and their major structural proteins. *From Wang, N., Shang, J., Jiang, S., & Du, L. (2020). Subunit vaccines against emerging pathogenic human coronaviruses. Frontiers in Microbiology, 28, 298.*

reading frame (ORF) 1a/b at the 5′-end, followed by structural proteins (surface spike (S) glycoprotein, envelope (E), membrane (M), and nucleocapsid (N)), which are encoded by other ORFs at the 3′-end (Huang et al., 2020). Spike proteins S are club-shaped projections that play a key role in viral cell entry, as they bind to the angiotensin–converting enzymes (ACE2) receptors on the host cell surfaces through a subunit called receptor binding domain, followed by activation by transmembrane serine protease 2 (TMPRSS2), a transmembrane protease protein (Hoffmann et al., 2020). The receptor-binding domain is a highly antigenic part of the S protein of SARS-CoV-2, that is responsible for binding with ACE2 receptors on the host cells (Tai et al., 2020). The M and E proteins are necessary for virus assembly (de Haan & Rottier, 2005; Surya et al., 2015). The N protein is one of the major structural proteins of the virus that is involved in the transcription and replication of the viral RNA and interference with the cell cycle processes of the host cells (Huang et al., 2020).

2.3 Clinical presentation, radiological features, and laboratory investigations

COVID-19 may be presented clinically as mild, moderate, or severe. Symptoms presented include fever, fatigue, dry cough, anorexia, myalgia, dyspnea, and, in some of the cases, diarrhea, nausea, and vomiting (Huang et al., 2020; Wang, Cao, et al., 2020; Wang, Hu, et al., 2020; Wang, Wang, et al., 2020). In one study, it was found that c. 81% of people testing positive for SARS-CoV-2 are asymptomatic or have mild symptoms (Ing et al., 2020). Clinical diagnosis of COVID-19 is mainly based on epidemiological history, clinical manifestations, and several investigations, such as real-time quantitative polymerase chain reaction, computed tomography (CT) scan, and immune identification technologies. Chest CT shows bilateral multilobar consolidation "ground glass appearance" in the lung (Chung et al., 2020; Wang, Cao, et al., 2020; Wang, Hu, et al., 2020; Wang, Wang, et al., 2020). Laboratory investigations performed on COVID-19 patients demonstrated decreased albumin, high C–reactive protein, lymphopenia, high erythrocyte sedimentation rate, prolonged prothrombin time, and elevated lactate dehydrogenase, in most of the patients (Rodriguez-Morales et al., 2020; Wang, Cao, et al., 2020; Wang, Hu, et al., 2020; Wang, Wang, et al., 2020). High levels of proinflammatory cytokines and chemokines including IL-1β, IL-2, IL-6, IL-7,

interferon-γ, G-CSF, IP-10, MCP-1, MIP-1a, TNF-α, CXCL10, and CCL2, were all observed in the COVID-19 severe cases, which is called "cytokine storm," that is one of the mechanisms of the acute respiratory distress syndrome. Cytokine storm can initiate viral sepsis and lung injury, thus leading to other complications, including, respiratory failure, shock, organ failure, and potentially death (Bani-Sadr et al., 2020; Huang et al., 2020; Kuppalli & Rasmussen, 2020; Ruscitti et al., 2020; Sun et al., 2020; Xu et al., 2020; Zhang et al., 2020). This massive rise in cytokines and chemokines levels indicates an increased activity of T helper 1 cells (Th1). A rise in antiinflammatory cytokines, such as IL-4 and IL-10, were also observed in COVID-19 infection, which are T helper 2 cells (Th2) cytokines, indicating an increased activity of these cells (Zhang et al., 2020). Higher risk of infection was observed in older age, male gender, and in individuals with comorbid conditions, such as hypertension, cardiovascular diseases, diabetes, malignancy, and, less commonly, cerebrovascular diseases, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, and human immunodeficiency virus infections (Chung et al., 2020; Wang, Cao, et al., 2020; Wang, Hu, et al., 2020; Wang, Wang, et al., 2020). These risk groups account for the majority of severe diseases and fatalities to date. Nucleic acid amplification tests using real-time polymerase chain reactions are considered as the most common effective method for detecting the virus, with a sensitivity of 50%−79%, depending on the protocol used, sample type, and the number of clinical specimens collected (Corman et al., 2020). The viral genes targeted so far include N, E, S, and RNA-dependent RNA polymerase (RdRP) genes (World Health Organization, Laboratory Testing for Coronavirus Disease 2019 (COVID-19) in Suspected Human Cases: Interim Guidance, 2020). The RdRP protein is essentially encoded in the genome of RNA viruses to catalyze the synthesis of the RNA complementary strand. Viral serological testing is an effective means of diagnosis of SARS-CoV-2 infection. The positive rate and titer variance of the human immunoglobulin IgG are higher than those of IgM in COVID-19 patients. The IgM-positive rate increases slightly at first and then decreases over time; whereas, the IgG-positive rate increases and remains higher than IgM (Zhou et al., 2020). Previous knowledge from literature indicated that neutralizing antibodies secreted by the host's body against SARS-CoV-2 are protective, but they last for a limited time (Hoffmann et al., 2020). However, for the vaccine to be effective, it should induce long-lasting immunity. T memory cells (i.e., CD4^{+} and CD8^{+} cells) are needed to pose this

long-lasting effect, and previous studies that investigated specimens from COVID-19 patients found CD4$^+$ and CD8$^+$ cells that fight against infection (Grifoni et al., 2020; Hoffmann et al., 2020). Globally, there is a trend to screen people for their immunocompetence toward COVID-19, to allow healthcare workers who have antibodies in their blood to return to work in high-risk situations. Identifying individuals with antibodies in their blood can be beneficial for use of their convalescent plasma for the treatment of people with severe COVID-19 infections, to boost their ability to fight the virus. However, experts worry that widespread antibody screening may give those who test positive a false sense of security.

2.4 Therapeutic attempts

The development of effective medical therapeutic strategies against the SARS-CoV-2 virus is a critical initiative to control the spread of COVID-19 and to reduce the burden on the economy and health services. Therapeutic strategies include symptomatic support (e.g., antipyretics) and administration of steroids, antiviral drugs, immunomodulators, vaccines, and convalescent plasma. Corticosteroids are commonly used to manage acute respiratory distress syndromes due to their antiinflammatory effects. However, their immune-suppressive effects have discouraged their use in patients with viral infections, and their use in COVID-19 is controversial (Bani-Sadr et al., 2020; Fadel et al., 2020; Lu et al., 2020). RECOVERY trial, a randomized trial investigating whether treatment with either lopinavir-ritonavir, hydroxychloroquine, corticosteroids, azithromycin, convalescent plasma, or tocilizumab prevents death in patients with COVID-19, was conducted on total 12,000 subjects. In this trial, 2104 patients were assigned to the dexamethasone group and 4321 patients were assigned to the standard care group (ClinicalTrials.gov: NCT04381936). Results indicated that dexamethasone could be beneficial for severely ill COVID-19 patients who required either mechanical ventilation or supplemental oxygen support. Dexamethasone reduced mortality and decreased time of hospitalization among these patients when compared to the standard care group. However, no benefits were observed for mildly and moderately infected patients who are not requiring oxygen support Covid-19 Treatment Guidelines (2021). In this section, we will briefly introduce some of the commonly utilized strategies for the potential treatment of COVID-19 and immunization against the virus (Fig. 2.2). Then, in the following sections, we will provide an
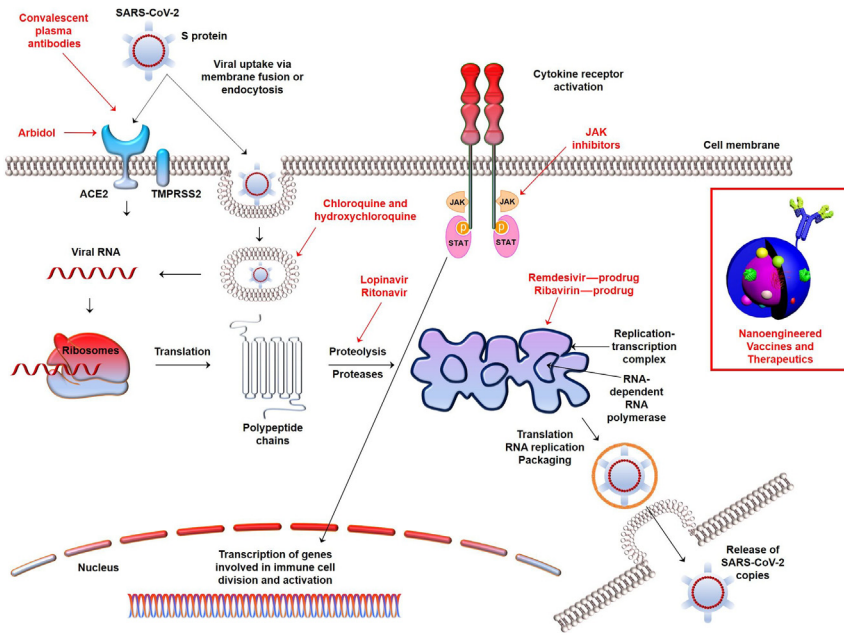
Figure 2.2 Demonstration of the antiviral drugs that are exploited in the management of COVID-19 and their underlying mechanisms of action. SARS-CoV-2 binds to ACE2 receptors on the host cell surface, with the aid of TMPRSS2 transmembrane protein, or the virus may fuse with the cell membrane and release the viral RNA into the cytoplasm. SARS-CoV-2 utilizes ribosomes to synthesize polypeptides that are being cleaved later by proteases into nonstructural proteins. In addition, the virus replicates its own RNA using the host cell machinery and utilizes RNA-dependent RNA polymerase to synthesize a copy of its RNA, besides several other cellular organelles and enzymes to continue translating the other structural proteins and transcribing the + RNA strands. Chloroquine and hydroxychloroquine mechanisms of action are not clearly known, although it is assumed that they inhibit viral entry, transport, postentry events and possibly increase the pH of endosomes and lysosomes. Remdesivir is a prodrug of GS-441524, and it resembles viral nucleoside. After viral entry, viral RNA initiates replication with the aid of RNA-dependent RNA polymerase. GS-441524 is incorporated into viral RNA rendering it defective. Ribavirin is a prodrug, which after being metabolized, it mimics RNA nucleotides, thus ultimately producing defective viral RNA. Lopinavir and ritonavir are protease inhibitors that prevent the formation of viral structural proteins. Arbidol inhibits membrane fusion of the virus with the host cells. JAK inhibitors block cytokine-mediated signals via the JAK-STAT pathway. Upon binding of cytokines to their receptors, JAK proteins initiate phosphorylation of STAT proteins rendering them active. Then, STAT transduces the signal to the nucleus by binding to the DNA, thus initiating the transcription of genes involved in immune cell division, activation, and recruitment. JAK inhibitors could therefore prevent cytokine storm associated with COVID-19. Nanoengineered therapeutics and vaccines might provide additional benefits via potentiating and prolonging the pharmacological effects of their loaded cargoes.

overview of the nanoengineering attempts for the design of therapeutics and vaccines for the management of COVID-19.

2.5 Antiviral therapy

Remdesivir (GS-5734) is a nucleoside analog. It is a prodrug of GS-441524, which resembles a viral nucleoside. It can inhibit the replication of multiple coronaviruses in respiratory epithelial cells by incorporating itself into the viral RNA with the aid of RNA-dependent RNA polymerase, thus producing defective RNA (Gordon et al., 2020). It has been used to treat the Ebola virus disease, and it is suggested for the management of COVID-19. It inhibited viral replication of clinical isolates of the SARS-CoV-2 virus in vitro. It also reduced viral load in animal models infected with MERS (de Wit et al., 2020; Sheahan et al., 2020). Results from clinical trials evaluating remdesivir in severe COVID-19 patients requiring no mechanical ventilation inferred no difference between a 5-days course and a 10-days course (Goldman et al., 2020). Because there was no placebo control in the study, the benefit of the therapy could not be determined. However, preliminary data from a placebo-controlled trial ($n = 1063$) in COVID-19 patients reported a lower mortality rate and shorter recovery time in patients treated with remdesivir versus placebo (Beigel et al., 2020). Remdesivir was evaluated in multiple clinical trials; a series of placebo-controlled double-blinded phase 3 trial ($n = 1062$) reported that remdesivir shortened the time to recovery and patients had less respiratory tract infection when compared with the placebo group (Beigel et al., 2020). Moreover, a *meta*-analysis was made to investigate remdesivir for the treatment of COVID-19 by obtaining databases from PubMed, EMBASE, Cochrane library, and ClinicalTrials.gov databases of three randomized trials ($n = 7334$) (from January 1, 2020 to November 5, 2020), it was found that there is very low certainty evidence of any association between remdesivir use and shorter recovery time; however, moderate certainty of evidence showed higher rates of patients recovery and discharge (Al-Abdouh et al., 2021). Remdesivir was the first to gain approval from the FDA for the treatment of COVID-19 (Food and Drug Administration, 2020). In an attempt to improve patient's compliance and dosage form convenience together with the reduction of personal contact, a self-injectable formulation of remdesivir was designed recently for the treatment of COVID-19. The formulation was fabricated using

biodegradable and biocompatible poly(lactic-*co*-glycolic acid) (Patki et al., 2021).

Chloroquine and *hydroxychloroquine* are cheap oral prescription drugs with well-established clinical safety profiles that have been used for more than 70 years for the treatment of malaria and amebiasis, and for other antiinflammatory applications, such as the treatment of rheumatoid arthritis. Chloroquine, 4-aminoquinoline derivative, is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration with a peak plasma concentration that is generally attained within 1−2 h. It is widely distributed in tissues, mostly excreted unchanged in the urine and partially metabolized in the liver. Its mechanism of action is not fully understood; however, it is believed to prevent viral entry, transport, and postentry events, and it possibly increases the pH of endosomes and lysosomes (Liu et al., 2020). The US Food and Drug Administration (FDA) has issued an emergency use authorization for chloroquine and hydroxychloroquine to treat patients hospitalized with COVID-19. Hydroxychloroquine and chloroquine have demonstrated in vitro activity against SARS-CoV-2 (Liu et al., 2020; Wang, Cao, et al., 2020; Wang, Hu, et al., 2020; Wang, Wang, et al., 2020). A combination of hydroxychloroquine and azithromycin had a synergistic effect in vitro on SARS-CoV-2 at concentrations compatible with that obtained in human lungs (Andreani et al., 2020). The use of hydroxychloroquine was increased recently in many countries as promising preliminary results regarding efficacy and safety in COVID-19 patients receiving a 10-days course were observed (Gao, Chen, et al., 2020; Gao, Tian, et al., 2020). In another bigger study ($n = 1061$), hydroxychloroquine and azithromycin combination were further investigated and good clinical outcomes and viral clearance were observed. In this study, it was concluded that the use of this combination was safe and resulted in a low fatality rate in patients when they were administered before COVID-19 complications occur (Million, 2020). In an attempt to further evaluate the clinical use of chloroquine, it was observed that high doses of chloroquine prolonged QT interval in the electrocardiography of patients; thus it is not recommended to use high doses in the management of COVID-19, especially in combination with azithromycin and oseltamivir and in old patients, due to safety concerns (Borba, 2020). In a multicenter, randomized, and controlled trial ($n = 250$), hydroxychloroquine did not improve therapeutic outcomes in mild-to-moderate COVID-19 patients at risk of disease progression (Vincent Dubée et al., 2021). However, in another single-center study

($n = 152$), it was found that hydroxychloroquine improved clinical condition in 91.4% of patients, and adverse effects were tolerable and were not associated with ventricular arrhythmia due to QT prolongation (Sogut et al., 2021). Despite these results, *meta*-analysis of multiple clinical trials reported no benefits with the use of hydroxychloroquine (Pathak et al., 2020). Yet more studies are being conducted on hydroxychloroquine, and future data availability will improve our knowledge about this drug (ClinicalTrials.gov: NCT04351620, NCT04329832, and NCT04429867).

Ivermectin is an antiparasitic drug that is approved by the FDA for the treatment of tropical diseases, including onchocerciasis, helminthiases, and scabies (Omura & Crump, 2014). There is an evidence from previous studies of the antiviral activity of ivermectin that it can inhibit RNA viruses such as Zika virus and Dengue virus (Barrows et al., 2016; Wagstaff et al., 2012). In an attempt to discover new treatments to overcome the rapidly upraising pandemic, in vitro studies were conducted and it was found that ivermectin reduced RNA replication of SARS-CoV-2 in vitro by 5000-fold within 48 h (Caly et al., 2020), and in vivo, in mice models, it demonstrated antiviral activity against mouse hepatitis virus, a type 2 family RNA coronavirus similar to SARS-CoV-2 (Arévalo et al., 2021). Clinically, ivermectin ($n = 24$) reduced COVID-19 symptoms and reduced viral load and antibody titers compared with controls (Chaccour, 2021). Furthermore, lower mortality was observed in COVID-19 patients treated with ivermectin, especially in those with severe pulmonary involvement (Rajter et al., 2021). Ivermectin is currently being tested in several clinical trials for the treatment of COVID-19 (NCT04425707, NCT04681053, NCT04723459, NCT04729140, and NCT04529525).

2.6 Lopinavir/ritonavir and Arbidol

Lopinavir and *ritonavir* are protease inhibitors that are used together in combination for the treatment of HIV infection. Results from a recent clinical trial ($n = 199$) evaluating either lopinavir or ritonavir treatment course (14 days) for severe COVID-19 demonstrated no benefits beyond the standard care (Cao et al., 2020). Lopinavir/ritonavir was further investigated in an ongoing trial "RECOVERY trial" ($n = 1919$), conducted across 176 hospitals in the United Kingdom. Released data showed no reduction in 28-days mortality, duration of hospital stay, and no risk of developing respiratory complications that might lead to respiratory intervention or death (Horby et al., 2020). Additionally, data from Solidarity

trial included 11,330 adults; 2750 received remdesivir, 954 received hydroxychloroquine, 1411 received lopinavir (without interferon), 2063 received interferon (including 651 received a combination of interferon plus lopinavir), and 4088 received no treatment. Results indicated little or no difference between the test groups and control group with regard to mortality, need for mechanical ventilation, and duration of hospital stay (Pan et al., 2021). Besides, multiple clinical trials were further investigated on the use of these drugs in COVID-19 patients (ClinicalTrials.gov: NCT04346147, NCT04372628, and NCT04330690).

Arbidol is a broad-spectrum antiviral that is being used for the treatment of Influenza viral infections. It displayed antiviral activity against SARS-CoV-1 in vitro (Khamitov et al., 2008). It was indicated that arbidol can be beneficial in the treatment of COVID-19 patients and it demonstrated superiority to lopinavir/ritonavir with regard to its antiviral effects, although further studies in a greater number of subjects are needed (Zhu, Li, et al., 2020; Zhu, Lu, et al., 2020). In another retrospective cohort, combination therapy of lopinavir/ritonavir with arbidol was compared with lopinavir/ritonavir, and favorable clinical outcomes were observed for the arbidol combination therapy (Lisi et al., 2020). However, there were no differences observed in the phase IV trial ($n = 86$) for the management of mild/moderate COVID-19 regarding clinical outcomes and rate of conversion from positive to negative of the viral RNA between the studied groups, implying no benefit could be obtained with lopinavir/ritonavir or arbidol (Li et al., 2020). However, arbidol was further evaluated in a randomized trial ($n = 100$); two groups of patients were included; patients in one group received hydroxychloroquine followed by KALETRA (lopinavir/ritonavir) and patients in the other group received hydroxychloroquine followed by arbidol. Results indicated that arbidol improved patients' condition significantly when compared to KALETRA (lopinavir/ritonavir) in terms of improved peripheral oxygen saturation, duration of hospital stay, ICU admissions, and chest CT involvement together with improved laboratory investigations (Nojomi et al., 2020). A retrospective case series showed that arbidol resolved fever, decreased duration of hospital stay, and accelerated viral clearance from respiratory specimens especially in male patients (Gao, Chen, et al., 2020; Gao, Tian, et al., 2020). It is also being evaluated in multiple clinical trials (ClinicalTrials.gov: NCT04273763, NCT04286503, and NCT04260594).

Oseltamivir is a neuraminidase inhibitor that has been used in cases of MERS-CoV infection, and it is currently being evaluated clinically for

efficacy and safety, for the management of COVID-19 (Borba, 2020). A recent study reported no benefit gained from administering oseltamivir to patients. It is being evaluated in several clinical trials in the management of COVID-19 (ClinicalTrials.gov: NCT04558463, NCT04516915, and NCT04338698).

2.7 Immune therapy

2.7.1 Convalescent plasma therapy

In a multicenter interventional study ($n = 368$); 135 COVID-19 patients received convalescent plasma, while 233 patients were controls. Moderate COVID-19 patients had a duration of 7 days to clinical improvement in the convalescent plasma group, while control group patients had a duration of 8 days ($P = .006$). Severe COVID-19 patients had a duration of 7 days to clinical improvement in the convalescent plasma group, versus 15.5 days in the control group ($P = .003$). Patients in the convalescent plasma group who were moderately ill had a significantly lower 30-day mortality rate than those from the control group. Moreover, after convalescent plasma transfusion, oxygen saturation improved within 3 days and lymphocyte counts increased on day 7 and day 14 in moderate COVID-19 patients and on day 11 and day 14 in severe COVID-19 patients. No adverse effects associated with convalescent plasma were reported in the study. Results showed possible benefits in reducing recovery time and rate in COVID-19 patients (Patki et al., 2021).

2.8 Tocilizumab

It is a recombinant humanized monoclonal antibody that blocks IL-6 receptors. It reduces cytokines production and acute-phase protein production. Its use has the potential to alleviate the hyperimmune state frequently reported in COVID-19 patients. Some cases reported improvement in clinical outcomes in patients with severe COVID-19 pneumonia who received anti-IL 6 (Cellina et al., 2020; Michot et al., 2020). Several retrospective cohorts found that the administration of tocilizumab reduced fever and the need for oxygen support and mechanical ventilation and led to an improvement in lung clinical presentation (Borku Uysal et al., 2020; Chilimuri et al., 2021; Guaraldi, 2020; Huang et al., 2021). However, data from recently conducted trial NCT04372186 ($n = 389$), which evaluated tocilizumab on COVID-19 patients with

pneumonia versus placebo reported that tocilizumab reduced the risk of progressing to the need for mechanical ventilation, but it did not improve survival (Salama et al., 2021). In another study ($n = 452$), the tocilizumab patient's group showed no significant improvement in the clinical status or lower mortality of the COVID-19 patients than the placebo at 28 days (Rosas et al., 2021). Tocilizumab is currently being evaluated in several trials; alone (NCT04479358, NCT04435717) and in combination with remdesivir (NCT04409262) and with heparin in the HEPAMAP study (NCT04600141).

2.9 Bamlanivimab (LY3819253 or LY-CoV555) and Etesevimab (LY3832479 or LY-CoV016)

Bamlanivimab and Etesevimab are recombinant monoclonal antibodies that were isolated from SARS-CoV-2 patients and were further investigated for their efficacy against the virus (Jones et al., 2020). It was observed that they can bind to the S protein of the SARS-CoV-2 (Shi et al., 2020). Bamlanivimab was approved by the FDA for the treatment of mild−moderate COVID-19. They were investigated in the BLAZE-1 study phase 2/3 at 49 US centers ($N = 613$). The study groups included bamlanivimab alone, combination of bamlanivimab plus etesevimab, and placebo. Data showed a significant reduction in viral load in the drug combination group (bamlanivimab and etesevimab) when compared to placebo while no significant difference was observed in the viral load in bamlanivimab monotherapy group (Gottlieb et al., 2021). Currently, they are being tested in some trials (ClinicalTrials.gov: NCT04656691, NCT04796402, and NCT04701658).

2.10 Casirivimab (previously REGN10933) and imdevimab (previously REGN10987)

Casirivimab (previously REGN10933) and imdevimab (previously REGN10987) are recombinant human monoclonal antibodies. They bind to S proteins of SARS-CoV-2 and prevent its binding to ACE receptors (Pallotta et al., 2021). They are authorized for an emergency use for the management of mild-to-moderate COVID-19 cases who are at high risk of progressing to a severe state or who require hospitalization (FDA). In an attempt to prevent the appearance of resistant mutants of the SARS-CoV-2, a combination of two monoclonal antibodies casirivimab plus

imdevimab were investigated in phase 1−3 trial ($n = 275$) and was assigned to a group of COVID-19 patients versus control group. Released results implied that the antibody combination is beneficial as it reduced viral load, especially in patients who had their immune response not yet elicited or who had a high baseline viral load (Weinreich et al., 2021). However, in a multicenter phase 3 trial (ACTIV-3), bamlanivimab, when given in combination with remdesivir, no benefit was reported in hospitalized COVID-19 patients who had no end-organ failure (Lundgren et al., 2021).

2.11 JAK inhibitors

JAK inhibitors are protein *kinases* that transduce cytokine-mediated signals via the *JAK*-STAT pathway including IL-6 and interferon-γ receptor signaling. They include *baricitinib*, *fedratinib*, and *ruxolitinib*, which are approved for rheumatoid arthritis, myelofibrosis, and psoriasis, respectively (Baricitinib for rheumatoid arthritis, 2019; Mesa, 2010; Mullally et al., 2020).

2.12 Baricitinib

Baricitinib is a JAK inhibitor that is selective for JAK1 and JAK2 and is FDA approved for the treatment of rheumatoid arthritis (Baricitinib, Olumiant, n.d.). Baricitinib received emergency use authorization from the FDA for treatment of COVID-19 (Fact Sheet for Healthcare Providers EUA for baricitinib, n.d.). It prevents inflammation by the inhibition of JAK1 and JAK2 in a pathway that involves STAT, in a dose-dependent manner, thus inhibiting subsequent proinflammatory signal of IL 6 in the immune cells (McInnes et al., 2019). Furthermore, an evidence of antiviral activity against SARS-CoV-2 was found, as it could prevent viral entry into the host lung cells. Also, in another study on macaques infected with SARS-CoV-2, it was found that baricitinib reduced inflammation in the lung and neutrophile recruitment and resulted in a reduction of macrophage-derived cytokines and chemokines production and decreased immune activation, thus limiting lung pathology (Hoang et al., 2021). Currently, it is being investigated in several clinical trials (NCT04421027, NCT04693026, and NCT04373044). A multicenter ACTT-2 trial ($n = 1033$) was conducted to evaluate baricitinib in combination with remdesivir for the treatment of moderate/severe

COVID-19 patients. Results demonstrated a median time to recovery of 7 and 8 days in the drug group and control group, respectively. Patients receiving high-flow oxygen or noninvasive ventilation had shorter recovery time in the tested group than the control group (10 vs 18 days). The 28-day mortality was 5.1% in the drug group and 7.8% in the control group. Moreover, patients from the tested group had less serious adverse events than those from the control group, thus implying the benefit that can be obtained from using this drug combination for hospitalized COVID-19 patients (Kalil et al., 2021).

2.13 Ruxolitinib

It is a JAK inhibitor that is used to manage myelofibrosis, policytemia vera, and hemophagocytic lymphohistiocytosis (Gálvez Acosta & Javalera Rincón, 2020; Hansen et al., 2021; Wang, Cao, et al., 2020; Wang, Hu, et al., 2020; Wang, Wang, et al., 2020). When tested in combination with steroids in a randomized clinical study versus placebo for the treatment of COVID-19, ruxolitinib significantly shortened recovery time in the treated group in contrast to that observed in the placebo group and no serious adverse events were encountered while using steroids nor ruxolitinib (D'Alessio et al., 2021). Data from another multicenter study ($n = 43$) conducted on severe COVID-19 patients reported promising results; patients had a numerically shorter time to clinical improvement. Significant chest computed tomography improvement and a faster recovery from lymphopenia were observed, and no serious adverse events were encountered with ruxolitinib. These data were enough to pursue further investigations (NCT04359290, NCT04355793, and NCT04377620).

2.14 Jakotinib

Jakotinib is another JAK inhibitor that is being tested in multiple clinical trials for various indications. JAK inhibitors could therefore prevent cytokine storm associated with COVID-19 (Felsenstein et al., 2020). However, JAK and STAT regulate interferon-controlled genes, thus blocking JAK-STAT will compromise interferon antiviral effects. Hence, their therapeutic use should be thoroughly evaluated in the management of COVID-19, and their potential therapeutic outcomes need to be weighed against possible adverse events (Favalli et al., 2020). Jakotinib and

ruxolitinib were investigated for the management of COVID-19 in China (ChiCTR2000030170 and ChiCTR2000029580, respectively).

2.15 Vaccines

Vaccine development is crucial to control the spread of the disease among populations. A common strategy to control the rapid spreading nature of the virus is to establish herd immunity among populations, which is successfully reached when slightly <80% of the population becomes immune to SARS-CoV-2 (Fine et al., 2011). This can only be established if either a large population gets infected with the virus that does not seem to be the best scenario or by successfully immunizing this population with an effective vaccine. The fact that there is no country has reached herd immunity yet, and the strict social distancing when being removed, a second wave of the virus will most likely take place (Kamps & Hoffmann, 2020). Since COVID-19 crisis, there have been multiple global attempts to develop a vaccine for the novel coronavirus to place a hold on this uprising event. Vaccines are biomaterials designed to stimulate the host immune response against a specific pathogen, mainly an antigen-specific antibody response. There are several types of vaccines including living attenuated, inactivated vaccines, conjugate vaccines (weak and strong antigen conjugated together), subunit vaccines (fragment of the infectious agent), and recombinant vaccines (Vetter et al., 2018). Recombinant vaccines are synthesized with aid of a live viral or bacterial vector that is genetically engineered to express a specific antigen. Classic vaccines are derived from the causative microorganism. It could be whole living attenuated or inactivated vaccines. Synthetic vaccines are made up of synthetic peptide or polysaccharide antigens that are synthesized with the aid of recombinant genetic engineering technology (genes from two different species are inserted into a host organism to produce a specific bioproduct). They are considered to be safer than traditional vaccines. A balance between the safety and immunogenicity of the vaccine is important to maintain optimized immunization. Subunit vaccines are relatively safer than traditional vaccines; however, they are weakly immunogenic. Antigen nanoparticle vaccines might provide balanced immunogenicity and safety, which will be described later (*vide infra*) (López-Sagaseta et al., 2016). The S protein is an important candidate for vaccine development against coronavirus due to the crucial role of S protein in receptor attachment, membrane fusion, and cellular entry (Li et al., 2019). The S protein

was used as a target for the design of mRNA, DNA, recombinant protein vaccines, and viral vector vaccines, for the SARS-CoV-2. In contrast, the whole virion was used to develop live attenuated vaccines and inactivated vaccines. Even though some immunization could be attained, previous studies have demonstrated that the whole inactivated SARS-CoV-1 vaccine results in pulmonary immunopathology and eosinophilic proinflammatory pulmonary response in vaccinated animals. Hence, recent efforts are being directed to other alternatives (Bolles et al., 2011; Lin et al., 2007; Spruth et al., 2006; Tseng et al., 2012).

2.16 Nanoengineered therapeutics and vaccines in development for management of COVID-19

2.16.1 Nanoengineered therapeutics

Several antivirals are being investigated for the treatment of COVID-19. Along the course of the investigation, many challenges regarding undesirable side effects, pharmacokinetic limitations, and pharmacodynamic issues are encountered. Nanoengineering constructs for encapsulation of these drugs could overcome the current challenges by enhancing cellular uptake of drugs, limiting undesirable side effects by controlling their bionavigation inside the body and reducing the dose needed to provide the desirable therapeutic effects. The ability to administer multiple drugs in the same vehicle can be also exploited for potential synergistic effects. Cellular uptake of nanoparticles encapsulating antivirals can be boosted by conjugating targeting moieties onto the surfaces of nanoparticles, which promote binding to cellular receptors and internalization, or by using specific polymer types that have an affinity to the target cells (Yang et al., 2002). Moreover, biodistribution can further be controlled with the aid of stimuli–responsive nanostructures. Pathological features describing a specific disease type can be exploited in the favor of nanoplatform design. For example, inflammation created during the course of infections leads to upregulation of intercellular adhesion molecule-1 (ICAM-1), which in turn increases the permeability of endothelial cells (Frank & Lisanti, 2008). In an attempt to exploit this phenomenon, γ3 peptide, which has a specific binding affinity to ICAM-1, was conjugated onto the surface of sparfloxacin- and tacrolimus-loaded poly(lactide-*co*-glycolide) nanoparticles, resulting in higher accumulation of nanoparticles in lungs (Yang et al., 2020). In COVID-19, the hyperimmune state can be exploited to control the bionavigation of nanoparticles inside the host body toward

diseased areas, thus decreasing undesired accumulation in other tissues and consequently adverse events can be limited. In a previous study, endocytosis by hepatitis C virus–infected huh7.5 cells and its impact on cellular uptake of nanoparticles were studied, with the aid of confocal microscopy and flow cytometry. It was found that transfected cells had a higher accumulation of nanoparticles than nontransfected cells; thus it was concluded that viral transfection affected cellular uptake.

Physicochemical features of nanoparticles as surface charge, type of polymer, and protein corona formation also played a role in increasing cellular uptake of nanoparticles (Abo–zeid et al., 2018). Previous literature investigated the effect of size and charge on the cellular internalization by multiple lung cells, in an attempt to evaluate the impact of size and surface charge on the cellular uptake of nanoparticles by primary human alveolar type 1 (AT2) and primary human alveolar type 2 (AT2) cells. It was observed that negatively charged particles were taken up by 75% of the AT1 cells, while positively charged particles were taken up by <55% of these cells (Kemp et al., 2008). Effects of nanoparticle size together with nanoparticles surface modification were further investigated, and it was found that nanoparticles of sizes c. 50 nm interacted more with lung cells, while 100 nm particles interacted more with phagocytic cells. Latex polystyrene nanoparticles of size c. 50 nm were taken up passively by human alveolar epithelial type I-like cells (TT1), while those particles featuring size range 100 nm were taken up via receptor-mediated endocytosis. Also, it was found that amine-surface modified nanoparticles (ANP) were taken up more rapidly than carboxyl-surface modified nanoparticles and unmodified polystyrene nanoparticles (UNP), unlike TT1 cells that internalized the three types of nanoparticles. Primary human alveolar type 2 (AT2) cells internalized ANP only (Kemp et al., 2008).

Nanoengineering drugs have considerably aided in their delivery to their target sites together with improved pharmacokinetics and enhanced overall therapeutic outcomes. Drug release from nanoparticles can be altered to be immediate or sustained depending on the structural features of the nanoparticles. Specific sites in the body can be targeted by conjugating various ligands onto the surfaces of nanostructures that in turn increases drug amount reaching specific tissues, consequently, improving bioavailability, decreasing the dose administered, limiting adverse events, and reducing cost. Several examples exist in which nanomaterials offered several advantages for the delivery of drugs that possess antiviral activities against COVID-19. For instance, ribavirin is associated with severe

hemolytic anemia due to massive accumulation in RBCs, which may require decreasing the ribavirin dose thus leading to a lower antiviral effect (Russmann et al., 2006). Ribavirin–loaded polymeric nanoparticles displayed lower accumulation in RBCs; thus therapeutic dose could be administered to preserve the antiviral activity of the drug (Abo-zeid & Garnett, 2020). When lopinavir was encapsulated inside nanoparticles, it possessed higher bioavailability as compared to free lopinavir (Ravi et al., 2014). Additionally, loading drugs in nanoengineered platforms allows for a dual administration of various drugs. Coadministration of ritonavir and lopinavir appeared to be quite beneficial as it lowers hepatic metabolism of lopinavir by cytochrome enzymes P450 3A4, thus improving bioavailability and reducing the administered dose. This dual administration was successfully approached by fabricating poly (lactide-*co*-glycolide) nanoparticles and loading both lopinavir and ritonavir into the nanoparticles (Abou-El-Naga et al., 2017). Nanostructures can be also employed to formulate poorly water-soluble drugs such as lopinavir. The poor water solubility of lopinavir results in low oral bioavailability. Loading of the drug into nanoparticles could enhance the overall solubility and could provide a dosage form that is more convenient for patients to improve patient compliance, especially with young children (the lopinavir formulation is currently available only in an adult form that should be extemporaneously divided into small doses for children) (Mahajan & Patil, 2020; Pham et al., 2016). It was reported that in situ self-assembly nanoparticles, based on oleic acid and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS), successfully encapsulated lopinavir and ritonavir at significantly high encapsulation efficiency, improved their bioavailability, and provided adequate and stable plasma concentrations of drugs over 8 h. In addition, nanoparticles improved biodistribution via significantly increasing lopinavir concentrations by 2.8-fold in the liver, 5.1-fold in the kidney, 2.7-fold in the brain, 6.1-fold in the lymph nodes, and 3.4-fold in the spleen, as compared to free lopinavir/ritonavir combination (Pham et al., 2016). Lopinavir was incorporated also into vitamin E-TPGS micelle, which resulted in an enhanced aqueous solubility by 2.6-fold. When tested in vivo, an increase in oral bioavailability by 3.17 folds was found. The use of TPGS, as an encapsulating polymer, increased the stability of micelles, improved absorption of lopinavir, and inhibited P-glycoprotein, thus inhibiting efflux of lopinavir from cells (Mahajan & Patil, 2020; Tian & Mao, 2012). In another study, oseltamivir decorated onto the surface of silver nanoparticles has demonstrated higher antiviral activity against

H1N1 viral infection in vitro in Madin–Darby Canine Kidney cells and lower toxicity than free silver nanoparticles and free oseltamivir (Li et al., 2016).

Polyphosphate (PolyP) is a biologically derived polymer of endogenous anti–SARS-CoV-2 activity. The PolyP-encapsulated nanoparticles demonstrated strong interaction with RBD of the SARS-CoV-2 by binding to the arginine amino acid that is present at its surface, forming a covalent–like interaction (Woods & Ferré, 2005), which will subsequently prevent the interaction of the viral S proteins with ACE2 receptors present at the host cells surface in lung and in some other organs (Neufurth et al., 2020).

2.16.2 Nanoengineered vaccines

Nanocarriers serve as excellent platforms to stimulate immune response, both humoral and cell-mediated responses, against specific antigens. They can be fine-tuned to modulate immune response. Their size, shapes, surface charge, amphiphilicity, antigen display, antigen concentration greatly influence the extent and type of immune response elicited. Nanoparticles fabricated at sizes <200 nm have excellent lymphatic trafficking, can be easily accumulated at lymph nodes, engulfed by antigen-presenting cells, processed and presented to T cells, and enhance activation of B cells to secret specific antibodies. Free peptides are weakly immunogenic, owing to their inability to stimulate dendritic cell maturation, and they are eliminated rapidly from the host body. Hence, the incorporation of immunogenic peptides into appropriately designed nanomaterials triggers a greater immune response.

Viral antigen could either be adsorbed or conjugated onto the surface or encapsulated inside nanocarriers. Self-assembling protein nanoparticles are single protein monomers that are designed to self-assemble into nanoscale structures (Vetter et al., 2018). Synthetic virus-like particles (SVLP) are protein structures that resemble viruses in one or more antigens and are designed using recombinant technology. SVLP contain no genetic material and thus do not cause infection and they are nonreplicating (Negahdaripour et al., 2017). PEGylated nanoparticles showed the ability to improve lymphatic trafficking and biodistribution of the administered nanoconstructs (Zhuang et al., 2012). PEGylation also promotes mucoadhesion of nanovaccines administered to the nasal mucosa, facilitating their permeation, due to network formation between PEG chains and mucus

from nasal mucosa (Huang et al., 2000; Sahlin & Peppas, 1997), and/or hydrogen bonds formation between the polymer and mucins (Lele & Hoffman, 2000; Yusuf et al., 2017).

There are many different shapes of nanoconstructs, each could be employed in a way to affect the properties of the nanovaccines, thus modifying the degree and duration of the elicited immune response. For example, utilizing nanofibers as vaccine platforms can enhance vaccine efficacy (Li et al., 2013; Si et al., 2018) and can allow for adjustable peptide display on their surfaces, which in turn, allow for improved peptide-specific immunization (Parlane et al., 2020). Dendrimers, repetitively branched polymeric constructs, have demonstrated intrinsic adjuvanticity that can be also utilized to boost the immune response (Lu et al., 2015). To enhance the immunogenicity of weakly immunogenic peptide antigens, dendrimers were constructed in star-shaped nanoparticles that allowed for modulating immunogen density and allowed for codelivery of T-helper antigens which also produced prolonged retention time at the injection site (Francica et al., 2019). Liposomes are phospholipid vesicles, with a structural mimicry to cell membranes. They can be used as vaccine delivery systems by loading them with viral antigens or via conjugation of antigens onto their surfaces. Moreover, liposomes possess intrinsic adjuvant activity, and they can stimulate dendritic cells by upregulating cytokines expression and activating ERK kinase (Yan et al., 2007). Over the past decades, liposomal adjuvanticity emerged to become frequently exploited as an important vaccine adjuvant-delivery system. Physicochemical features of liposomes that control the type, extent, and duration of the elicited immune response include surface charge, membrane fluidity, liposomal size, and whether antigens are loaded inside or conjugated/adsorbed onto their surfaces (Wang et al., 2019). The fluidity of membranes forming the liposomes depends primarily on the type of lipids. Longer chain lipids increase membrane rigidity while shorter ones decrease rigidity (Perrie et al., 2016). Incorporating cholesterol in liposomal structure showed to decrease membrane fluidity besides additional effects on particle size, morphology, and release of hydrophilic cargoes (Kaddah et al., 2018). Previous studies on the effect of membrane fluidity on the adjuvant activity of liposomes demonstrated that rigid membrane liposomes produced greater immune response, release of more antigens at the injection site, and higher stimulation of Th1 cells (Christensen et al., 2012). Additionally, it was previously observed that cationic liposomes trigger a higher immune response than

that generated with either neutral or anionic liposomes (Davidsen et al., 2005). As well, cationic liposomes displayed an additional advantage, as they can deliver their cargos to the depot. Their surface positive charges allow for interaction with proteins from extracellular fluids leading to their aggregation, therefore, forming a depot at the administration site. This allows for retained antigen release and consequently prolonged immune response (Chatzikleanthous et al., 2020; Wilson et al., 2009).

Polymeric nanoparticles have been also frequently utilized for the design of nanovaccines, due to their intrinsic adjuvant properties (Zhang et al., 2018, 2019). Several polymers have been utilized in the fabrication process, such as chitosan (Bolhassani et al., 2014), poly(lactide–*co*–glycolide) (Yang et al., 2016), polyethylene glycol (Jain et al., 2010), and polypeptides (Xiang et al., 2018). Cationic nanoconstructs proved to improve cellular internalization and subsequent antigen delivery to cellular targets (Yue et al., 2011; Yusuf et al., 2017). Furthermore, complexation with nanoparticles could protect cargoes from enzymatic degradation, thus increasing whole vaccine stability, which is particularly important for mRNA and DNA-based vaccines due to their susceptibility to enzymatic degradation (Elsabahy et al., 2011). Utilization of nanostructures allows for optimizing antigen display in terms of antigen surface distribution and density, consequently, enhancing immune response (Francica et al., 2019) and improving B cell receptor cross-linking (Ingale et al., 2016). In addition to antigen display modulation, multiple antigens can be displayed simultaneously to receptors, and thus more effective stimulation of B cells can be attained (Kanekiyo et al., 2019).

Vaccine development can further be advanced by utilizing the relatively large loading capacity of nanostructures and fine-tuning of their structures and composition, thus encapsulating both antigens and additional adjuvants together. Furthermore, various immunomodulators can be incorporated into the formulation, either encapsulated inside the nanocarrier or conjugated onto the surface to further improve the effectiveness of the vaccine (Tallapaka et al., 2019). Moreover, nanoplatforms allow for controlled bionavigation with the aid of surface decorating moieties that improve cellular uptake via receptor-mediated endocytosis. The ability to control the release of the loaded cargoes allows control over the immune reactions generated. Controlling the release of antigens can be particularly useful for DNA vaccines due to the risk of insertional mutagenesis if high doses are administered. Hence, nanoplatforms can advance the overall safety of vaccines (Lu, 2020).

Upon introducing the vaccine into the host body, it enters the lymphatic system and becomes engulfed by antigen–presenting cells and presented to B cells. Then, B cells are stimulated to produce antigen-specific antibodies and IgM during an early primary immune response, and IgG is produced later and lasts longer than IgM. Multiple previous attempts to utilize nanomedical approaches in the design of coronavirus vaccines were frequently conducted for efficient immunization via the production of antigen-specific antibodies. For instance, homologous MERS spike protein nanoparticles and heterologous adenoviral vector/MERS-spike protein stimulated immunoglobulin IgG production. Simultaneous stimulation of Th1 and Th2 cells was only observed with heterologous adenoviral vector/MERS-spike protein, but not with spike protein nanoparticles alone, thus ultimately producing longer-lasting immunization. However, it was found that the host body secreted antibodies against the viral vector antigen, which led to decreasing antigen presentation to antigen–presenting cells, thus compromising the immune response elicited (Jung et al., 2018). Likewise, another study group developed two protein nanoparticle vaccines, one from S protein of SARS-CoV-1 and the other is from S protein of MERS. Both nanoparticles produced neutralizing antibodies against their respective antigens in mice. Two types of adjuvants, Alum and Matrix-M1, were evaluated in this study. Matrix-M1 induced immune response more effectively than Alum. However, no cross-immunity was observed, that is, each nanoparticle resulted in the immune response against the respective virus but not the other coronavirus (Coleman et al., 2014). Matrix-M1 is a saponin-based adjuvant that upon incorporation into the vaccine design increases vaccine immunogenicity and elicits both cellular and humoral immune responses while keeping a balance between Th1 and Th2 responses and eliciting cytotoxic T cell responses (Cox et al., 2011; Madhun et al., 2009; Magnusson et al., 2018; Pedersen et al., 2014). In an attempt to develop a vaccine against MERS-CoV, Matrix-M1 was combined with MERS-CoV S protein nanoparticles. Specific immunoglobulins were generated and the vaccine was able to stop replication in an in vivo mice model of MERS infection. The generated immunoglobulins were higher than those produced with MERS S nanoparticles alone, highlighting the immunomodulatory effect of Matrix-M1 in potentiating the immunogenicity of vaccines (Coleman et al., 2017). In another study, SVLP was fabricated by adsorbing S protein onto the surface of gold nanoparticles. SVLP showed an increased antigen delivery, lymphatic transport, lymph node localization, higher IgG

production than the free S protein. The results imply the activation of other immune mechanisms such as complement activation, increased cellular internalization, and enhanced antigen presentation by antigen-presenting cells (Chen et al., 2016; Heesters et al., 2014; Reddy et al., 2006), thus highlighting the potential benefits nano-approaches could add up to the coronavirus vaccine design.

In agreement with previous literature, data from a recent study indicated that multivalent display of RBD on 2-protein components self-assembly nanoparticles (I53−50) boosts immune response elicited, the vaccine nanoparticles stimulated immune response and generated 10-fold higher levels of antibody titers than with that generated with perfusion-stabilized spike protein even when given at fivefold lower dose. Antibodies produced could react with several antigen epitopes of the RBD; therefore it is expected to stay effective despite the mutations that might occur. Furthermore, the vaccine produced a relatively lower binding: neutralizing ratio than that of convalescent serum (Walls, n.d.).

Moreover, multivalent antigen display can activate B cells to a greater extent than soluble antigens (Antanasijevic et al., 2020). Two-component self-assembly protein nanoparticles vaccine study reported relatively greater B cells activation than with that elicited with soluble antigens in vitro. In vivo, the vaccine nanoparticles elicited a humoral immune response with a relatively high level of antibody titers in macaques in addition to reduced viral infection and replication (Brouwer et al., 2021). Conformational design of nanoparticle vaccine platform for SARS-CoV-2 and HIV-1 viruses that constituted 1,2-Dioleoyl-sn-glycero-3-phosphocholine, n-(succinimidyloxy−glutaryl)-L-α-phosphatidyl-ethanolamine, dioleoyl and monophosphoryl lipid A demonstrated an increased cellular uptake of antigens, antigen presentation, and enhanced dendritic cell activation. A high accumulation of antigen at lymph nodes was observed. When compared with soluble antigen proteins, a greater immune response was reported with regard to higher serum antibody titers against RBD of S receptor of the SARS-CoV-2 in mice (Park et al., 2021).

Multiple nanoplatforms can be employed in designing vaccines and therapeutics for the management of COVID-19 (Table 2.1), such as polymeric nanoparticles, inorganic nanoparticles, lipid-based nanostructures, virus–like nanoparticles, and self-assembled peptide nanoparticles (Keech et al., 2020; Press Release, 2021; Ramasamy et al., 2020).

Table 2.1 Nanoengineered vaccines and therapeutics in development for management of COVID-19.

Nanodevice	Type	Composition	Remarks	Reference
NVX-CoV2373	Vaccine	Solid lipid nanoparticle; comprised of ionizable lipid, SM-102, and 3 commercially available lipids, cholesterol, DSPC, and PEG2000-DMG	Results showed that the vaccine is safe and effective	ClinicalTrials.gov Identifier: NCT04368988
mRNA-1273 LNP	Vaccine	Recombinant peptide nanoparticle vaccine	Vaccine combined with Matrix-M1 as an adjuvant currently tested in phase 2	https://ir.novavax.com/news-releases/news-release-details/novavax-identifies-coronavirus-vaccine-candidate-accelerates (accessed on June 2021)
Ribavirin-loaded polymeric nanoparticles	Therapeutic	Polyglycerol–adipate (PGA) polymeric nanoparticles	Lower accumulation of ribavirin inside RBCs —lower toxicity	Abo-zeid et al. (2018)
Lopinavir-vitamin E-TPGS Micelle	Therapeutic	D-α-tocopherol polyethylene glycol 1000 succinate	Higher oral bioavailability than the free drug suspension	Mahajan and Patil (2020) and Pham et al. (2016).
Lopinavir-loaded polymeric nanoparticles	Therapeutic	Pullulan acetate polymer	Higher bioavailability than the free lopinavir	Ravi et al. (2014)

(Continued)

Table 2.1 (Continued)

Nanodevice	Type	Composition	Remarks	Reference
Lopinavir/ ritonavir– loaded polymeric nanoparticles	Therapeutic	Poly(lactide-*co*-glycolide) copolymer	Higher bioavailability of lopinavir	Abou–El-Naga et al. (2017)
Lopinavir/ ritonavir– loaded in situ self– assembly nanoparticles	Therapeutic	Oleic acid and D-α-tocopherol polyethylene glycol 1000 succinate	Enhanced oral bioavailability, stable therapeutic plasma concentrations, and improved biodistribution	Pham et al. (2016)
Oseltamivir modified silver nanoparticles	Therapeutic	Oseltamivir–modified silver nanoparticles	Higher antiviral activity and lower toxicity than the free drug and the unloaded silver nanoparticles	Li et al. (2016)

2.17 Current status and perspectives

Vaccines comprising *mRNA* are effective at eliciting immune responses, both innate and adaptive ones. Also, they are a relatively safe versatile approach in immunization, and their use neither involves the risk of insertional mutagenesis nor the risk of infection, although their instability necessitates their incorporation into a protecting platform (Pardi et al., 2018). They are safer than inactivated or protein-based vaccines because they are free from the risk of protein contamination or activation of an injected virus. Furthermore, mRNA vaccine possesses a superior advantage, which is on a large scale, and mRNA does not involve problems arising with the purification processes of viral proteins which are appreciated in saving time spent in standardization. In addition to the negative charge and the hydrophilic nature, the RNA cannot be taken up easily by the cells during in vivo conditions. Thus it requires highly efficient carriers such as nanoparticles. The lipid nanoparticle promotes mRNA vaccine stability and protects it from intracellular and extracellular degrading enzymes. In addition, the nanoparticles were biologically compatible and could aid in their cellular internalization (Elsabahy et al., 2011; Goswami et al., 2019; Samaridou et al., 2020).

Vaccines developed by Biontec and Pfizer are two mRNA encapsulated lipid nanoparticles vaccine candidates BNT162b1 and BNT162b2 that were tested in phase 1 trial ($n = 195$) in the United States and it involved multiple age groups (18−55 years and 65−85 years). Results elucidated showed similar serum antibody titers of the two vaccines and higher than that of convalescent individuals. Side effects were tolerable and were less with BNT162b2 than BNT162b1 (Walsh et al., 2020). The vaccine needs to be stored at $-70°C$, which can be very challenging when considering mass immunization. Data published from the phase 2 trial showed some early protection 12 days after the first dose, 7 days after the second dose, and 95% efficacy was reported (Polack et al., 2020).

University of Oxford together with AstraZeneca developed a *ChAdOx1 nCoV-19 vaccine*, which employs a chimpanzee adenoviral vector as a delivery vehicle that is being modified to be unable to replicate in the vaccinated host (Folegatti et al., 2019). The RNA encodes the S protein of the SARS-CoV2. The vaccine can be stored at regular refrigerator temperature that could be advantageous. Preclinical data in mice and in rhesus macaque models showed humoral and cellular immune responses. No pneumonia was observed in vaccinated rhesus macaques and no

immune adverse events occurred (Doremalen, 2020). Upon testing this vaccine for safety, efficacy, and immunogenicity in two phase I/phase II clinical trials, one in the United Kingdom ($n = 1090$) and the other one in South Africa ($n = 2000$) (ClinicalTrials.gov: NCT04444674 and NCT04324606), similar neutralizing antibody titers between the study groups were observed, and T cell responses during the phase II trial ($n = 560$) were reported (Ramasamy et al., 2020). Currently, it is being evaluated in ongoing trials, phase II/III and phase III, respectively (ClinicalTrials.gov Identifier: NCT04400838 and NCT04516746).

The nanoengineered vaccine mRNA–1273 LNP showed promising preclinical and clinical results and is currently being tested in phase III trial ($n = 30,000$) (ClinicalTrials.gov: NCT04283461). The mRNA strand coding for the S protein of SARS-CoV-2 is encapsulated inside a lipid nanoparticle. It was developed by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health together with Moderna, Inc. The vaccine requires $-20°C$ to be stored, which could be available in developed countries and well-equipped health centers; however, in rural areas that are less equipped especially in developing countries, storage and transportation can be difficult.

Recombinant peptide nanoparticles vaccine (NVX-CoV2373) developed by Novavax, Inc. was tested in phase I clinical trial for safety and immunogenicity (ClinicalTrials.gov: NCT04368988), and results from phase I/II revealed that it is safe and potent as it elicited immune responses that exceeded levels in COVID-19 convalescent serum. Also, M–matrix is incorporated in the formulation as an adjuvant to boost immune response (Keech et al., 2020; Press Release, 2021).

iBioPharma, Inc. is developing two vaccines for COVID-19. *VLP* is a virus–like particle that is prepared by combining self-assembled proteins and SARS-CoV-2 antigen protein, and the resulting particles are further decorated with oligomannose monomers. The subunit vaccine is derived from SARS-CoV-2 S protein combined with lichenase booster molecule (LickM), a carrier protein molecule that is capable of augmenting the immune response generated by the vaccine.

CureVac Co. developed an mRNA vaccine that generated high levels of virus-neutralizing titers in animal models, and it is currently being tested in phase II/III trial (ClinicalTrials.gov Identifier: NCT04652102). Viral vector–based vaccines are also being developed. DNA vaccines are designed usually to encode specific antigens that can elicit immune responses against specific pathogens.

DNA vaccine for COVID-19 is being developed by Inovio Pharmaceuticals, Inc., which is called *INO-4800.* The vaccine encodes for the S protein of the SARS–CoV-2. Electroporationby a device called CELLECTRA produces a brief electrical pulse that makes small pores in the cell membrane to allow the transfection of plasmids. Preclinical data in animal models demonstrated that it is an effective vaccine in stimulating an immune response, both humoral and cell-mediated. It also produced neutralizing antibodies against the receptor–binding domain and results showed its effective neutralizing capacity of SARS-CoV-2, together with its competitive inhibition of the ACE2 receptors. The plasmid is stable at room temperature thus making it appropriate for mass immunization. Further investigations in bigger mammalian models and in human subjects are still needed (Smith et al., 2020).

Recombinant adenovirus type-5 (Ad5) vectored vaccine expressing S protein of SARS-CoV-2 was evaluated for safety and immunogenicity in phase I clinical trial ($n = 108$) (ClinicalTrials.gov: NCT04313127). Results published revealed that adverse events encountered with vaccine escalating dose were tolerable and no serious adverse effects were observed till 28 days postimmunization, and humoral and cellular immune responses were reported (Zhu, Li, et al., 2020; Zhu, Lu, et al., 2020).

The uprising global issue of COVID-19 motivated all parties to put in efforts to rapidly develop treatment and/or vaccines to limit the spread of the disease. Several recommendations and enormous efforts and endeavors have been proposed based on previous knowledge and expertise. In this chapter, the use of nanomedical approaches to develop potent therapeutics and vaccines against SARS-CoV-2 has been highlighted. Numerous structural and functional features of nanotherapeutics and nanovaccines have the potential to improve therapeutic efficacy and immunization strategies. However, it should be considered that to ultimately have an effective vaccine in the market available to mass populations worldwide, there are numerous stages of vaccine development. Vaccines might be also associated with immunopathologies, and thus investigating these candidate vaccines must be done with caution and all immune effects must be taken into consideration (Kamps & Hoffmann, 2020). For instance, the effect of immunizing ferrets with recombinant virus Ankara expressing S protein of SARS-CoV was studied, and severe hepatitis was demonstrated in the animal models (Kamps & Hoffmann, 2020; Weingartl et al., 2004). Furthermore, due to the complexity of the scale-up process, particularly with innovative and sophisticated technologies, nanoengineered

therapeutics and vaccines may take up to several years to provide the market with sufficient amounts of safe yet efficient therapeutics and vaccines that can fulfill global demands.

Acknowledgment

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