



Pharmacotherapeutics of SARS-CoV-2 Infections

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Abstract

The COVID-19 pandemic has affected more than 38 million people world-wide by person to person transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Therapeutic and preventative strategies for SARS-CoV-2 remains a significant challenge. Within the past several months, effective treatment options have emerged and now include repurposed antivirals, corticosteroids and virus-specific antibodies. The latter has included convalescence plasma and monoclonal antibodies. Complete viral eradication will be achieved through an effective, safe and preventative vaccine. To now provide a comprehensive summary for each of the pharmacotherapeutics and preventative strategies being offered or soon to be developed for SARS-CoV-2.

Keywords SARS-CoV-2 · COVID-19 therapeutics · Antivirals · Antibodies · Vaccine

Introduction

The novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), after its first appearance in Wuhan, China, spread globally and soon it was declared the third global pandemic by zoonotic coronaviruses, succeeded by SARS-CoV in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (Coronaviridae Study Group of the International Committee on Taxonomy of V 2020; Lu et al. 2020; Zhu et al. 2020). The disease is mainly manifested by the acute respiratory distress syndrome (ARDS) causing pulmonary demise and ultimately death especially affecting patients

with comorbid conditions like diabetes, hypertension (Machhi et al. 2020; Xu et al. 2020; Yang et al. 2020a). The SARS-CoV-2 enters the lung after binding to the epithelial angiotensin-converting enzyme 2 (ACE2) receptors and spread to the distal organs including heart, liver, kidney, gastrointestinal tract and brain, to induce systemic inflammatory immune responses (Gu and Korteweg 2007; Grasselli et al. 2020; Meredith Wadman et al. 2020; Yuki et al. 2020). The rapidly spread of SARS-CoV-2 demands immediate needs to develop containment treatment with parallel adoption of public hygiene etiquette and practice (National Institute of Health (NIH) 2020a, 2020b; Udagama et al. 2020; Wölfel et al. 2020).

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Clinical Signs and Symptoms

Infection by SARS-CoV-2 ranges in outcome severity. Among individuals testing positive for SARS-CoV-2, 56 to 88% report no symptoms at the time of testing (Arons et al. 2020; Mizumoto et al. 2020). Nonetheless, in the absence of universal screening, estimating true asymptomatic rates remains challenging. The clinical progression of COVID-19 disease is often associated with the length of the pathogen's incubation (Machhi et al. 2020). Most COVID-19 patients develop symptoms three to six days after viral exposure (Backer et al. 2020; Guan et al. 2020; Li et al. 2020b). Similarly, the median time from symptom onset to the development of pneumonia and the ARDS is up to eight days (Wang et al. 2020b). Symptom duration is 13 days (Young et al. 2020). A 14-day quarantine is recommended following exposure to SARS-CoV-2. This is in accordance with the upper limits of the virus' incubation period. Mild COVID-19, defined as no or mild respiratory compromise, is present in 81% of infected persons (Wu and McGoogan 2020). At presentation, the most common COVID-19 symptoms are fever, dry cough, and sore throat (Young et al. 2020). As disease progresses, the signs of early infection include shortness of breath, myalgias, and rhinorrhea. A minority of patients have abdominal pain, nausea or diarrhea (Cheung et al. 2020). Alternatively, smell and or taste dysfunctions are present at the onset of disease in up to 19% of patients (Giacomelli et al. 2020). SARS-CoV-2 induces aggressive respiratory pathologies in a subset of those infected. Severe disease, present in 14% of patients, is marked by dyspnea and hypoxia and can be recorded by radiographic infiltrates in >50% of chest X-rays or CT scans (Wu and McGoogan 2020). Approximately 5% of infected individuals progress to a state of critical disease, frequently requiring treatments in an ICU. Critical COVID-19 complications encountered within the ICU include ARDS (19.6%), arrhythmia (16.7%), shock (8.7%), acute cardiac (7.2%) or acute kidney (3.6%) injuries (Wu and McGoogan 2020). ARDS is marked by respiratory failure. Like other viral pneumonias, COVID-19 ARDS is managed with supplemental oxygen, prone positioning, mechanical ventilation, antiviral or glucocorticoid therapies and extracorporeal membrane oxygenation (Murthy et al. 2020; Wang et al. 2020b). Other atypical disease features can include dermatologic findings and inflammatory syndrome-like manifestations in children. Vesicular skin eruptions are described early in the disease course whereas purple nodules on peripheral digits have led to the term, "COVID toes" (Galvan Casas et al. 2020). SARS-CoV-2 infection appears milder in children, with only 73% of those who are symptomatic reporting fever, cough, or dyspnea compared to 93% of the symptomatic adults (Centers for Disease Control and Prevention (CDC) 2020a). Some pediatric COVID-19 cases reported detail gastrointestinal symptoms and myocarditis, reflective of atypical

Kawasaki's disease (Jones et al. 2020). The mortality rate of COVID-19 is between 3 and 6% worldwide (World Health Organization (WHO) 2020b; Centers for Disease Control and Prevention (CDC) 2020b). Deaths of COVID-19 in children are rare. Among ICU patients, the mortality rate increases to 26% and more prevalent with male gender, age (> 63 years) and hypertension (Grasselli et al. 2020). The main causes of death is massive alveolar damage and respiratory failure with pulmonary interstitial fibrosis (Tian et al. 2020). Serologic hallmarks of terminal COVID-19 include elevated neutrophils, D-dimer, renal failure (high blood urea nitrogen and creatinine) and lymphopenia (Wang et al. 2020b). SARS-CoV-2 also promotes coagulation, neutrophilia and systemic shock during acute infection, often precipitating a cytokine storm and chronic immune exhaustion (Barnes et al. 2020; Yang et al. 2020b). These events, along with hypoxia, may stress the kidneys, contributing to final multisystem organ failure (Meredith Wadman et al. 2020; Puelles et al. 2020).

Pharmacology and Pharmaceuticals: Antivirals and Immune Modulators

As the global coronavirus pandemic unfolds, treatments already approved by the U.S. FDA represent the only therapeutics available to physicians. None of them are currently able to prevent the spread of the infection, and most of the available therapeutic options are adjuvants of supportive care, mainly repurposed antiviral agents, or drugs to treat the immune responses to the infection.

Remdesivir and Favipiravir Remdesivir is a well-known, novel nucleotide analogue developed initially as a treatment for Ebola and Marburg viruses. Remdesivir has an acceptable clinical safety profile. This was reported during prior clinical research activities with ~500 individuals, including healthy volunteers and patients treated for acute Ebola virus infection (Mulangu et al. 2019). Remdesivir demonstrated antiviral activity against different coronaviruses (including SARS and MERS-CoV), both in vitro and in animal studies (Sheahan et al. 2020). Recent reports showed its efficacy against SARS-CoV-2 in vitro as well (Wang et al. 2020c). Remdesivir has been evaluated in multiple clinical trials for moderate to severe COVID-19 (Sheahan et al. 2017; Grein et al. 2020). Remdesivir is given parenterally and has reported side effects that include nausea, vomiting, and serum transaminase elevations. The use of remdesivir for COVID-19 also has been described in several case series (Gilead 2020; Holshue et al. 2020; Lescure et al. 2020). In one multicenter, multinational study, 53 patients with severe COVID-19 and hypoxia received remdesivir for up to 10 days with a median of 18 days of follow-up. In this study, 68% of the patients had clinical improvement with decreased oxygen requirements and hospital discharge. Based upon these positive reports,

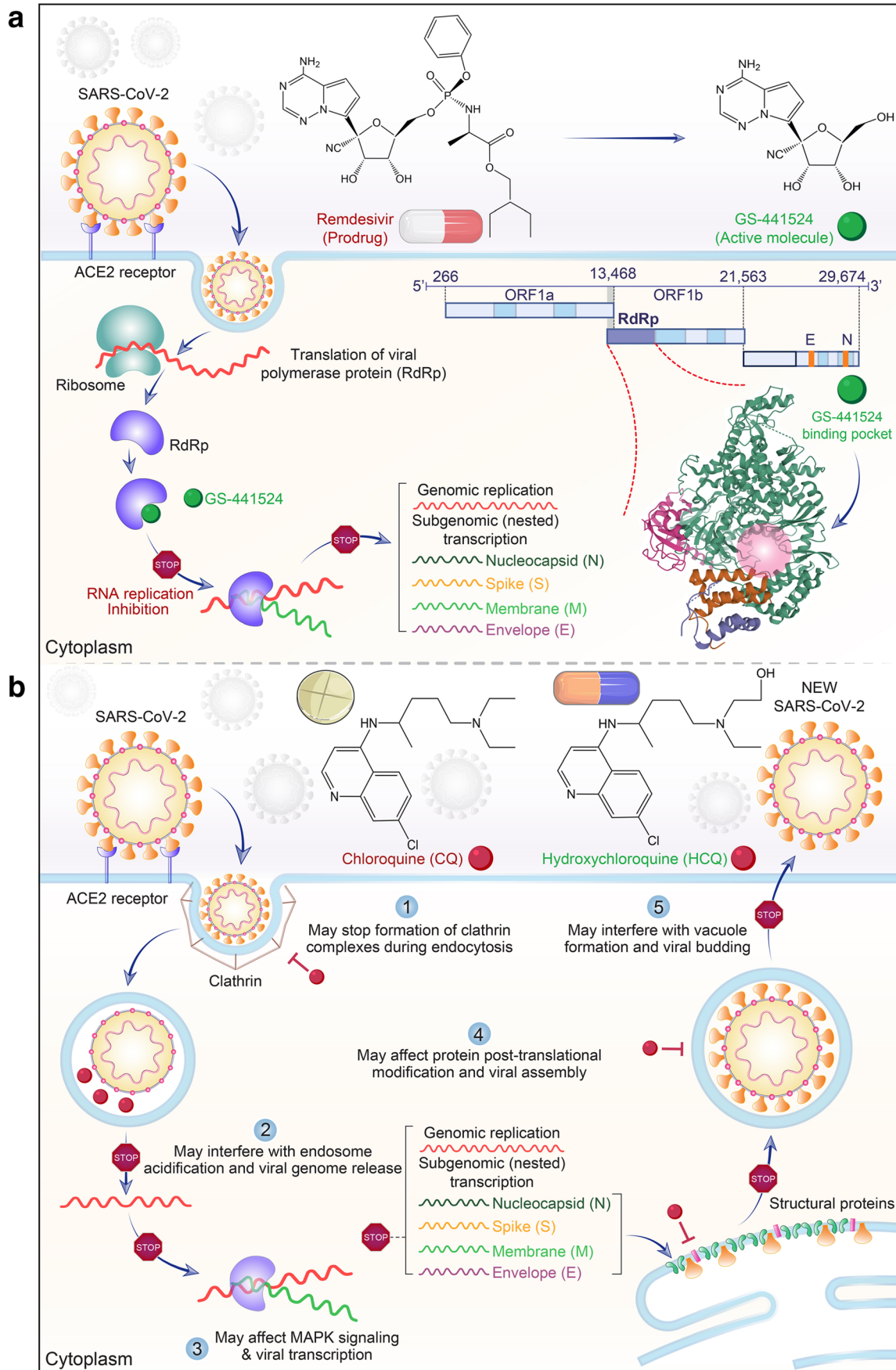
remdesivir received EUA from the US FDA for COVID-19 treatment and recently extended its use in all hospitalized suspected or confirmed adults and pediatric patients irrespective of the disease severity (Beigel et al. 2020; Grein et al. 2020). The largest double blinded, randomized, and placebo controlled clinical study of remdesivir with more than 1000 patients demonstrated that mean recovery time for the remdesivir treatment group (11 days) was significantly lower compared to the placebo group (15 days) ($P < 0.001$). The study also found a non-significant lower mortality rate after 14 days in the remdesivir treatment group compared to the placebo group. Incidences of adverse effects due to remdesivir treatment were comparable to the placebo group. Secondary analysis looked at treatment efficacy among groups categorized on the eight-category ordinal scale. The most apparent benefit was seen in patients given remdesivir with a baseline ordinal score of five (requiring oxygen). Baseline ordinal scores of four (not receiving oxygen), six (receiving high flow oxygen), and seven (receiving extracorporeal membrane oxygenation or mechanical ventilation) showed wide confidence intervals. These findings underscore the importance of starting antiviral therapies before severe pulmonary disease onset that require mechanical ventilation (Beigel et al. 2020). Design and development of drug delivery systems to improve drug absorption and facilitate targeted remdesivir delivery to the lungs are at various stages of preclinical development. Such approaches include development of inhalable particles for localized drug delivery (UT News 2020). Furthermore, strategies to enhance the antiviral potency of remdesivir (higher-dose regimens in combination with other antivirals or SARS-CoV-2 neutralizing antibodies) and to mitigate immunopathological host responses contributing to COVID-19 severity (e.g., inhibitors of IL-1, IL-6 or tumor necrosis factor alpha (TNF α)), will require rigorous studies in patients with severe COVID-19 (Wang et al. 2020e). Favipiravir, an RNA polymerase inhibitor previously used for the treatment of influenza, is now being evaluated for SARS-CoV-2 infection. In an open-labelled study, favipiravir has shortened viral clearance time and improved CXR test results in COVID-19 patients compared to the lopinavir/ritonavir (Cai et al. 2020). Both remdesivir and favipiravir are promising therapies for COVID-19.

The mechanism of action for both drugs involves the inhibition of the viral RNA translation (Fig. 1a). After encoding, genomic RNA of SARS-CoV-2 acts as a mRNA for producing two polyproteins (pp1a and pp1b). Proteolytic cleavage of the polyproteins results in the production of RNA-dependent RNA polymerase (RdRP), helicase, and non-structural proteins 3, 4 & 6 (nsp3, nsp4 & nsp6). Nsp3, nsp4 & nsp6 are responsible for anchoring the SARS-CoV-2 replication transcription complex by recruitment of intracellular endoplasmic reticulum membranes to form double-membrane vesicles (DMV). RdRP and helicase localize to double-membrane

vesicles and drive the production of subatomic RNAs, from which the structural and accessory proteins are produced in the next phase of translation. Early testing of both remdesivir and favipiravir showed that they can inhibit RdRP and, therefore, could be useful in the management and treatment of early or mid-stage COVID-19 (Furuta et al. 2017; Gordon et al. 2020) (Fig. 1a).

Dexamethasone Dexamethasone is a potent anti-inflammatory corticosteroid and its nanoformulation is well known for the development of macrophages depot after intravenous and inhalation administration (Lammers et al. 2020). The long-acting nanoformulation of anti HIV-1 drugs showed success as a macrophage-based drug carrier for anti-HIV-1 therapy compared to the free drug (Dash et al. 2020; Kevadiya et al. 2020; Kulkarni et al. 2020; Mukadam et al. 2020). Hence, this strategy might also work in COVID-19 treatment if alveolar macrophages targeting dexamethasone nanoparticles are designed (Fig. 2). A recent study on SARS-CoV-2-infected patients showed that dexamethasone decreased mortality in COVID-19 patients. The UK-based firm and the RECOVERY Collaborative Group carried out a randomized, controlled clinical trial consisting of 2140 patients receiving dexamethasone, either by oral or inhalation route, while 4321 patients received standard care. The study showed that in hospitalized COVID-19 patients, the use of dexamethasone resulted in lowered 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone, but not in those without respiratory support (Group RC 2020).

Hydroxychloroquine (HCQ) and Chloroquine (CQ) Despite the widespread use of HCQ and CQ to treat COVID-19, few controlled clinical trials were performed; hence, the drug benefits remain controversial (Khuroo 2020; Patel et al. 2020). While past successes were reported for the treatment of malaria, rheumatoid arthritis and systemic lupus erythematosus, toxicities were seen associated with both medicines when used at high doses during chronic administration. However, the antiviral, anti-inflammatory and anti-thrombotic activities of HCQ (Quiros Roldan et al. 2020) led to its further exploration for SARS-CoV-2 treatments (Wang and Lim 2016). In cell-based assays, both CQ and HCQ were shown to increase endosomal pH, interfere with virus-cell binding and ACE2 receptor glycosylation, thereby inhibiting SARS-CoV-2 infection (Fig. 1b) (Wang et al. 2020c; Yao et al. 2020). However, in-contrast to cell-based efficacy, the more potent CQ analog (de Wilde et al. 2014) was found to be ineffective in SARS-CoV-2-infected Balb/c mice (Barnard et al. 2006). Mechanistic studies to address the discrepancy were performed to assess therapeutic efficacy of CQ and HCQ. In vitro Vero (kidney), Vero-TMPRSS2 and Calu-3 (lung) cells were used to test CQ and HCQ antiviral efficacy



◀ **Fig. 1 Remdesivir, chloroquine and hydroxychloroquine for treatment of SARS-CoV-2 infection.** **a**, Remdesivir is a phosphoramidate ProTide of an adenosine nucleotide analog GS-441524. After intracellular uptake, GS-441524 converted into nucleotide triphosphate and served to inhibit viral RNA-dependent RNA-polymerase (RdRp, crystal structure adopted from (Sehna et al. 2018)) as required for SARS viral transcription and translation. **b**, Chloroquine (CQ) and hydroxychloroquine (HCQ) are commonly used to treat malaria patients. The mechanism by which CQ block virus infection is by elevating endosomal pH required for viral cell fusion and by interfering with the glycosylation of cellular viral receptors. Thus, it is theorized that the drugs block viral entry and post-entry infection. However, its most active steps in affecting viral pathobiology are presumed mediated by its anti-inflammatory and immunomodulatory actions during the cytokine storm perpetuated by SARS-CoV-2 infections. However, the mechanism of HCQ's inhibition of SARS-CoV-2 remains not completely understood and could be at any point in the viral life cycle. Potential targets may include clathrin coating during endocytosis, endosome acidification, viral transcription, trafficking, formation, and viral release/budding (1–5)

(Hoffmann et al. 2020a). The cell lines were chosen to activate the SARS-CoV-2 S and served to mediate intracellular viral entry. Notably, Vero cells utilize a pH dependent intracellular cysteine protease cathepsin L (catL) enzyme to activate the receptor needed for viral entry while Calu-3 cells utilize a pH independent plasma membrane resident serine protease (TMPRSS2) enzyme. Since cathepsin L requires an acidic environment to function and that CQ and HCQ are known to inhibit endosome-lysosomal system acidification, CQ and HCQ efficiently blocked SARS-CoV-2 infection of Vero but failed to block infection of Calu-3 cells. This study underscores the importance of using appropriate assays and cell lines when screening antiviral activity of compounds that target host cell-based functions. However, due to HCQ and CQ's ability to inhibit pro-inflammatory cytokines (e.g., IL-1b, TNF- α and IL-2) which form major components of the cascade of events leading to ARDS in SARS-CoV-2 patients, HCQ/CQ was considered as a potential treatment (Colson et al. 2020; Multicenter collaboration group of Department of Science and Technology of Guangdong P, Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus p 2020). Subsequently, however, both drugs were found to be ineffective for treatment of viral infections, including COVID-19. First, CQ treatment actually exacerbated chikungunya viral infection, with worsening of patient outcomes secondary to CQ induced delayed adaptive immune responses (Gallart et al. 1988). A single-arm, open-label trial of 600 mg daily HCQ in 20 COVID-19 patients reported that HCQ alone, or in combination with azithromycin reduced viral load (Gautret et al. 2020a). A follow-up trial in 80 patients with HCQ and azithromycin combinations reported that 93% of patients had a negative RT-PCR result by eight days of treatment. However, both trials had no control arms (Gautret et al. 2020b). Rigorous statistical analyses by others found limited evidence for efficacy (Hulme et al.

2020; Lover 2020). A subsequent double-blind randomized clinical trial for HCQ COVID-19 treatment (ChiCTR2000029559) (Chen et al. 2020b) showed clinical resolution a day earlier than controls. Subsequent reports showed no significant differences for HCQ therapy in median duration of hospitalization, time to fever resolution, or progression of disease as measured by chest CT (Chen et al. 2020a). The largest randomized clinical trial to date enrolled 150 patients with mild COVID-19 across 16 centers in an open-label trial of HCQ versus standard of care (ChiCTR2000029868) and found no significant group differences in conversion to negative SARS-CoV-2 RT-PCR or decrease in the rate of symptom resolution (Tang et al. 2020c). Finally, a meta-analysis of all performed studies found no clinical benefits for HCQ in the treatment of SARS-CoV-2 (Shamshirian et al. 2020). Instead, worsening of clinical progression and a death were reported (Molina et al. 2020). For severe COVID-19, a double-mask, randomized phase IIb trial (NCT04323527) was performed in 81 patients who were given high compared to low doses of HCQ (600 mg/day for 10 days or 450 mg/day for 5 days) (Borba et al. 2020). The high-dose arm was halted due to greater adverse events with prolonged QTc intervals, higher lethality, requirements for mechanical ventilation and no difference in detectable viral RNA when compared to the low-dose arm. In another observational study, 1376 patients hospitalized with COVID-19 received HCQ, but the treatment did not alter the need for intubation or death rate (Geleris et al. 2020). Taken together, HCQ alone or in combination with azithromycin show no clinical benefits in measurable outcomes for treatment of COVID-19. [ClinicalTrials.gov](https://www.clinicaltrials.gov) showed 254 clinical trials involving HCQ and COVID-19, which attests to the continued interests in the investigation of this drug as potential therapy for COVID-19. However, long-term administration of HCQ was found to be associated with increased risk of cardiovascular mortality (Feng et al. 1988; Lane et al. 2020). The WHO on July 4th, 2020 recommended discontinuation of HCQ based on Solidarity Trial's International Steering Committee's recommendation (World Health Organization (WHO) 2020a). This decision was taken after their review of all completed trials (Cohen 2020).

Azithromycin and HCQ As outlined above, azithromycin in combination with HCQ should not be used for the treatment of COVID-19. In a retrospective study of 1438 COVID-19 patients hospitalized in metropolitan New York, the death rate was much higher for patients receiving HCQ and azithromycin (25.7%) than that for HCQ alone (19.9%), azithromycin alone (10.0%) or neither drug (12.7%). Furthermore, the likelihood of cardiac arrest was 2.1 times greater in patients receiving HCQ and azithromycin (Rosenberg et al. 2020). Both azithromycin and HCQ toxicities are related to QTc prolongation, and their combined use might have potentiated this adverse effect (Borba et al. 2020).

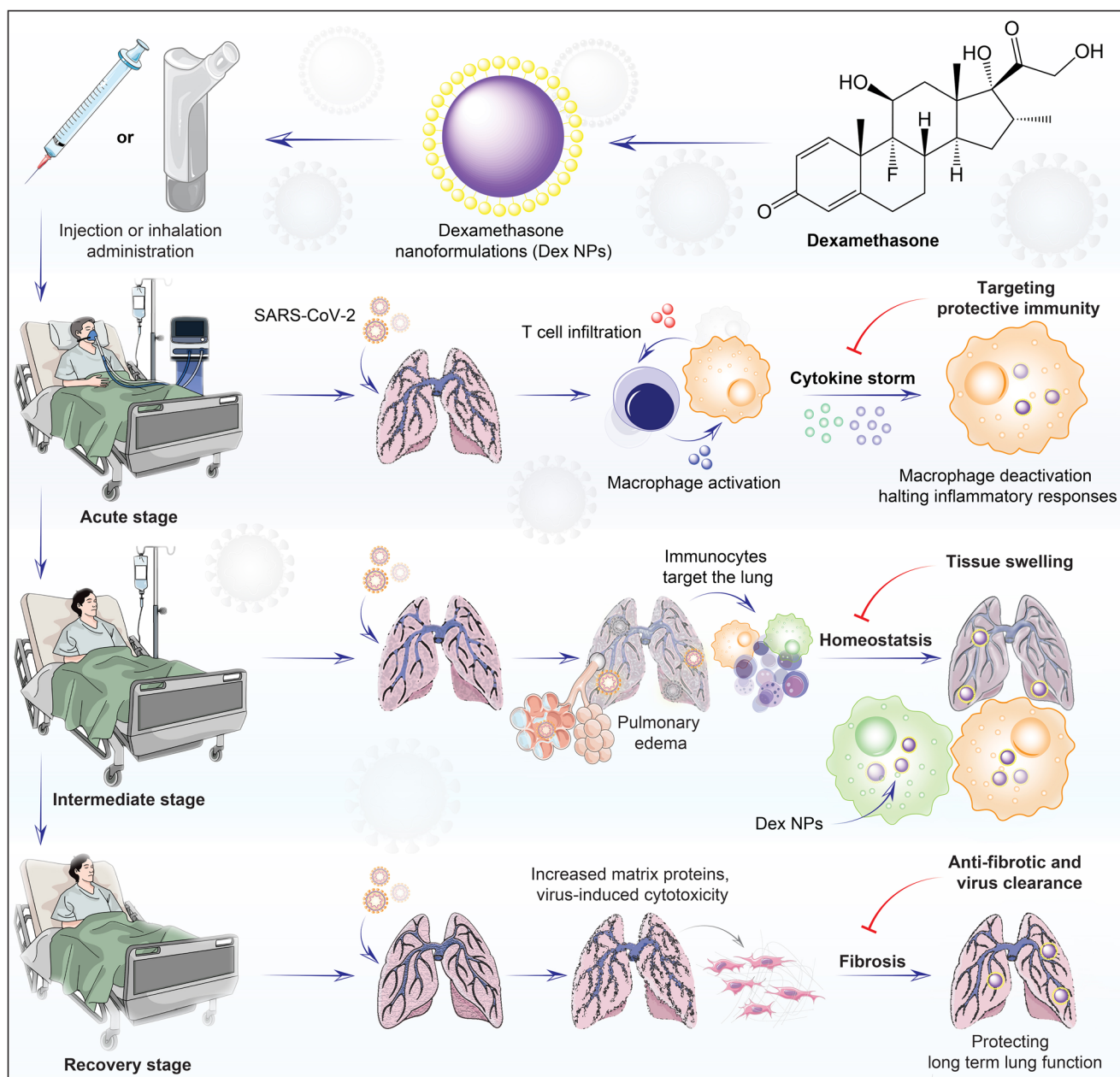


Fig. 2 Dexamethasone formulations for COVID-19 patient treatments. Nanoparticles or liposome encased dexamethasone proposed for treatment of COVID-19 patients with various stage of SARS-CoV-2 infections such as account, intermediate and recovery

stage. This drug is given through intravenous injection or inhalation to hyper-activated immune cells, by potentiating its anti-edema activity and by exploiting its anti-fibrotic effects (Concept of this figure sourced from(Lammers et al. 2020)

Lopinavir/Ritonavir Lopinavir is a protease inhibitor that, in combination with ritonavir, has been used primarily for the treatments of HIV infection (Chandwani and Shuter 2008) and/or hepatitis C (Brayer and Reddy 2015). Combination treatment reduced risk of severe hypoxia or death in SARS-CoV-infected patients (Chu et al. 2004) and improved clinical outcomes in MERS-CoV patients with interferon beta (IFN-β) (Arabi et al. 2018). Unfortunately, lopinavir/ritonavir showed limited benefit for SARS-CoV-2 (Choy et al. 2020b). In a clinical trial including 199 patients with

laboratory confirmed SARS-CoV-2 infection, no benefit was observed for lopinavir/ritonavir compared to controls (Cao et al. 2020a).

Antiviral Therapies in Development

Targeting viral proteins as potential antiviral targets. Since the sequencing of the genome of SARS-CoV-2 was first reported, research laboratories have moved quickly to characterize critical proteins in the novel coronavirus as potential antiviral

targets (Lefkowitz et al. 2018; Decaro and Lorusso 2020). Preliminary structural data, in silico modeling, and plaque reduction assays have elucidated five potential anti-coronavirus targets. Two of these targets (furin-like proteases and cathepsin B/L) are human proteins, and three targets (3CL-pro, RdRP, S protein) are viral proteins imperative for the viral life cycle (Theerawatanasirikul et al. 2020). An in-depth understanding of each target's biological role creates a framework through which informed decisions can be made regarding clinical treatment and experimental design (Masters 2006; Yan et al. 2020). The viral 3-chymotrypsin-like cysteine protease (3CL-pro) plays an essential role in the viral life cycle by cleaving polypeptides pp1a and pp1ab at 11 sites to yield functional proteins (Ziebuhr and Siddell 1999; Barretto et al. 2005). The active site of 3CL-pro consists of a catalytic histidine/cysteine dyad and is highly conserved among SARS coronaviruses. Along with the absence of a similar human homolog, SARS-CoV-2 3CL-pro is an attractive antiviral target (Barretto et al. 2005; Stoermer 2020). The x-ray structure of SARS-CoV-2 3CL-pro, as well as the structure of the protein in complex with novel cysteine protease inhibitors, has been reported (Zhang et al. 2020). A vital component of the viral replication and transcription complex is SARS-CoV-2 RdRP, sometimes referred to as non-structural protein 12 (nsp12) (te Velthuis et al. 2010; Yin et al. 2020). With other viral cofactors, such as nsp 7/8, RdRP catalyzes the synthesis of viral RNA components as well as the replication of the viral genome. RdRPs are one of the few conserved proteins across all RNA viruses. Several groups have reported novel RdRP inhibitors targeting different viral replication complexes (Huang et al. 2020b; Ju et al. 2020b). Most RdRP inhibitors are nucleotide analogs designed to prematurely arrest the synthesis of viral RNA by incorporating inhibitor molecules into the growing transcription (Ju et al. 2020b). Recent structural information which shows SARS-CoV-2 RdRP in complex with a nucleotide analog supports the further development of chain-terminating RdRP inhibitors (Wrapp et al. 2020; Yin et al. 2020; Zhang et al. 2020). The S protein is a transmembrane tetramer protein critical for viral cell entry. As one of four structural proteins, the S protein facilitates both host cell receptor binding as well as membrane fusion (Wrapp et al. 2020). Although the receptor-binding domain is variable among coronaviruses, the membrane fusion domain of S protein is highly conserved, which presents this region as an attractive antiviral target (Baig et al. 2020; Srinivasan et al. 2020; Wrapp et al. 2020). Biomimetic peptides that inhibit viral envelope fusion may prove to be effective therapeutics in COVID-19 treatment (Tang et al. 2020b). Antigens derived from the S protein, which boost recognition of the virus by immune cells or the development of monoclonal antibodies that bind to the coronavirus S protein and block the interaction with a human cell, are becoming an important field of research (NCT04334980, NCT04283461, NCT04341389, NCT04299724, NCT04276896).

Blocking the ACE-2 Receptor SARS-CoV-2 S protein binds specifically to human ACE-2 receptor, and this interaction contributes significantly to the viral tropism (Yan et al. 2020). However, recent studies showed that proteolytic cleavage of S protein by host proteases may also strongly influence SARS-CoV-2 tropism (Hoffmann et al. 2020b; Yan et al. 2020; Zhang et al. 2020). ACE-2 is highly expressed in type 2 alveolar cells found in the lungs. However, ACE-2 receptors are also found in many extrapulmonary tissues, including heart, kidney, endothelium, intestinal tissues and brain (Hamming et al. 2004; Baig et al. 2020). The interface between S protein and ACE-2 is a potential drug target (Yan et al. 2020). Hesperidin, a compound which has shown promise during a recent computational study, is predicted to bind with the binding interface of the S protein/ACE-2 complex and disrupt this protein-protein interaction (Wu et al. 2020). Two pathways for ACE-2 receptor-mediated viral cell entry have been suggested and each presents new antiviral targets (Yan et al. 2020). Viral S protein requires cleavage by host proteases in order to initiate fusion. Human type II transmembrane serine proteases (TTSPs) and furin-like proteases (FLP) have been implicated as essential regulators of viral entry via an, “early” plasma membrane route (Duda et al. 2004; Hantak et al. 2019; Hoffmann et al. 2020b). Proteolytic cleavage of S protein induces a conformational change that enables viral envelope fusion only after binding to ACE-2 receptors. Thus, any antiviral therapeutics targeting host TTSPs or FLPs may show greater efficacy in combination with fusion inhibitors (Hantak et al. 2019; Hoffmann et al. 2020b). The virus utilizes the second viral entry mechanism, or, “late” pathway, in the absence of TTSPs (Hantak et al. 2019; Tang et al. 2020b). After binding to ACE-2 receptors, the viral particle may be brought into the cell through an endocytic pathway where acidic conditions activate early endosomal proteases such as cathepsin B or the late endosomal protease cathepsin L. In the absence of TTSPs, this endocytic route may have a significant impact on disease pathogenesis (Hantak et al. 2019; Tang et al. 2020b). In an in vitro study comparing cell entry inhibition by TTSP inhibitors, a combination of endosomal pH modulators and cathepsin B/L inhibitors showed the most significant efficacy by targeting both the early and the late viral entry pathways (Hoffmann et al. 2020b). Thus TMPRSS-2 plays an essential role in viral cell entry and spread and therefore serves as a potential therapeutic target. This finding warrants further experimental and clinical considerations regarding acute COVID-19 treatment strategies.

Camostat Mesylate TMPRSS-2 is a serine protease that governs S protein priming in coronaviruses and is essential for virus-host cell entry. Camostat mesylate, an inhibitor of TMPRSS-2, is effective against SARS-CoV and prevents its spread and pathogenesis (Kawase et al. 2012). A similar

mechanism is expected against MERS-CoV as well (Rabaan 2017). A recent study identified the role of TMPRSS-2 in SARS-CoV-2 cell entry and camostat mesylate effectively abrogated viral infection in vitro (Hoffmann et al. 2020b). Earlier clinical trials on camostat mesylate against dyspepsia associated with non-alcoholic mild pancreatic disease showed mild, but no severe side effects (Sai et al. 2010), indicating its safety. Currently, clinical trials are ongoing to assess camostat mesylate alone in mild to severe COVID-19 patients (NCT04353284, NCT04321096). Other clinical trials are registered to determine efficacy of camostat mesylate in combination with HCQ (NCT04338906, NCT04355052).

Recombinant human ACE-2. As SARS-CoV-2's S protein has a strong binding affinity to human ACE-2 receptors, it can serve as an entry port for the coronavirus (Hoffmann et al. 2020b; Wang et al. 2020d). Therefore, the delivery of an excessive soluble form of an ACE-2 may competitively bind with SARS-CoV-2 and not only neutralize the virus, but also rescue cellular ACE-2 which regulates the renin-angiotensin system to protect the lungs from injury. One small study has found recombinant human ACE-2 to be safe with no adverse hemodynamic effects in healthy subjects (Khan et al. 2017). Although, antiviral agents can improve pathology, research is ongoing in search of better candidates to prevent disease spread.

Targeting Immune Responses against SARS-CoV-2

Harnessing immunity to suppress or eliminate COVID-19 is an adjunctive, but potentially potent therapeutic approach (Golonka et al. 2020). For example, SARS-CoV-2 ORF3b is a potent interferon (IFN) antagonist. Thus, the ability to suppress induction of type I IFN has been explored beyond what is stimulated by SARS-CoV alone (Konno et al. 2020). However, IFN commonly has a paradoxical effect on viral growth; hence, whether to stimulate or suppress immune responses is a notable question (Jamilloux et al. 2020). Indeed, 5–15% of COVID-19 patients who respond to SARS-CoV-2 infection with robust innate immune responses showed excessive production of cytokines beyond IFNs. This, “cytokine storm” can lead to hyperactivation of the defense mechanisms with vascular permeability, multiorgan failure and death. The cytokine profiles of serum from some patients with moderate to severe COVID-19 are similar to what was reported for the macrophage activation syndrome (MAS) (Pedersen and Ho 2020). Pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts (Choy et al. 2020a; Liu et al. 2020). Specifically elevated levels of interleukin-1, 6 (IL-1 and IL-6), C-reactive protein, D-dimer and ferritin are readily detected in patients with COVID-19 disease (Huang et al. 2020a; Wang et al. 2020b). Several immune-based therapies directed at modifying COVID-19 under investigation include those that target the

virus (convalescent plasma) or modulate the immune response (IL-1 or IL-6 blockers) and can be seen below.

IL-6 Pathway Inhibitors SARS-CoV infection induces IL-6 expression from bronchial epithelial cells (Yoshikawa et al. 2009). Elevations in IL-6 levels mediate the severe systemic inflammatory responses in patients with SARS-CoV-2 infection. COVID-19-associated systemic inflammation and hypoxic respiratory failure is associated with the, “cytokine storm”, including marked increases in the levels of IL-6. Tocilizumab is an IL-6 receptor inhibitor used for rheumatic diseases and cytokine release syndrome. Case reports have described good outcomes with tocilizumab in patients with COVID-19 (Luo et al. 2020; Michot et al. 2020), but systematic evaluation of the clinical impact of tocilizumab on COVID-19 has not yet been published. Treatment guidelines from China's National Health Commission include the IL-6 inhibitor tocilizumab for patients with severe COVID-19 and elevated IL-6 levels. Tocilizumab, as well as sarilumab and siltuximab, which also target the IL-6 pathway, are being evaluated in clinical trials (Choy et al. 2020a; Khan et al. 2020).

Interleukin-1 Inhibitors SARS-CoV-2 infection triggers an exacerbated host immune response and the role of proinflammatory cytokine storm is now well established. Targeting or suppressing proinflammatory cytokine IL-1 could be effective in COVID-19 patients to control ARDS and avoid mechanical ventilation (National Institute of Health (NIH) 2020a; Jamilloux et al. 2020; Pedersen and Ho 2020). IL-1 inhibitor anakinra is currently being tested for the treatment of COVID-19. Anakinra is a recombinant human IL-1 receptor antagonist. It is approved for the treatment of rheumatoid arthritis, and used off-label for different inflammatory conditions and severe chimeric antigen receptor T cell (CAR-T)-mediated cytokine release syndrome (CRS) and MAS (National Institute of Health (NIH) 2020b). A case series of anakinra use in moderate to severe COVID-19 pneumonia was published recently (Aouba et al. 2020). In this study, anakinra was found to be safe and reduced the risk of hemophagocytic lymphohistiocytosis in patients along with improved oxygen flow. Overall, anakinra showed improved clinical outcomes. In another case report from Italy, a critical COVID-19 patient was successfully treated with anakinra, with reduced inflammatory markers and improving respiratory functions (Filocamo et al. 2020). Fifteen ongoing clinical trials on anakinra in COVID-19 patients are registered on [ClinicalTrials.gov](https://clinicaltrials.gov).

Interferons (IFNs) As the COVID-19 pandemic ensues, opposing findings characterizing the roles of interferon-based pathogenesis and therapies continue to emerge. What remains clear, however, is that anatomical location, duration of

infection, and timing of treatment significantly skew how SARS-CoV-2 infection progresses in the presence of interferons. Accordingly, numerous clinical trials explore the utility of early treatment with type I or type III interferons in improving outcomes for COVID-19 patients. Interferons serve as prototypical signaling proteins of the innate immune system whose paracrine release aims to protect neighboring cells from microbial invasion or metastasis. Individual interferons are divided into three types based on their abilities to bind common receptors. Type I interferons (IFN- α , IFN- β , IFN- ϵ , IFN- ω) and type III interferons (IFN- λ_{1-4}) demonstrate antiviral activities, whereas type II interferon (IFN- γ) promotes systemic Th1 and cytotoxic T lymphocyte responses. Release of IFNs by virally infected cells signals neighboring cells to destroy RNA and reduce protein translation, induce apoptosis, and upregulate major histocompatibility complex molecules as well as various cytokines that cumulatively trigger immunocyte-based clearance. These various processes are mediated by interferon-stimulated genes (ISG) that trigger downstream signaling cascades. Much of the confusion over whether interferons directly contribute to COVID-19 disease stems from patient data. Sera from SARS-CoV-2-infected patients and lung tissue explants challenged *ex vivo* revealed low levels of types I and III interferon proteins (Blanco-Melo et al. 2020; Chu et al. 2020). Similarly, transcriptional profiling of nasopharyngeal swab and bronchioalveolar lavage samples from these patients did not detect upregulation of interferon types I and III mRNA (Lieberman et al. 2020; Zhou et al. 2020c). Nonetheless, these latter studies also implicate interferon-stimulated gene pathways (notably OAS1–3 and IFIT1–3) as contributing to the cytokine storm. Two rationale may explain induction of ISG in the absence of elevated type I and III interferon levels: Firstly, SARS-CoV-2 may trigger type II interferon protein production. Higher circulating IFN- γ , was readily measured in symptomatic adults and acute multisystem inflammatory syndrome in children with COVID-19 (Carter et al. 2020; Montalvo Villalba et al. 2020). Secondly, *ACE2* is an interferon response network gene as identified in nasal epithelia of highly-expressing interferon subjects (Sajuthi et al. 2020) and its upregulation may potentiate even greater SARS-CoV-2 infection set points. These clinical findings suggest that although elevated type I and III interferons are not directly observed in COVID-19 patients, interferon stimulated genes are nonetheless triggered.

Laboratory studies elucidate how SARS-CoV-2 may induce and elude host interferon responses. Model systems characterizing SARS-CoV-2 infection in the lung reveal a causal nature to type I interferon production. RNA-Seq profiling of ciliated bronchial epithelial cells found upregulation of interferons (types I and III) and IL-6 after SARS-CoV-2 exposure, which potentiated the infection to spread to neighboring basal and club cells (Ravindra et al. 2020). Human *ACE2*-

expressing transgenic mice recapitulated increased interferons in lung infiltrates following SARS-CoV-2 infection (Winkler et al. 2020), whereas knockout of the type I interferon receptor (*ifnar^{-/-}*) attenuated this response (Israelow et al. 2020). Gastrointestinal symptoms observed in approximately 18% of COVID-19 patients has prompted investigations into SARS-CoV-2 pathogenesis in the colon. Type I (and to a lesser degree, type III) interferon receptor knockout prevented the establishment of SARS-CoV-2 infection in colon carcinoma T84 cells (Stanifer et al. 2020). After lung dendritic cells were exposed to viral RNA, secreted IFN- λ induced mucosal barrier damage leading to lethal bacterial superinfection (Broggi et al. 2020). The discrepancy between low interferons observed in patients and pathogenic levels encountered in these models can, at least partially, be explained by exploring how SARS-CoV-2 has adapted to blunt interferon responses in human hosts. Interference has been described at three levels: prior to ISG-signaling, before nuclear localization, or post-translationally. SARS-CoV-2 Orf9b interacts with adaptor protein TOM70, which prevents cytoplasmic pattern recognition receptors RIG-I or MDA5 from signaling for interferon responses (Jiang et al. 2020). Alternatively, the C-terminus of Orf6 antagonizes STAT1 nuclear translocation, again precluding the production of interferon (Lei et al. 2020). Finally, the virus' papain-like protease (PLpro), which generates a functional replicase complex, attenuates type I interferon responses by cleaving two complexed ISG proteins (Shin et al. 2020). In summary, these datasets enable investigation of particular immunologic responses following SARS-CoV-2 exposure, yet their utility in recapitulating the full depth of COVID-19 pathogenesis in humans requires additional investigation. Medical treatment using interferon for COVID-19 largely relies on early intervention for therapeutic success. *In vitro* pretreatment with type I interferons (IFN- α (Felgenhauer et al. 2020) or IFN- β (Lei et al. 2020; Shuai et al. 2020) reduced SARS-CoV-2 infection in Calu-3 lung cancer cells by approximately 33%–75%. IFN- β further limited Caco-2 colorectal adenocarcinoma cells to <1% of control infection levels (Shuai et al. 2020). Coronavirus replication can be suppressed by IFN- β synthesized from the cell. However, coronaviruses have evolved mechanisms to escape interferon mediated growth inhibition by specifically preventing the induction of IFN- β (Spiegel et al. 2005). In such condition, treatment with exogenous IFN- β can be useful to attenuate virus replication. IFN- β demonstrated protection of Vero 6 cells from infection with highly pathogenic coronavirus strains including SARS-CoV, MERS-CoV and SARS-CoV-2 (Mantlo et al. 2020; Synairgen 2020). Viral control using type I interferons has also been observed clinically. Currently, a phase-II clinical trial on the inhaled formulation of IFN- β , SNG001, in COVID-19 patients is ongoing (NCT04385095). An uncontrolled exploratory study in Wuhan, China revealed that treatment with nebulized

IFN- α 2b along with the antiviral, arbidol, significantly reduced the duration of detectable virus in the upper respiratory tract and reduced the duration of blood inflammatory markers (Yin et al. 2020). Two randomized drug trials utilizing IFN- β 1a as part of lopinavir-ritonavir-based regimens demonstrated clinical benefit. In one study, Iranian inpatients receiving combination therapy observed a reduced 28-day mortality and increased 14-day discharge rate (Dastan et al. 2020). A larger multicenter phase 2 clinical trial in Hong Kong, wherein COVID-19 patients were hospitalized on average 5 days after symptom onset, reported shortened time until SARS-CoV-2 negative nasopharyngeal swabs were collected (Hung et al. 2020). Type III interferon may also prove beneficial in abrogating coronavirus infection. Pretreatment of primary human airway epithelia with PEG-IFN- λ ₁ or human intestinal epithelial cells with IFN- λ reduced viral replication by 5 logs and 2 logs, respectively (Dinnon et al. 2020; Stanifer et al. 2020). Prophylactic administration of PEG-IFN- λ ₁ to mice challenged with a murine form of SARS-CoV-2 also exhibited 90% reduction in recovered virus in the lungs (Stanifer et al. 2020). Whether such benefits will extend to humans remains to be seen. PROTECT (NCT04344600) is a phase 2b prospective, randomized, single-blind, placebo-controlled clinical trial currently recruiting patients to assess whether single subcutaneous injection of PEG-IFN- λ ₁ prevents SARS-CoV-2 infection among individuals with known household exposure to COVID-19. Overall, early intervention with interferons may aid in the arsenal of therapies necessary to prevent SARS-CoV-2 infection, both within an individual and from spreading to others.

Tableted Heat-Inactivated Plasma This is another alternative option which may lead to faster recovery in patients with COVID-19. One clinical trial aims to administer once daily pills of therapeutic vaccine made from COVID-19 donor heat-inactivated plasma to the healthy volunteers for 15 days. The primary objective of this study is to evaluate safety and characterize the immune responses in the recipients. By presenting both heat-inactivated virus and human antibodies, this trial hopes to elicit protective immune responses (NCT04380532).

Anticoagulants Recent reports emphasize the risk of coagulopathy in severely ill COVID-19 patients, especially in those with comorbid conditions such as cancer, congestive heart failure, hypertension and obesity (Barnes et al. 2020; Kollias et al. 2020). For instance, among 183 hospitalized patients, disseminated intravascular coagulation (DIC) was much more common (71.4%) in patients who died from COVID-19 than the survivors (0.6%) (Tang et al. 2020a). The coagulopathy may be related to the cytokine storms, and elevated D-dimer levels that were reported in patients with cerebrovascular events, both thrombotic and

hemorrhagic, as well as concurrent peripheral thrombotic events, such as deep vein thrombosis or pulmonary emboli (Tang et al. 2020a). Recently, the Anticoagulation Forum, a North American organization of anticoagulation providers, evaluated the increased risk of venous thromboembolism (VTE) in COVID-19 patients, and provided guidelines regarding the use of anticoagulation therapies for their management (Barnes et al. 2020). In severely ill COVID-19 patients, daily D-dimer monitoring is recommended to surveil VTE severity and provide prognosis and adjustment for dosing of anticoagulants (Barnes et al. 2020). For COVID-19 patients presenting a risk for VTE, thromboprophylaxis or a full course of therapeutic anticoagulation is recommended (Barnes et al. 2020; Kollias et al. 2020).

Transformative Immunity Bacillus Calmette–Guérin (BCG) is a live attenuated vaccine that was developed against tuberculosis at the Institute Pasteur in Paris during early 1921 (Luca and Mihaescu 2013). BCG has been the most used vaccine in the world, with around 130 million children vaccinated every year to reduce infant mortality and the incidence of tuberculosis. Later, BCG vaccination was reported to decrease susceptibility to unrelated infectious agents such as respiratory tract infections (Butkeviciute et al. 2018; Moorlag et al. 2019). BCG also has been shown to provide non-specific protection against other respiratory tract infections which might lower the rate of absenteeism in health care workers (NCT04328441). Experimental studies have shown that BCG reduced viral titers of influenza A virus in mice, an effect dependent on macrophages (Spencer et al. 1977). BCG vaccination also protected mice from herpes simplex virus type 2 (HSV2) infection (Starr et al. 1976). BCG vaccination resulted in enhanced production of pro-inflammatory cytokines, such as IL-1 β , TNF- α and IL-6, when monocytes from vaccinated healthy individuals were stimulated *ex vivo* with unrelated pathogens. These effects are mediated by transcriptional, epigenetic and metabolic reprogramming of the myeloid cells for improved anti-microbial responses (Netea et al. 2016). The long-term innate immune memory seen with BCG vaccination has been termed, “trained immunity”. Upon challenge with unrelated pathogens, these trained innate immune cells promote host defense. Thus, BCG vaccination provides significant protection against multiple viral infections. Lower infection rates and reduced mortality from COVID-19 were observed in countries that practice BCG vaccination, although a causal relationship has not been established (Miyasaka 2020). Based on these previous observations, BCG vaccination is hypothesized to be a potent preventive measure against SARS-CoV-2 infection, and it may well be a bridge until a specific COVID-

19 vaccine is developed (O'Neill and Netea 2020). Indeed, trials assessing the efficacy of BCG vaccination to prevent COVID-19 are currently being carried out in the Netherlands, Australia, Greece, and the United States, with more being planned in many other countries. Unlike influenza, SARS-CoV-2 seems to disproportionately affect older populations as compared to children. One hypothesis for this disparate manifestation of COVID-19 is that cross protective antibodies generated in response to the measles vaccine may be protecting the children. In vivo experiments showed recombinant measles vaccine fully protected animals from intranasal challenge with SARS-CoV. A clinical trial aims to test this hypothesis by immunizing health care workers with the measles

vaccine and tracking the rates of infection (NCT04357028).

Vaccines (an Overview)

The limited antiviral medications and their variant therapeutic efficacies are pressing for the development of a vaccine to provide global immunity against SARS-CoV-2 virus (Lurie et al. 2020). Vaccine development is an extended process that typically involves five to ten years of rigorous pre-clinical trials, followed by clinical trials. However, COVID-19 is changing that paradigm. This is based on the critical needs for effective vaccines; therefore, the medical, scientific, and administrative stalwarts

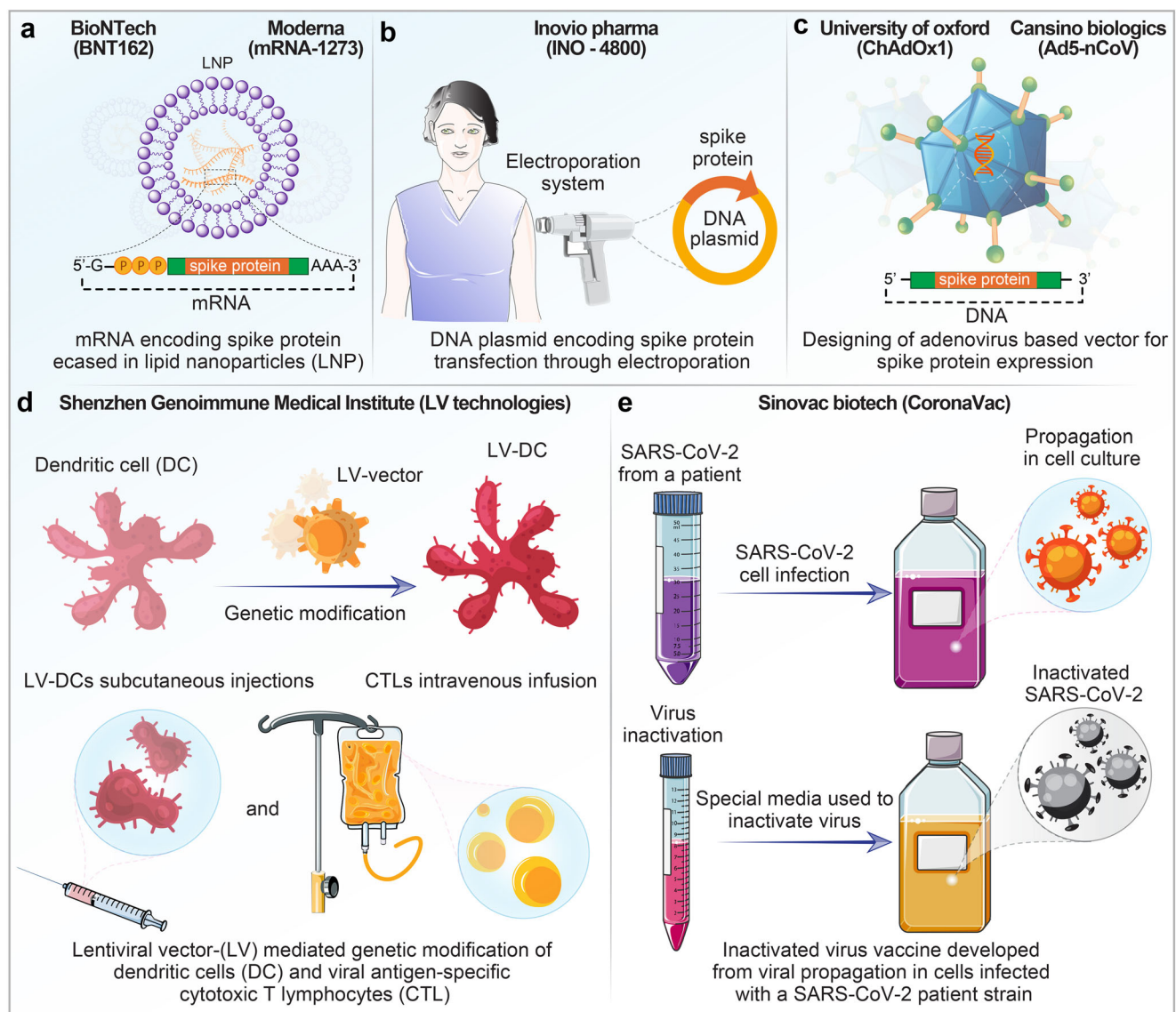


Fig. 3 Current vaccine strategies for SARS-CoV-2. Clockwise from top left: (a), delivery of mRNA encoding viral protein through lipid nanoparticle; (b), direct delivery (electroporation) of plasmid DNA

encoding viral protein; (c), human and chimpanzee adenovirus-based delivery of DNA encoding viral protein; (d), injection of inactivated viral vector; (e), injection of genetically modified immune cells

have moved with alacrity to reschedule the vaccine development regime and simultaneously develop multiple vaccine candidates with accelerated clinical trials. For the first time in the vaccine development history, and only 63 days after the publication of the sequence of COVID-19 on January 12th, 2020 (European Centre for Disease Prevention and Control (ECDC) 2020), two vaccines, mRNA 1273 (NCT04283461) and Ad5-nCoV (NCT04313127) entered phase-I human clinical trial. Currently, the 213 vaccines (Callaway 2020; Milken Institute 2020) developed by academic research teams and pharmaceutical companies against SARS-CoV-2 worldwide have offered divergent technologies for vaccine development, several of which have never been used in a licensed vaccine. These various platforms, along with the human clinical trial forerunners, are described based on the approach and composition of the vaccine (Fig. 3).

Protein-Based Vaccines Most vaccines now in development are protein-based. Researchers use viral proteins either as fragments or as protein shells. Protein subunit vaccines use the S protein as a whole or its receptor-binding domain as an antigen to elicit antibody responses.

Viral-Vector-Based Vaccines Another protein-based vaccine includes virus-like particles (VLPs). These particles are virus shells devoid of viral genomic RNA that mimic the coronavirus structure but are not infectious. The next most common vaccines are viral vectors or VLPs. These use genetically engineered non-pathogenic viruses (for example, measles or adenovirus) that produce coronavirus proteins and can be one of two types: The first can replicate within cells and the second cannot. For those that can replicate in the cells, key genes known to be pathogenic are disabled. One of the forerunner candidates, Ad5nCoV, developed by CanSino Biogenics, Beijing Institute of Biotechnology, and Canada's National Research Council, has already begun phase-II clinical trials as of April 12th, 2020 (NCT04341389). Built upon CanSinoBio's adenovirus-based viral vector vaccine technology platform, Ad5nCoV is a genetically engineered vaccine candidate with the replication-defective Adenovirus of the human serotype 5 (AdHu5) as the vector for expressing SARS-CoV-2 S protein. A notable limitation of the use of such human adenovirus-based vectors is that a significant portion of the population is immune to the virus as a result of previous natural infections. Thus, host immunity could lead to the persistent production of neutralizing antibodies and blunt the vaccine's effectiveness (Chirmule et al. 1999). Adoption of simian adenoviral vectors, to which the human population is less exposed, has circumvented this problem (Tatsis et al. 2006): ChAdOx1, another non-replicating viral vector candidate developed by the University of Oxford, uses a vector platform derived from chimpanzee adenovirus Y25 to express

SARS-CoV-2 S protein and started human Phase-I/II clinical trials as of April 23rd, 2020 (NCT04324606).

Nucleic Acid-Based For these vaccines, S protein-expressing DNA or RNA plasmids are injected into the cell which replicate and strengthen the natural physiological immune response via targeted T cell and antibody responses. Although the RNA and DNA-based vaccines are safe and easy to develop, they are unproven in clinical trials, as no licensed vaccine has used this platform to date (Rauch et al. 2018). BNT-162 developed by BioNTech, Fosun Pharma, and Pfizer, is an RNA-based vaccine candidate that entered phase-I clinical trials on April 29th, 2020 (NCT04368728). This is a unique approach in that four mRNA vaccine candidates (a1, b1, b2, c2) are screened simultaneously. Two candidates have nucleoside modified mRNA (modRNA), one has uridine containing mRNA (uRNA) and one has self-amplifying mRNA (saRNA). Two encode the large S sequence while the other two encode the smaller optimized receptor-binding domain (RBD) from S (Carlson 2020). The mRNA is then encapsulated in a lipid nanoparticle formulation. The novel design of the clinical trial allows for the simultaneous evaluation of safety, immunogenicity, and the optimal dose level. This approach drastically cuts the pre-clinical phase to less than four months and, as a result, rapidly accelerates development (Businesswire 2020). The other lead vaccine candidate, mRNA-1273, developed by Moderna and the US National Institute of Allergy and Infectious Diseases, is a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized S protein of SARS-CoV-2 (NCT04283461). INO-4800, an interesting vaccine developed by Inovio Pharmaceuticals, CEPI, Korea National Institute of Health and International Vaccine Institute, is a DNA-based vaccine candidate that entered phase-I clinical trials on April 3rd, 2020 (NCT04336410). This platform uses the innovative technology of *collectra*®, Inovio's proprietary platform, which uses a novel hand-held device that utilizes a brief electrical pulse to reversibly open small pores in the cells and allow plasmid vaccine candidate to elicit a robust immune response intracellularly (International Vaccine Institute 2020).

Virus One form of virus-based vaccine uses viruses that have been chemically attenuated by formaldehyde or heat. This is a well-established process employed in many now current vaccines. They are easy to prepare, develop, and considered safe. Sinovac biotech developed a vaccine candidate that went on phase-I/II clinical trial on April 16th, 2020 (NCT04352608) in Xuzhou, China, and another phase-I/II clinical trial on May 20th, 2020 (estimated) (NCT04383574) in Renqiu, China. This vaccine uses inactivated clinical strains of SARS-CoV-2 fused with alum to induce an immune response. Another form, live attenuated vaccines, are viruses that have

weakened replication or viral protein production due to mutations generated when grown in animal or human cell lines. These attenuated vaccines provide a robust immune response, but have a potential reversion to virulence (Roper and Rehm 2009).

Other Innovative Platforms Non-viral nanoparticle-mediated delivery of gene-encoded antibody vaccines, replicating bacterial vectors expressing multiple SARS-CoV-2 antigens and heat shock protein fused to avidin self-assembling vaccines are some other innovative vaccine platforms in the pre-clinical pipeline. Another important platform uses lentiviral vectors to genetically modify components of immune cells, such as antigen-presenting cells and dendritic cells, to alter SARS-CoV-2 immune mediated responses. LV-SMENP DC is a novel lentiviral-based dendritic cell and T cell vaccine candidate developed by Shenzhen Geno-Immune Medical Institute which went into phase-I/II clinical trial on March 24th, 2020 (estimated) (NCT04276896). This vaccine modifies dendritic cells using lentiviral vectors expressing SARS-CoV-2 minigene SMENP and induces expression of SARS-CoV-2 antigens and immune-modulatory genes. The vaccine uses cytotoxic T lymphocytes, which get activated by the SARS-CoV-2 specific antigens presented on the lentivirus modified-dendritic cells. Antigen-specific cytotoxic T cells will be injected intravenously while the lentivirus-SMENP-dendritic cell (LV-SMENP DC) vaccine will be subcutaneous (NCT04276896).

Neutralizing and Functional Antibodies The US FDA is accepting investigational new drug applications to use convalescent plasma for patients with severe or life-threatening COVID-19 (US Food and Drug Administration (US FDA) 2020a). The pathways to achieve these applications include clinical trials, expanded access programs, and individual emergency use. The use of convalescent plasma has been described, “just in case series” (US Food and Drug Administration (US FDA) 2020a; Duan et al. 2020). In a randomized clinical trial enrolling 103 patients, transfusion of convalescent plasma did not improve clinical condition in severe or life threatening COVID-19 patients compared to the standard treatment. This trial was terminated early, before reaching the target enrollment of 200 patients, which might have contributed to the negative results (Li et al. 2020a). One case series described the administration of plasma from donors who had recovered entirely from COVID-19 to 5 patients with severe COVID-19 who were on mechanical ventilation and presented with persistently severe viral symptoms despite investigational antiviral treatment (Shen et al. 2020). The recipients showed decreased nasopharyngeal viral load, decreased disease severity score, and improved oxygenation by 12 days after the transfusion. In another study at the Houston Methodist hospital, 25 patients with severe and/or life

threatening COVID-19 disease were transfused with the convalescent plasma obtained from confirmed SARS-CoV-2-infected and fully recovered donors. Seven days after transfusion, 36% of the patients clinically improved and 28% of the patients were discharged after complete recovery. 14 days after transfusion, clinically improved patients increased to 76% and 44% of patients were discharged. No adverse events were observed following plasma transfusion (Salazar et al. 2020). This study has been extended and 74 critically ill COVID-19 patients were treated, 50 of whom were discharged from the hospital after recovery (News Wise 2020). The convalescent plasma therapy outcomes in COVID-19 patients were very similar to the compassionate-use of remdesivir. Earlier this year, the US government initiated an Extended Access Program for convalescent plasma, with funding from the HHS’ Biomedical Advance Research and Development Authority (BARDA) in collaboration with Mayo Clinic and have transfused more than 70,000 COVID-19 patients with convalescent plasma. After significant reduction in mortality in COVID-19 patients and no observed side effects, U.S. FDA recently issued an EUA for convalescent plasma as a promising treatment of COVID-19 (US Food and Drug Administration (US FDA) 2020b). However, these findings do not establish a causal effect; therefore, further studies are required to determine the efficacy of convalescent plasma. Finding appropriate donors and establishing testing that validates the neutralizing activity of the plasma poses logistical challenges (Duan et al. 2020; Shen et al. 2020). A randomized controlled clinical trial at Houston Methodist hospital is enrolling COVID-19 patients to determine the therapeutic efficacy of convalescent plasma and to determine the optimal timing of transfusion after the onset of symptoms, frequency of transfusion and required antibody concentration for precise treatment (News Wise 2020).

The therapeutic outcomes of convalescent plasma are attributed to the antibodies that neutralize the SARS-CoV-2 (Fig. 4). Several researchers have identified the human antibodies that block the receptor binding domain (RBD) of the S protein to abrogate virus interaction with the host cell receptor, a key step of virus host entry. Wang et al. developed SARS-CoV-2 neutralizing antibody from SARS-CoV hybridoma, in which four of the candidates showed reactivity with the SARS-CoV-2 S protein. The lead candidate 47D11 showed potent neutralizing activity against both SARS-CoV and SARS-CoV-2 (Wang et al. 2020a). Others isolated potent RBD binding antibodies from COVID-19 patients and evaluated their SARS-CoV-2 neutralizing efficacy. From 149 COVID-19 convalescent patients, only 1% of the patients had high antibody titers with SARS-CoV-2 neutralizing capability. Further, researchers isolated antibody secreting B cells from the high to moderate titer COVID-19 patients and identified potent antibodies against SARS-CoV-2 RBD in both patient groups. Surprisingly, sequential similarity was

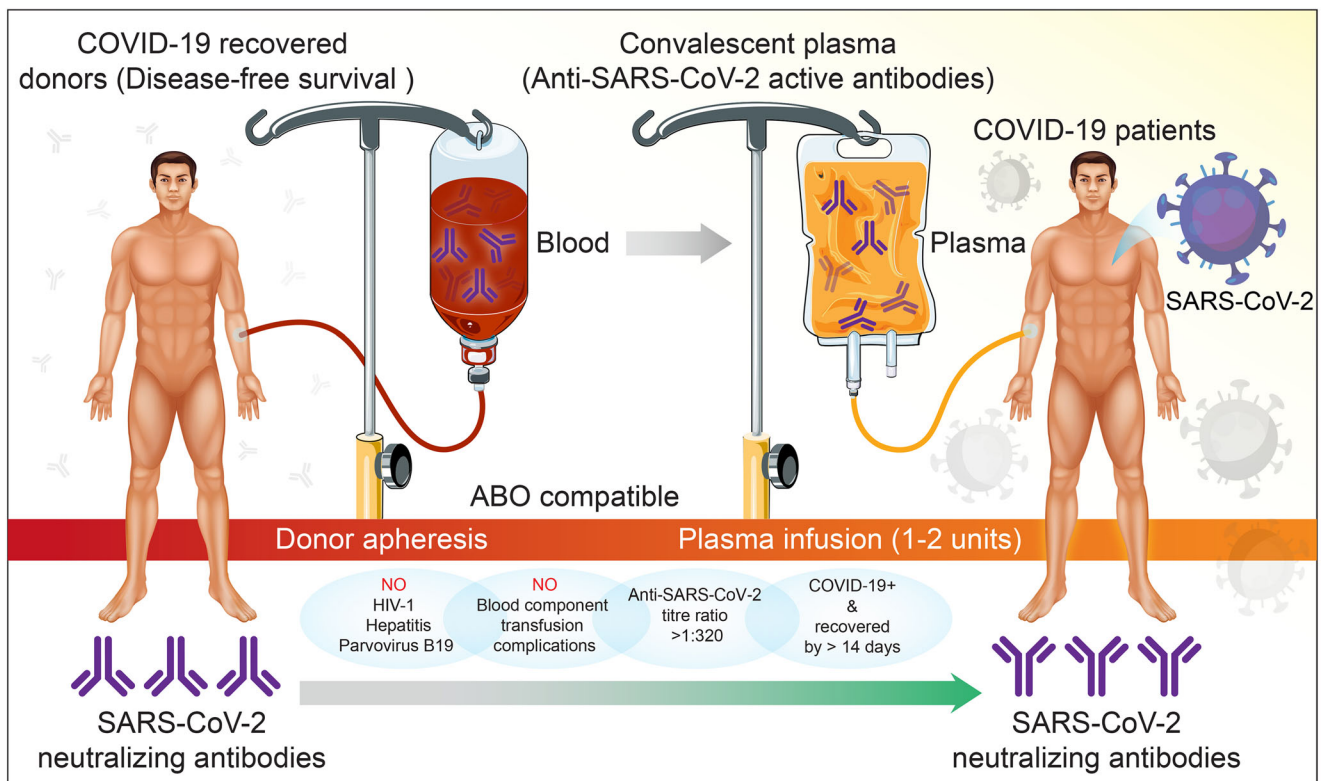


Fig. 4 Convalescent plasma therapy. The use of convalescent plasma to treat COVID-19 requires donor testing of a person who has recovered from disease and has substantial titers of SARS-CoV-2 neutralizing antibodies. The plasma of recovered COVID-19 patients contains SARS-CoV-2 antibodies. These are present in plasma, which are collected then used as therapies. Convalescent plasma is safe, specific and effective. This schematic describes how convalescent plasma therapy is administered. It is as follows: (1) *Donor apheresis*. Blood is collected from the patient and antibody containing plasma is harvested by apheresis. (2)

Plasma infusion. Convalescent plasma is collected from plasma of the donor then administered to the COVID-19 patient intravenously to deliver virus-specific antibodies. The plasma is collected through blood banks and given to blood-type-compatible patients with active SARS-CoV-2 infection. All donors are screened for HIV-1 and for hepatitis viruses and parvovirus B19. There are no other blood components uncovered that could yield secondary complications. The anti-SARS-CoV-2 titer must be at or greater than 1:320. Donors should have no systemic illness for at least 14 days after recovery

identified in the epitope binding sites of the neutralizing antibodies from different patients, suggesting that RBD specific antibody with potent antiviral activity had developed in the COVID-19 patients (Robbiani et al. 2020). In another study, scientists isolated a total of 389 RBD specific SARS-CoV-2 neutralizing monoclonal antibodies from the B cells of two COVID-19 convalescent patients. Two of these antibodies, COV2–2196 and COV2–2130, demonstrated potent SARS-CoV-2 neutralization by blocking non-overlapping sites of RBD on viral S protein. In mouse models of SARS-CoV-2 infection, COV2–2196 and COV2–2130 treatment alone or in combination protected mice from weight loss and reduced viral load and inflammation in the lungs. COV2–2196 and COV2–2130 also protected rhesus macaques from SARS-CoV-2 infection as monotherapy (Zost et al. 2020). Investigators isolated and characterized 206 RBD specific monoclonal antibodies from the B cells of eight SARS-CoV-2-infected individuals. The most potent neutralizing antibodies (P2C-1F11, P2B-2F6 and P2C-1A3) showed highest competitive inhibition of ACE2 binding with the RBD from

the SARS-CoV-2. Surprisingly, these anti-SARS-CoV-2 antibodies did not cross-react with the RBD from the SARS-CoV or MERS-CoV. Hence, competitive inhibition might be a better predictor of antiviral efficacy than virus-neutralizing capacity of the antibody (Ju et al. 2020a). Brouwer et al. isolated 19 monoclonal antibodies from the three convalescent COVID-19 patients that targeted diverse antigenic sites, including RBD and non-RBD epitopes from the SARS-CoV-2. A subset of antibodies showed potent nanaomolar neutralizing activity against authentic SARS-CoV-2 (Brouwer et al. 2020). SARS-CoV-2 neutralizing antibodies were also identified by high-throughput single cell sequencing of antigen-enriched B cells from convalescent COVID-19 patients. A subset of potent antibodies showed nanomolar neutralizing activity against both pseudo and authentic SARS-CoV-2. Clinical studies with the most potent neutralizing antibody, BD-368-2, are underway (Cao et al. 2020b). In another study, more than 1000 human monoclonal antibodies were isolated from the convalescent COVID-19 patients using a high-throughput pipeline. Out of them, a small fraction of

antibodies showed strong neutralizing activity against SARS-CoV-2. The most potent monoclonal antibody, CC12.1, protected Syrian Hamster against weight loss and viral replication of the SARS-CoV-2 in the lung (Rogers et al. 2020). Together, these studies provide a structural guide for designing vaccines and antibodies as a potential therapy of SARS-CoV-2 infection. Human recombinant antibodies were also identified from the healthy individuals using antibody phage display tool. From the 309 unique human recombinant antibodies, several antibodies were able to bind SARS-CoV-2 RBD and displayed potent inhibition of S protein binding to the ACE2 receptor expressing cells. Antibodies also neutralized the SARS-CoV-2 infection in VeroE6 cells. Another study suggested a quick development of SARS-CoV-2 neutralizing human recombinant antibodies from healthy donors independent of SARS-CoV-2 recovered patients (Bertoglio et al. 2020). Development of recombinant human antibodies specific for SARS-CoV-2 is essential for the prophylactic or curative treatment of COVID-19. Academic and industrial researchers are exploring almost every available platform for efficient antibody production against SARS-CoV-2 (Renn et al. 2020). Currently, eight SARS-CoV-2 neutralizing antibodies are under clinical investigation that include LY-CoV555 (NCT04537910, NCT04411628), JS016 (NCT04441918), REGN-COV2 (NCT04425629, NCT04426695, and NCT04452318), TY027 (NCT04429529), BRII-196 (NCT04479631), BRII-198 (NCT04479644), CT-P59 (NCT04525079), and SCTA01 (NCT04483375). Practically, antibody development is a costly and extensive. Developing successful antibody against SARS-COV-2 quickly requires a new pandemic paradigm, with a fast start and many steps executed in parallel before confirming a successful outcome of another step, which results in elevated financial risk. Further, large scale monoclonal antibodies production and distribution to clinics is challenging. The main factor affecting development of antibodies include SARS-CoV-2 mutation (Starr et al. 2020). Since the onset of COVID-19, several mutations have been identified in the S protein and other ACE2 binding sites of the SARS-CoV-2 that affect RBD expression and infectivity. D614G mutation in the S1 protein of SARS-CoV-2 increases the virus infectivity (Korber et al. 2020). Mutations within the antibody binding sites have also been detected (Korber et al. 2020; Pinto et al. 2020). Although the frequency of such mutations is low, they might affect the efficacy of the neutralizing antibodies (Renn et al. 2020; Starr et al. 2020). The use of antibody in combination with non-overlapping epitopes is a promising approach to overcome these limitations. AstraZeneca is developing an antibody combination therapy AZD7442, which is a mixture of two potent antibodies AZD8895 and AZD1061 and is currently in a phase 1 clinical trial (NCT04507256). Similarly, Regeneron Pharmaceuticals which developed a mixture of three monoclonal antibodies

against Ebola virus, is now developing REGN-COV2, a mixture of REGN10933 and REGN10987 antibodies in collaboration with the National Institute of Allergy and Infectious Disease (NIAID). Currently, REGN-COV2 is under phase 3 clinical trial (NCT04452318).

Vaccines for the Elderly Population The human body's immune system becomes weaker with age, especially in individuals with comorbid conditions such as hypertension, diabetes, kidney, liver, cancer, coronary artery and chronic obstructive lung diseases (Alpert et al. 2019; Pan et al. 2020; Wang et al. 2020b). COVID-19 is commonly viewed as a, “disease of the older people”, owing to the exponential risk of age-related mortality (Le Couteur et al. 2020; Promislow 2020). Of the total number of COVID-19 deaths worldwide, almost 50 % are above 65 years of age (Centers for Disease Control and Prevention (CDC) 2020c). This is reflected in the high death rates in Spain (Bonanad et al. 2020) and Italy (Boccardi et al. 2020); both have larger recorded aged populations associated with immunosenescence and comorbid conditions (Wang et al. 2020b; Zhou et al. 2020b). Prominent comorbidities including hypertension, followed by diabetes, coronary heart disease, chronic obstructive lung disease, carcinoma, and chronic kidney disease all attributed to increased mortality in COVID-19 patients (Wang et al. 2020b; Zhou et al. 2020a). The elderly are socially vulnerable to infectious diseases when housed in institutions and can acquire the disease from close contact exposure with their caregivers (Bonanad et al. 2020). During the COVID-19 pandemic, we cannot divert our focus on the vaccine development without considering the elderly population, who typically have one or more underlying disease conditions. The older adults are more susceptible to SARS-CoV-2 infection and develop more severe COVID-19. Moreover, with older age, the co-progressions in cellular senescence, immunosenescence and inflammation can lead to deterioration of the immune function, starting with thymal involution (Fagnoni et al. 2000; Fulop et al. 2017). Immunosenescence results from the progressive deterioration of the innate and adaptive immune system which not only diminishes the ability to fight off infections, but also blunts the competence to surmount a vaccine induced antibody or cell-mediated immune response, thus attenuating immunity (Chen et al. 2009). The aging cells may also produce misfolded self-antigens, mitochondrial fragments, extracellular vesicles and senescent cells. These aging processes in turn evoke a pro-inflammatory immune response against self-antigens (Franceschi et al. 2000; Fulop et al. 2017; Franceschi et al. 2018). Additionally, certain immune cells were found to secrete senescence-related components like cytokines, chemokines and extracellular matrix remodeling proteases (Callender et al. 2018). This high inflammatory status aids in promoting the cytokine storm, comprised of IL-6 and other mediators that attribute to the increased

pathophysiological response to SARS-CoV-2 in elderly individuals (Mueller et al. 2020; Salimi and Hamlyn 2020; Sargiacomo et al. 2020). Furthermore, upregulation of SARS-CoV-2 specific host receptors by senescent cells were also observed (Sargiacomo et al. 2020). Cellular senescence due to telomere shortening in virus-specific memory immune cells reduce CD4+ and CD8+ T cells and regulatory T cell count (Mueller et al. 2020). The reduced T cells then lead to a shift in T cell subset distribution and loss of CD27 and CD28 co-stimulatory molecule expression, which is considered an underlying mechanism for severe adult COVID-19 pneumonia cases, by increasing susceptibility to infections (Li et al. 2019; Scarpa et al. 2020). This reduction or absence of thymopoiesis also exacerbates the cytokine storms (Scarpa et al. 2020). Hence, older individuals have a diminished ability to combat infections along with an impaired ability to develop antibody or cell-mediated immune responses to pathogens, cancer cells and vaccines (Chen et al. 2009). Progress of vaccine development targeting the elderly individuals is slow. This is partly due to the lack of understanding of SARS-CoV-2 mechanisms in immune systems under comorbidity conditions (Pelicioni and Lord 2020). All of these factors are affecting the development of vaccines or the excessively strong immune responses against the SARS-CoV-2 in the elderly (Chen et al. 2009). To develop effective and improved vaccination strategy for older population, adjuvants, higher antigen dose, alternative routes of administration and

immunostimulatory agents can be adopted (Weinberger 2018). System biology approach are needed to identify proteins or pathways associated with diminished immune responses which can be stimulated by senolytes and other immunomodulatory drugs. Senolytes can lead to selective apoptosis of the senescent cells to compensate for age-related deficiencies, and thereby improve immunoprotection in aged people (Kirkland and Tchkonja 2017). SARS-CoV-2 vaccines have been made by conjugating adjuvants with the coronavirus S protein to broaden and induce immune response (Fig. 5). Unique screening systems identified potent adjuvant vaccine targets (American Scientific, 2020). Currently, the Boston Children’s Hospital is developing a novel approach to conjugate an adjuvant with the coronavirus S protein for vaccine development, particularly targeting the elderly population (Centers for Disease Control and Prevention (CDC) 2020c). Additionally, the U.S. FDA is facilitating the evaluation of hyperimmune globulin for elderly patients with COVID-19 (US FDA, 2020c). (Fig. 6).

General Disease Management

COVID-19 can be managed at home, for patients with mild infection (e.g., fever, cough, and myalgias without dyspnea), or for individuals with asymptomatic infection who are adequately isolated within the outpatient setting. Management of such patients should focus on the prevention of transmission

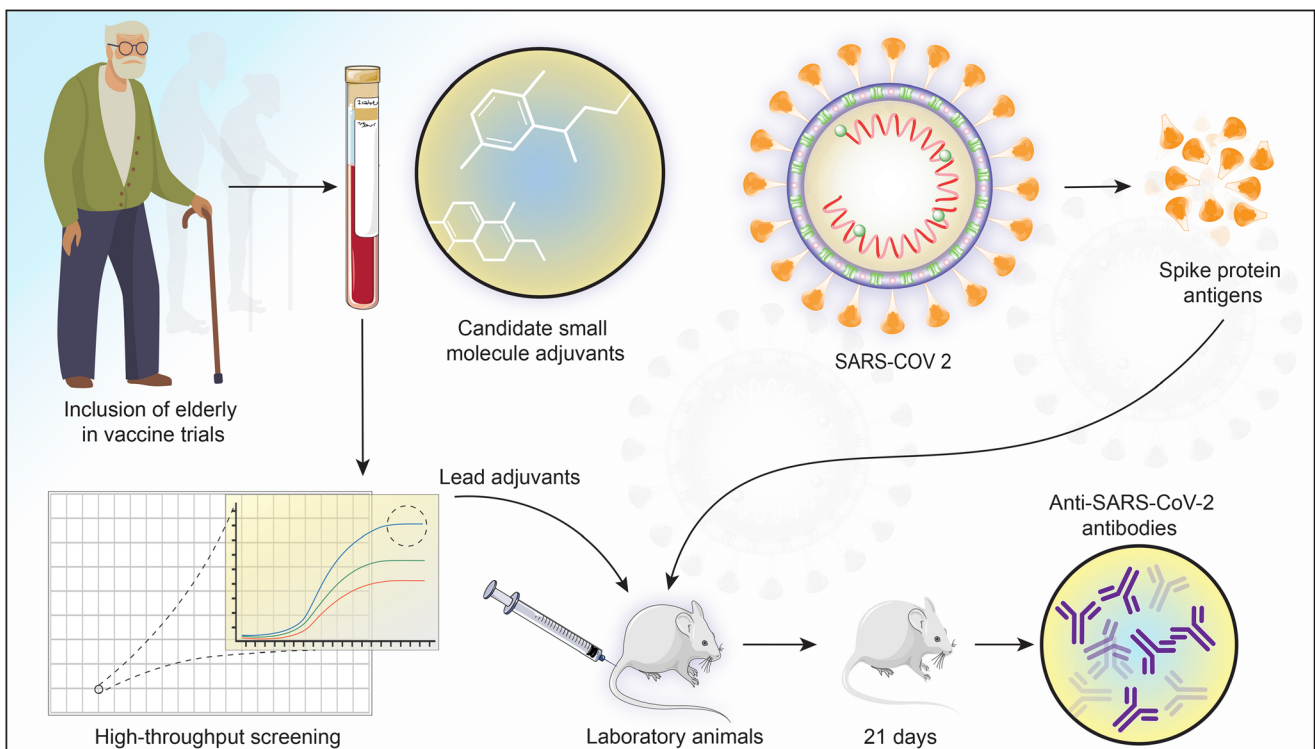
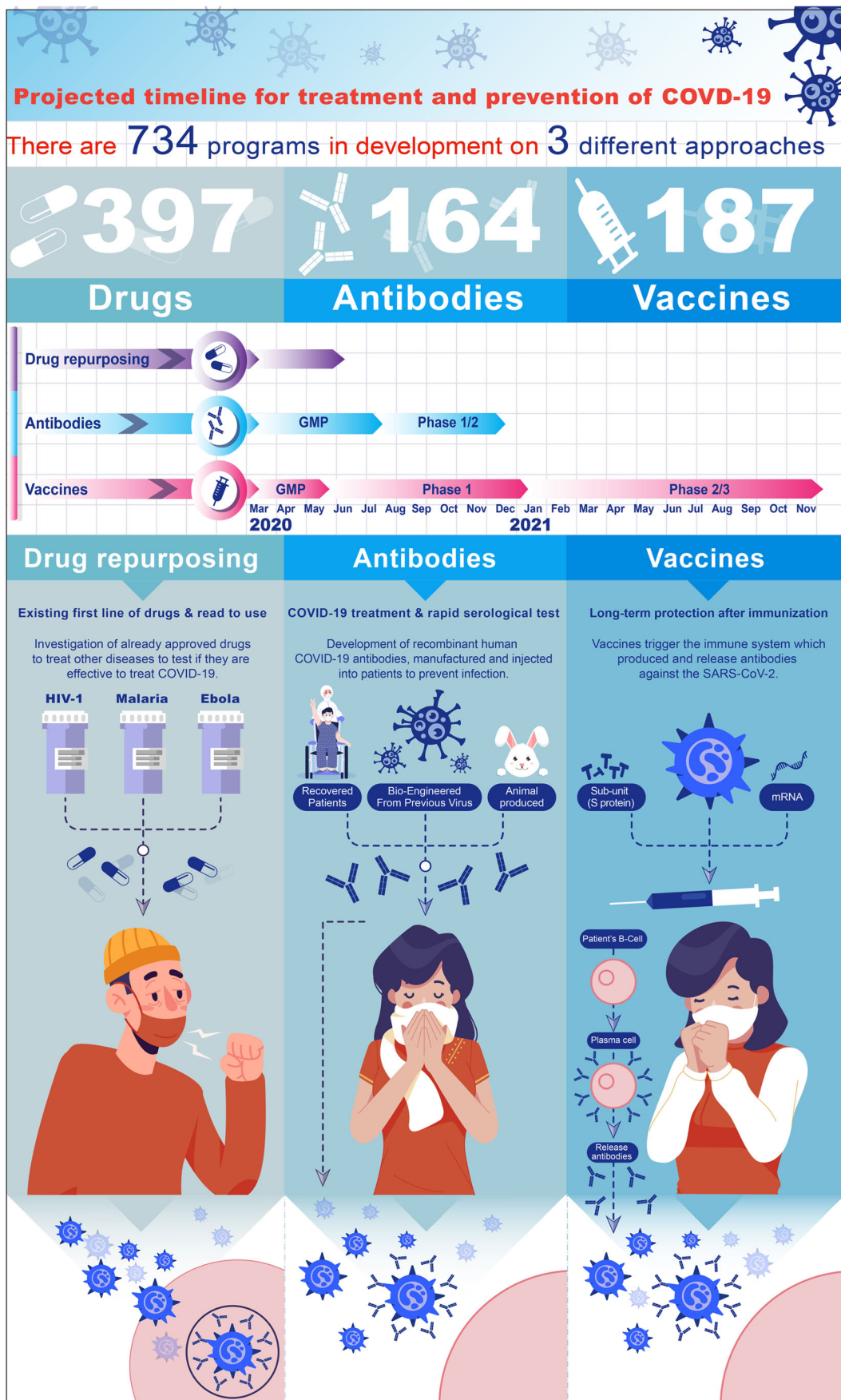


Fig. 5 Vaccines for the elderly. Blood samples are collected from elderly are used to test the immunogenicity of small molecule adjuvant conjugated spike protein as vaccine candidates. The lead adjuvants are tested for their ability to induce humoral and cellular immune responses against SARS-CoV-2



◀ **Fig. 6 Treatment and prevention.** There are multiple treatment and prevention measures in play for SARS-CoV-2. These include, but are not limited to, repurposing drugs, producing neutralizing antibodies, mobilizing immunity through boosting or modulating antiviral immunity, and by preventing infection through vaccines. Repurposing U.S. FDA approved medication have the shortest turnaround given the extensive background information. Antibodies will be used to sequester viruses after passing clinical trials but may be limited by production scaling. Finally, vaccines will likely take over 18 months to produce and will allow for a secondary adaptive immune response to COVID-19 once complete (Bio 2020; Yang et al. 2020a, 2020b)

to others and monitoring for clinical deterioration, which should prompt hospitalization (Cheng et al. 2020; World Health Organization (WHO) 2020e). Management of patients who warrant hospitalization consists of ensuring appropriate infection control and supportive care, including oxygenation and potentially ventilation support for ARDS (World Health Organization (WHO) 2020e). Whether at home or in the hospital, standard precautions include hand and respiratory hygiene, utilization of appropriate PPE consistent with a risk assessment, injection safety practices, safe waste management, proper cleaning of linens, environmental cleaning, and sterilization of patient-care equipment (World Health Organization (WHO) 2020c). Individuals should make sure that the subsequent respiratory hygiene measures are used including proper coverage of nasal and oral emissions with a tissue or an elbow when coughing or sneezing, proper application of a face mask to patients with suspected COVID-19 while they are in waiting/public areas or in cohort rooms, and performance of hand hygiene after contact with respiratory secretions (Centers for Disease Control and Prevention (CDC) 2020d). Each person should apply WHO's My 5 Moments for Hand Hygiene approach before touching a patient, before any clean or aseptic procedure is performed, after exposure to a liquid bodily secretion, after touching a patient, and after touching a patient's surroundings (Sax et al. 2007). Hand hygiene includes either cleansing hands with an alcohol-based hand rub or with soap and water. Alcohol-based hand rubs are preferred if the hands are not visibly soiled, but the washing of hands with soap and water is recommended once they are visibly soiled (Sax et al. 2007). It is vital to make sure that environmental cleaning and disinfection procedures are followed. Thoroughly cleaning environmental surfaces with water and detergent and applying commonly used hospital-level disinfectants (such as sodium hypochlorite) are effective and sufficient procedures (World Health Organization (WHO) 2020d). Medical devices and equipment, laundry, food service utensils, and medical waste should be managed following safe routine procedures (World Health Organization (WHO) 2020c) Face mask use by the general public has received growing acceptance as a means of reducing the spread of SARS-CoV-2. This measure should be performed in

conjunction with good hand hygiene. But global public health messaging on the need for face masks worn by the general public has been inconsistent since the start of the pandemic. The reasons are attributed to cultural standards and magnification of comments by mainstream media outlets. Prior experience with SARS-CoV from 2003 in East Asia, and general social acceptance of wearing facemasks outside of pandemic circumstances helped to make face mask adoption by the general public quickly commonplace throughout the region's dense urban populations. Such acceptance and adoption of face masks came less readily in the West, notably in the United States where the US Surgeon General initially advised against using facemasks for the general public but later encouraged facemask usage when the WHO and CDC revised their positions on the use of face coverings in public. These measures taken together with PPE for health care workers and caregivers, good cleanliness and hygiene standards, social distancing, and use of face covering by the general public can forestall the further evolutions of the COVID-19 pandemic.

Conclusions

The SARS-CoV-2 pandemic has significantly affected the health, well being and socioeconomic status of the world's population. The beacon of light is the emergence of effective therapeutics and more recently vaccine strategies. Both serve to suppress or eliminate disease signs and symptoms. Remdesivir, dexamethasone, potent virus-specific antibodies, and immune modulators are effective in curtailing disease morbidities. The deployment of effective vaccines are likely in early 2021. Together with public health measures for contact tracing, social distancing, protective masks, and hand washing the pandemic control is soon to be realized. The review has offered the underpinnings of a therapeutic road map that will in the time ahead see SARS-CoV-2 elimination.

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