Heliyon 10 (2024) e26423

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Next-generation treatments: Immunotherapy and advanced therapies for COVID-19

Jenny Andrea Arevalo-Romero [a,b], Sandra M. Chingaté-López [a], Bernardo Armando Camacho [a], Carlos Javier Alméciga-Díaz [b], Cesar A. Ramirez-Segura [a,*]

[a] Laboratorio de Investigación en Ingeniería Celular y Molecular, Instituto Distrital de Ciencia, Biotecnología e Innovación en Salud, IDCBIS, 111611, Bogotá, DC, Colombia

[b] Instituto de Errores Innatos del Metabolismo, Facultad de Ciencias, Pontificia Universidad Javeriana, 110231, Bogotá, D.C., Colombia

ARTICLE INFO

Keywords:
Next-generation vaccines
Advanced therapies
Host-directed therapies
Pandemic response strategies
SARS-CoV-2
Therapeutic advancements

ABSTRACT

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in 2019 following prior outbreaks of coronaviruses like SARS and MERS in recent decades, underscoring their high potential of infectivity in humans. Insights from previous outbreaks of SARS and MERS have played a significant role in developing effective strategies to mitigate the global impact of SARS-CoV-2. As of January 7, 2024, there have been 774,075,242 confirmed cases of COVID-19 worldwide. To date, 13.59 billion vaccine doses have been administered, and there have been 7,012,986 documented fatalities (https://www.who.int/)

Despite significant progress in addressing the COVID-19 pandemic, the rapid evolution of SARS-CoV-2 challenges human defenses, presenting ongoing global challenges. The emergence of new SARS-CoV-2 lineages, shaped by mutation and recombination processes, has led to successive waves of infections. This scenario reveals the need for next-generation vaccines as a crucial requirement for ensuring ongoing protection against SARS-CoV-2. This demand calls for formulations that trigger a robust adaptive immune response without leading the acute inflammation linked with the infection.

Key mutations detected in the Spike protein, a critical target for neutralizing antibodies and vaccine design —specifically within the Receptor Binding Domain region of Omicron variant lineages (B.1.1.529), currently dominant worldwide, have intensified concerns due to their association with immunity evasion from prior vaccinations and infections.

As the world deals with this evolving threat, the narrative extends to the realm of emerging variants, each displaying new mutations with implications that remain largely misunderstood. Notably, the JN.1 Omicron lineage is gaining global prevalence, and early findings suggest it stands among the immune-evading variants, a characteristic attributed to its mutation L455S. Moreover, the detrimental consequences of the novel emergence of SARS-CoV-2 lineages bear a particularly critical impact on immunocompromised individuals and older adults. Immunocompromised individuals face challenges such as suboptimal responses to COVID-19 vaccines, rendering them more susceptible to severe disease. Similarly, older adults have an increased risk of severe disease and the presence of comorbid conditions, find themselves at a heightened vulnerability to develop COVID-19 disease. Thus, recognizing these intricate factors is crucial for

* Corresponding author. Laboratorio de Investigación en Ingeniería Celular y Molecular, IDCBIS, 111611, Bogotá D.C., Colombia.
E-mail address: cramirezbiologo@gmail.com (C.A. Ramirez-Segura).

https://doi.org/10.1016/j.heliyon.2024.e26423
Received 12 October 2023; Received in revised form 12 February 2024; Accepted 13 February 2024
Available online 19 February 2024

effectively tailoring public health strategies to protect these vulnerable populations. In this context, this review aims to describe, analyze, and discuss the current progress of the next-generation treatments encompassing immunotherapeutic approaches and advanced therapies emerging as complements that will offer solutions to counter the disadvantages of the existing options. Preliminary outcomes show that these strategies target the virus and address the immunomodulatory responses associated with COVID-19. Furthermore, the capacity to promote tissue repair has been demonstrated, which can be particularly noteworthy for immunocompromised individuals who stand as vulnerable actors in the global landscape of coronavirus infections. The emerging next-generation treatments possess broader potential, offering protection against a wide range of variants and enhancing the ability to counter the impact of the constant evolution of the virus. Furthermore, advanced therapies are projected as potential treatment alternatives for managing Chronic Post-COVID-19 syndromeand addressing its associated long-term complications.

1. Introduction

SARS-CoV-2, like other coronaviruses, can infect animal species and humans due to mutations in the spike (S) protein, specifically within the receptor-binding domain (RBD), which interacts with the angiotensin-converting enzyme 2 (ACE2) receptor on host cells [1]. Coronaviruses (CoV) have been identified as agents that pose a significant risk to public health, causing mild to upper respiratory tract infections that are associated with 15–30% of colds. Four seasonal coronaviruses—HCoV-OC43, NL63, HKU1, and 229E—have been identified in recent history [2]. In addition to these seasonal coronaviruses, the potential of dynamic transmission made it possible to evolve to more severe forms identified as three notable outbreaks in recent decades: In 2002, SARS-CoV emerged in China. In 2012, Middle East respiratory syndrome CoV (MERS-CoV) was detected in Saudi Arabia. Finally, in 2019, the pandemic SARS-CoV-2 was first identified in China. These viruses have a natural reservoir in bats with the ability to adapt and infect human respiratory tracts, whose severity can vary among individuals [3].

SARS-CoV-2, like other RNA viruses, has a high mutation rate because its RNA-dependent RNA polymerase (RdRp) lacks proofreading mechanisms. In addition, the large genome of SARS-CoV-2, a common feature of members of the *Coronaviridae* family, increases the likelihood of mutations during replication. Recent research has provided essential data on the intrinsic characteristics of SARS-CoV-2, paving the way for the rapid development of biotechnological tools to combat COVID-19, such as vaccines and drugs. These scientific advances and public health measures have mitigated the impact of the COVID-19 pandemic [4].

While the public health emergency linked to the COVID-19 pandemic officially ended on May 11, 2023 [5], the swift molecular adaptation patterns of SARS-CoV-2 are quickly giving rise to new lineages, signifying a potential new threat [6]. The mutations associated with these new lineages confer an adaptive evolution ability, altering the transmission's impact [7], the severity of illness, and enabling the virus to evade immunity acquired through vaccination or infection [8–10]. Due to the dynamic nature of the virus, the vaccination process is constantly updated to address emerging lineages, which can make it both expensive and challenging. Additionally, the available vaccines are focused on preventing symptomatic disease for short periods and may provide less protection against preventive infection [11]. This scenario underscores the urgency for the implementation of next-generation SARS-CoV-2 vaccines and drugs that effectively provide enhanced breadth of protection to variants and improve durability [12–14]. Initiatives like Project NextGen could accelerate the arrival of this new technology to stay ahead of COVID-19 [15]. This implementation would be socioeconomically beneficial for low- and middle-income countries that lack the technological platforms for local production and rely on importation processes to obtain vaccines [16].

Aligned with this perspective, advanced therapy options represent a hallmark of the new medical era, enriching the repertoire available to complement current strategies in mitigating the impact of SARS-CoV-2 infection. As the battle against the virus persists, these promising therapies are initially prioritized for individuals at higher risk of severe disease or complications, encompassing immunocompromised individuals, severely ill COVID-19 patients, and high-risk populations [17,18].

Within the subset of immunocompromised individuals, a heterogeneous population constituting approximately 3% of US adults [19], exhibit a limited response to standard vaccine strategies [20] that made vulnerable with a higher impact by SARS-CoV-2. Recent studies have associated this population with challenges linked to COVID-19 on healthcare systems [21], attributed 22% of hospitalizations, 28% of ICU admissions and 24% of deaths on 2022 [22]. That way, innovative molecular and cell-based therapeutic platforms against SARS-CoV-2 have preliminary outcomes from clinical trials that unveiled encouraging findings, demonstrating in many cases both safety and remarkable effectiveness exhibiting the potential to eliminate viruses adeptly, alleviate the distressing symptoms of acute respiratory distress syndrome (ARDS), and foster the regeneration of damaged tissues [23]. Initial results strongly indicate that therapies promise to significantly diminish the mortality rates linked with SARS-CoV-2 infections, while also substantially improving the spectrum of symptoms and syndromes associated with severe cases of COVID-19.

Next-generation strategies play a pivotal role in combating the ongoing evolution of SARS-CoV-2, serving as critical initiatives to counteract potential pathogenic effects. These strategies are designed to alleviate the burden on health systems by addressing broader aspects, including the challenges faced by the immunocompromised population. Despite constituting a smaller proportion, it is imperative to highlight the substantial impact of COVID-19 on these individuals. Vaccination schemes alone may not be entirely sufficient to safeguard their lives, underscoring the necessity for additional approaches.

Moreover, it is crucial to recognize the impact of extended infections by SARS-CoV-2 in fostering an environment conducive to virus

mutation, particularly in immunocompromised individuals. Additionally, dedicating increased resources to research and development, specifically focusing on initiatives like the Disease X initiative, holds significant importance [24]. These endeavors are essential in fortifying our preparedness for the next pandemic, ensuring more resilient responses to novel challenges.

2. Literature search strategy

The literature search commenced with a comprehensive query in PubMed, incorporating key terms related to each thematic section. The search was meticulously executed, covering titles and abstracts, followed by a meticulous evaluation of the full text of selected studies to determine eligibility. In addition to this, our search strategy encompassed a thorough review of reference lists from identified publications and targeted searches within key journals. To gauge the scholarly impact and relevance, the papers were further examined on Google Scholar for citation metrics. To ensure the inclusion of the most recent information, a subsequent search was conducted in PubMed for recently indexed papers.

2.1. SARS-CoV-2: current landscape and challenges by Omicron variant

SARS-CoV-2 has emerged as one of the most extensively researched pathogens in recent years due to its notable pathogenicity and disease-causing potential due its recombination mechanisms, principally product of cross-species transmission [25,26]. One of the first efforts performed was the comprehensive molecular characterization of the virus [27] (Supplemental Fig. 1). This endeavor led to the development of crucial biotechnological tools, including vaccines and monoclonal antibodies, which played a pivotal role in containing the outbreak [28–31]. Interestingly, SARS-CoV-2 has exhibited significant diversification in its genome due to various adaptation patterns stemming from its biological features. These include mutation, substitution, and recombination mechanisms [32], which extend even to structural proteins. Notably, the Spike protein has been a focal point of mutations, particularly within the receptor-binding domain (RBD) [33]. These mutations have the potential to alter the binding affinity to the ACE2 receptor, potentially conferring resistance to neutralizing antibodies (NAbs), thereby altering viral infectivity [34]. Following this pattern, five variants of concern (VOC) emerged and have been characterized (Alpha, Beta, Gamma, Delta, and Omicron) (Fig. 1) [35].

The Omicron variant, identified in November 2021, has attracted substantial attention owing to its remarkable genetic diversity compared to its predecessors. The virus has demonstrated the ability to evolve into multiple subvariants, among which JN.1 (commonly known as June), a descendant of BA.2.8635 [37], currently holds the status of the predominant variant. With the detection of BA.2.86 in July 2023, scientist observed interesting findings, including approximately 30 Spike mutations in comparison to the ancestral BA.2. Furthermore, virus exhibited the ability to neutralize using bivalent-vaccinated sera or XBB.1.5-adapted vaccine but displayed distinct biological tropism compared to BA.2 and XBB variants. Notably, there was a striking increase in infectivity in the CaLu-3 cell line, a model derived from human lung epithelia with endogenous expression of ACE2 and the transmembrane protease serine 2 (TMPRSS2), suggesting a changing pattern of tropism attributed to S50L and K356T mutations, resembling the tropism of the initial variants [38,39].

On the other hand, JN.1, initially identified in the United States in September 2023, demonstrates comparable antigenic diversity to BA.2.86, coupled with an additional mutation in the RBD region (L455S). This mutation is linked to a potent immune evasion feature, as evidenced by pseudovirus-based neutralization assays. The assays involved exposing the JN.1 variant to plasma from individuals who had previously gained immunity against XBB through prior exposure [40]. Another intrinsic characteristic of this variant is its ability to develop resistance against RBD domain class 1, 2, and 3 antibodies, exhibiting lower affinity to hACE2 when compared to its predecessor, BA.2.86 [40,41].

The molecular characterization of Omicron subvariants reveals a broader perspective on their genetic evolution. The subvariants demonstrate significant adaptive changes, accumulating over 50 amino acid mutations compared to the ancestral virus. Of particular interest, 15 of these mutations are concentrated within the Spike-RBD region, shedding light on the intricate molecular landscape and emphasizing the dynamic nature of the Omicron lineage [42–44] (Fig. 2).

These novel antigenic modifications are linked to an antigenic shift [47], responsible for modifying virological features of SARS-CoV-2, impacting the knowledge acquired of its biological behavior [48]. Recent studies relate an increased transmissibility of Omicron when compared to its predecessor's variants [49,50]. This feature is also associated with escape antibody-mediated neutralization acquired by vaccination, previous infection, or treatment by therapeutical antibodies [51–55], suggesting a potential role for mutations R346T, K444T, and F486S [56]. Moreover, recent research has demonstrated that many Omicron subvariants may utilize an alternative mechanism for host cell entry. This mechanism involves endocytosis, setting it apart from the entry strategies

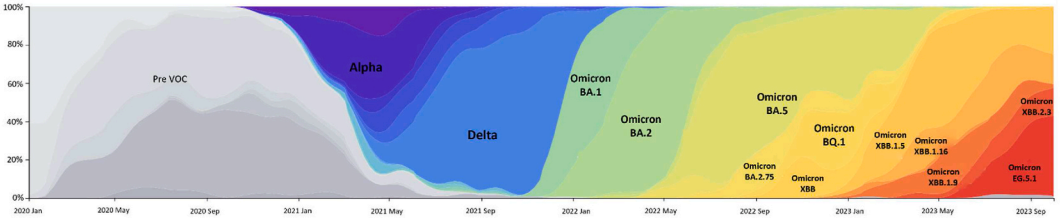
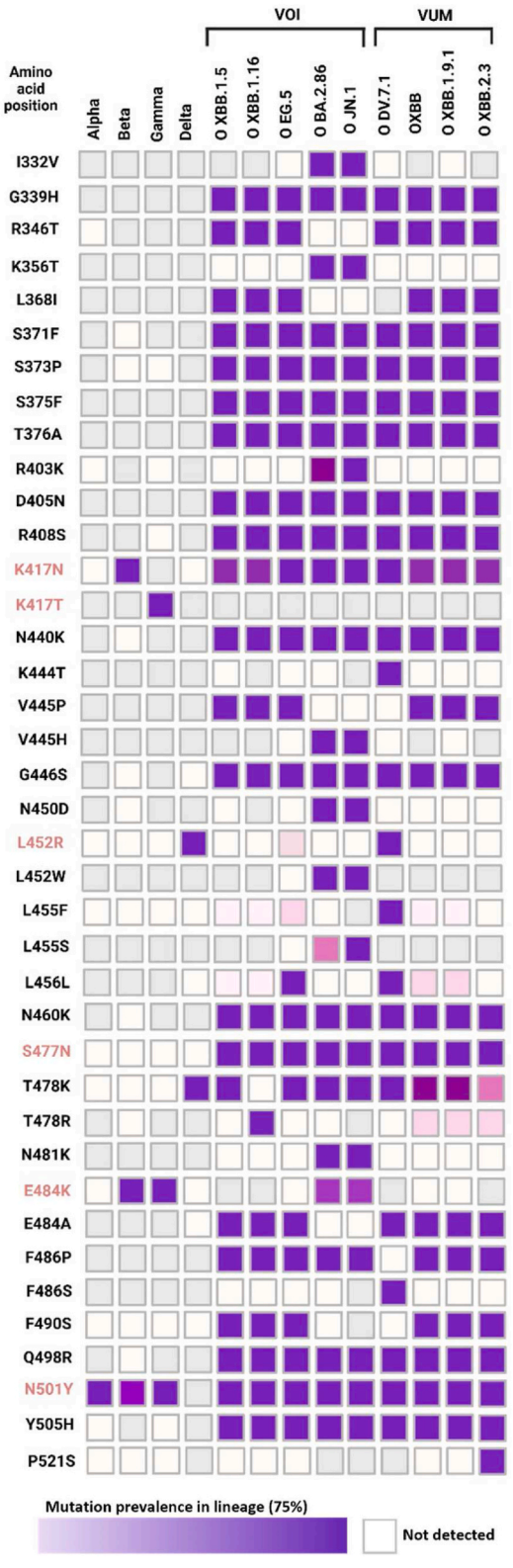


Fig. 1. SARS-CoV-2 variants over time. Data retrieved from Nextstrain [36].



(caption on next page)

Fig. 2. RBD mutations in SARS-CoV-2 variants and subvariants. including the prevalence of mutations is shown in purple, highlighting Omicron subvariants with multiple mutations compared to the predecessor variants. Data were taken from outbreak.info [45,46] (updated on January 28, 2024).

employed by previous SARS-CoV-2 variants. Unlike its predecessors, Omicron SARS-CoV-2 exhibits the ability to enter cells without depending on transmembrane serine protease 2 (TMPRSS2). This innovative mode of cellular entry obviates the requirement for TMPRSS2 and the subsequent plasma membrane fusion, resulting in changes in cellular tropism [57,58]. These alterations are being linked to upper respiratory tract infection, associated with milder clinical symptoms.

Considering the adaptation mechanisms observed in SARS-CoV-2, exemplified by the genetic divergence of Omicron subvariants, promising advancements are being made in the realm of next-generation vaccines, passive immunotherapy, and cell-based platforms. These emerging strategies have shown initial success and are poised to complement each other effectively. Their collective potential holds promise in mitigating the impact of SARS-CoV-2 [19].

3. NEXT-GENERATION vaccine strategy as a promising approach

The unwavering global commitment in the fight against SARS-CoV-2 has emphasized the pivotal role of vaccination as a paramount tool for disease control. Current vaccines have proven effective in not only diminishing illness severity but saving lives. Recent studies, particularly highlighting the efficacy of the AZD1222 vaccine, reveal compelling statistics. In the age group of 40–59 years, mortality reduction reaches an impressive 88%, soaring to a remarkable 100% in both the age groups of 16–44 years and 65–84 years. Similarly, mRNA vaccines such as BNT162b2 and mRNA-1273 exhibit substantial efficacy, reducing mortality rates across different age groups, ranging from 80.3% to a comprehensive 100% [59].

However, the swift emergence of new variants—marked by multiple mutations in the S protein, as seen notably in the Omicron variant—continuously challenges the effectiveness of existing vaccines [60,61]. The altered dynamics of spread and tropism associated with these variants further underscore the urgency for adaptive vaccine strategies. Recognizing the imperative for sustained immunity and the pressing need for innovative, cost-effective, and swift technologies, there is a compelling call for the development of a next generation of vaccines. This imperative reflects the evolving nature of the virus and emphasizes the necessity to stay ahead in the ongoing battle against the ever-changing SARS-CoV-2 landscape.

A new generation of broader platform vaccines is presently in the developmental and evaluative phases, with ongoing exploration of innovative initiatives. A pivotal aspect to enhance for the initial vaccine generation is the induction of immunity in the nasal and oral cavities, considering these are the entry points for SARS-CoV-2 [62,63]. A live-attenuated SARS-CoV-2 mucosal vaccine named IBIS is currently in development, displaying promising potential to offer broad-spectrum protection against SARS-CoV-1, SARS-CoV-2, and their variants in small rodents. The capacity for cross-protection, the induction of a robust lung $CD8^+$ T cell response, and the activation of mucosal virus-specific $CD4^+$ T cells are crucial attributes that position it as a candidate for a pan-*sarbecovirus* vaccine [64].

Furthermore, another parameter to be scrutinized involves the use of nanoparticle platforms as vaccine delivery systems, aimed at improving vaccine efficacy and immunogenicity while showcasing attributes of safety, tolerability, and effectiveness [65]. Ferritin is a biological product currently under exploration for its potential use in nanoparticle platforms due to its notable biological stability, biocompatible features, and its ability to simultaneously integrate various antigens, holding promise for enhancing the host immune response [66], This platform is being utilized in SARS-CoV-2 next-gen vaccines, displaying spike proteins or RBD regions and offering potential pan-coronavirus capabilities [67,68]. On the other hand, although the S protein is the most immunogenic region of the virus, unfortunately, it is the most susceptible to adapting mutations under immune pressure, potentially leading to immune escape. Thus, new approaches are targeting more conserved regions of the virus, with the Nucleocapsid (N) protein emerging as a candidate. The N protein has shown the ability to induce strong T-cell immunity and could represent a promising approach [14].

In summary, developing next-generation vaccines against SARS-CoV-2 involves addressing viral variability, ensuring long-term immunity, enhancing global accessibility, fostering cross-protection, and harnessing cutting-edge technologies to improve the possibilities for effectively managing pandemics in the future. Initiatives like Project NextGen, under the auspices of the U.S. Department of Health & Human Services, have received an initial investment of $5 billion. This project aims to coordinate with laboratories to develop vaccines with a broader spectrum against variants and include different Sarbecoviruses. Additionally, it emphasizes the protection of mucosal tissues to block the initial phase of infection. Furthermore, the initiative aims to develop a new generation of monoclonal antibodies that can remain effective amidst the continuous evolution of SARS-CoV-2 [15].

4. Passive immunotherapy as an immunotherapeutic approach

Passive immunotherapy strategies have played a central role in the COVID-19 pandemic. Their use has proven especially beneficial in the recovery of patients, with a notable impact on immunocompromised individuals who are particularly susceptible to the virus.

COVID-19 convalescent plasma remains a topic of debate within the medical community due to heterogeneous outcomes associated with the lack of consensus on application criteria. On the other hand, the efficacy of monoclonal antibodies is encountering challenges in response to the emergence of various Omicron subvariants. Nonetheless, these therapeutic tools remain relevant, and ongoing clinical studies continually refine the criteria for their enhanced application.

4.1. Transfusion of COVID-19 convalescent plasma (CCP)

This therapeutic strategy involves plasma transfusion from individuals who have successfully recovered from COVID-19 to patients with COVID-19 infection to provide immediate antibody-mediated passive immunity [69]. This approach treats different viral infections [70], including the SARS outbreak [71]. During the SARS-CoV-2 pandemic, the U.S. Food and Drug Administration (FDA) initially issued an Emergency Use Authorization to use CCP in hospitalized patients affected by the disease. However, after several revisions, the FDA has limited the use of CCP with elevated anti-SARS-CoV-2 antibody titers, restricting it to treating patients with immunosuppressive disease or receiving immunosuppressive therapy [72]. Results of clinical trials of CCP therapies have exhibited a wide range of findings, often characterized by heterogeneity and contradictions. These disparities may be due to differences in treatment protocols, such as varying dosages, specific units of CCP used, and types of antibodies employed [73–78]. Consequently, establishing a meaningful basis for comparing and evaluating the efficacy of this therapy has proven to be a challenging endeavor.

Reports have indicated improved efficacy of CCP therapy when administered during the early stages of the disease, with higher dosage levels and increased antibody concentrations (>160 of neutralizing titer) [79–82] all while maintaining a heightened degree of safety [73,83].

While standardizing protocols for CCP application is an ongoing process, recent research underscores its broader potential effectiveness in immunocompromised patients, particularly considering the current challenge posed by immune system evasion by Omicron subvariants. Recent clinical reports describe two cases involving patients with B-cell depletion associated with a clinical history of lymphoma who experienced prolonged COVID-19 infection. Following the administration of CCP in two doses, each ranging from 300 to 500 ml and featuring significantly elevated levels of IgG anti-spike antibodies (12,635.3 Au/mL to >40,000 Au/mL; 5680 Au/mL), the CCP therapy proved safe and effective. Subsequently, these patients exhibited significant clinical improvement, with their long COVID-19 symptoms resolving or markedly improving. Afterward, SARS-CoV-2 infection was confirmed to have remitted, based on negative qualitative PCR results from a series of nasopharyngeal swabs [84]. Similarly, Denkinger and colleagues conducted a randomized, open-label, multicenter trial involving patients with solid and hematological tumors. Their study revealed a notable rise in anti-SARS-CoV-2 neutralizing antibodies (Nabs) in the plasma of patients following CCP infusions. This increase in NAbs correlated with enhanced overall recovery while maintaining a favorable safety profile [85].

Preliminary findings from a comprehensive systematic review reveal promising outcomes in enhancing the efficacy of CCP. This plasma was obtained from donors who received vaccinations or recovered from pre-Omicron Variants of Concern (VOC). Consequently, this hybrid plasma can neutralize Omicron subvariants. These findings indicate that protection titers of CCP under these conditions were nearly 100% effective against the BA.1, BA.2, and BA.4/5 Omicron subvariants. Thus, these results suggest a significant role for vaccinated convalescent plasma as a broad-spectrum therapeutic option during the Omicron wave [86].

Recent studies have revealed additional effector properties of CCP beyond its NAbs. The antibodies exhibit antiviral effects through their conventional neutralizing activity and contribute to complement activation and enhance phagocytosis [87]. Furthermore, a potential immunomodulatory role for CCP is suggested, given the presence of anti-inflammatory cytokines that can potentially be associated with diminishing C-reactive protein (CRP) levels after CCP transfusion [82,88].

Although the conditions for the universal use of CCP have not yet been fully standardized, this therapeutic strategy has found strategic significance in the recent Omicron era, playing a vital role in the battle against SARS-CoV-2. This prominence has emerged

Table 1
Anti-SARS-CoV-2 RBD therapeutic monoclonal antibodies.

Therapeutic mAb	Use	mAb-resistant SARS-CoV-2 variants	Status	PDB ID
Bebtelovimab	Treatment	Omicron: (BQ.1; BQ.1.1; BA.2; BA.2.12.1 and BA.5) [52,115]	Not currently authorized by the FDA [116]	7MMO [103]
Regdanvimab (CT-P59) (Regkirona)	Treatment	Gamma [117] Delta [118] Omicron: B.1.1.529 [119]	Paused by Omicron resistance	7CM4 [99]
Sotrovimab (S309)	Treatment	Delta [120] Omicron [121]	Strong recommendation against its use [121]	7TN0 [107]
Amubarvimab (BrII-196), Romlusevimab (BRII-198)	Treatment [122]	Omicron [123]	Available in China	–
Bamlanivimab (LY-CoV555) and Etesevimab (CB6)	Treatment Post-exposure prophylaxis	Beta [124] Gamma [124] Omicron [124]	Paused by Omicron resistance	7KMH [104] 7F7E [125]
REGEN-COV: [**Casirivimab** (REGN10933)/ **Imdevimab** (REGN10987)]	Treatment	Omicron [51]	Paused by Omicron resistance	6XDG [106]
	Post-exposure prophylaxis			6XDG [106]
Evusheld [126] [**Cilgavimab** (COV2-2130 [105, 126]/**tixagevimab** (COV2-2196 [126])]	Pre-exposure prophylaxis	Omicron [123]	Not authorized for emergency use in the U.S [127].	7ZJL 8D8Q [128] 8D8R [128]

[a]PDB ID. Protein Data Bank identification code.

due to the impairment of the efficacy of mAbs approved for emergency use [89]. Currently, in efforts to standardize global conditions, there are 45 ongoing clinical studies with heterogeneous outcomes [90].

4.2. Monoclonal antibody-based therapy

The pressing need to find new therapeutic strategies to combat the COVID-19 pandemic led to the design of numerous anti-SARS-CoV-2 mAbs [91]. Plasma from patients recovered from COVID-19, enriched in anti-SARS-CoV-2 antibodies, as well as the memory B-cells that synthesize them, have been used as primary sources to produce mAbs against the SARS-CoV-2 S protein and the RBD domain [92,93]. Other methods to generate anti-SARS-CoV-2 mAbs comprise transgenic mice, genetically engineered proteins, and yeast library screening [93,94].

Monoclonal antibodies against the SARS-CoV-2 S protein act through mechanisms related to their structure. First, the antigen-binding fragments (Fab) prevent the virus from binding to the ACE2 receptors, and second, the Fc fragment can activate the complement system and bind to the Immunoglobulin Fc receptors (FcRs) on cytotoxic cells that can eliminate virus-infected cells through Ab-dependent cell-mediated cytotoxicity (ADCC) [95]. Unfortunately, some mAbs can bind to macrophage FcRs and induce a hyperinflammatory response resulting from Ab-dependent enhancement (ADE) of cytokine production [96,97].

The SARS-CoV-2 RBD has become the main target of mAbs because of its crucial role in virus entry into host cells **(Table 1)** [91,93]. Analysis of the structural relationship between RBD and anti-RBD NAbs has led to the classification of these antibodies according to structural features and mechanism of action [98]. Class 1 NAbs, *e.g.,* CT-P59 (regdanvimab) [99], target the receptor binding motif (RBM). They recognize the RBD in the up conformation, thus blocking the interaction with the ACE2 receptor [100–102]. Class 2 NAbs, *e.g.* LY-CoV1404 (bebtelovimab) [103], target the ACE2 binding site of the RBD in both up and down conformations [104–106]. Class 3 antibodies, *e.g.*, S309 (sotrovimab) [107], target the conserved core domain of the RBD without altering interactions with the ACE2 receptor [106,108]. Class 4 antibodies, *e.g.*, S2X259 [109], target epitopes in both the RBM and the core domain of the RBD [110]. Unfortunately, frequent mutations in the RBD have modified the epitopes recognized by mAbs, resulting in the emergence of viral variants resistant to mAbs [111–113]. To address this issue, researchers are exploring other SRS-CoV-2 regions as potential targets for therapeutic mAbs [114].

5. Advanced therapies for COVID-19

5.1. ACE2 decoys

Preventing SARS-CoV-2 from entering human cells by neutralization is a logical strategy to reduce mortality resulting from pulmonary infection [129,130]. To SARS-CoV-2 enter into host cells, the RBD of the viral S protein must interact with the ACE2 receptor on host cells [131–135]. Therefore, blocking such protein-protein interaction (PPI) becomes an important alternative to prevent SARS-CoV-2 infection [130,136]. The binding surface on ACE2 that directly interacts with the RBD is a good template for designing neutralizing proteins. Indeed, clinical-grade human recombinant soluble ACE2 (hrsACE2) is a decoy receptor that enhanced SARS-CoV-2 recovery from cultures in Vero cells and *in vivo* hamster models [137–139]. Furthermore, the hrsACE2 showed encouraging results in the treatment of severe COVID-19 [140,141]. Theoretically, engineered ACE2 decoy receptors could overcome SARS-CoV-2 scape variants, as it is unlikely that the virus could evade the hrsACE2-mediated neutralization without simultaneously decreasing its affinity for the native ACE2, which would prevent its entry into target cells [142,143]. Certainly, in practice, ACE2 decoy receptors are resistant to mutations of Omicron escape subvariants and other emerging SARS-CoV-2 variants [138,144]. Recent updates to the platform have demonstrated improved functionality. As highlighted by Kegler et al. in their 2023 study, they developed an ACE2-minibody target module lacking the capacity to activate Fc gamma receptors (FcγR) but equipped with an epitope tag at the C-terminal end, enabling recognition by T-cells bearing a universal artificial receptor. This innovation efficiently contributes to the elimination of viral reservoirs by effectively targeting and eliminating virus-infected cells, all the while exerting immunomodulatory effects. Moreover, the ACE2-minibody target module has shown remarkable proficiency in neutralizing various VOCs, including BQ.1.1 and XBB.1.5 [145].

Given the evolutionary tendency of SARS-CoV-2 to retain its ACE2 binding capacity, research groups worldwide have used the extracellular domain of the ACE2 to insert modifications to increase affinity for RBD and fuse a human Ig Fc fragment to combat COVID-19. This engineered ACE2-Fc construct would neutralize the virus while triggering Fc-mediated effector functions [138,143,144,146–148] and would be resistant to SARS-CoV-2 scape variants [142,149,150].

Using virus-targeted receptors to design specific blocking proteins is a clever approach that could be widely applied to design therapeutic strategies to control other pathogenic viruses. Of course, it depends on the knowledge about the entry mechanisms characteristic of each viral agent.

5.2. Cell-based therapy

Cell therapy emerges as a promising strategy in the comprehensive management of COVID-19, specifically addressing diverse vulnerable populations grappling with severe pulmonary and systemic consequences of the disease. This approach holds therapeutic potential, notably for the immunocompromised population [151], individuals burdened with comorbidities like diabetes mellitus (DM) and chronic obstructive pulmonary disease (COPD) [152,153] and elderly individuals, where the mortality rate for severe cases in the 70–89 age group reaches 67% [154].

While vaccination stands as the optimal therapeutic alternative to prevent diseases associated with SARS-CoV-2 [155], it is occasionally insufficient to prevent all severe cases. In such instances, cellular therapy emerges as a potential therapeutic platform to enhance the quality of life for affected patients. Encouragingly, the preliminary results from early-phase clinical studies are promising, hinting at the potential for cell-based therapy to emerge as a proactive platform for addressing future pandemic outbreaks.

6. T-CELL-ASSOCIATED therapies

6.1. SARS-CoV-2-specific T cell-based therapy

Adoptive cell therapy with SARS-CoV-2-specific T-cells (SSTs) is a well-established strategy widely used over the past two decades for prophylactic and therapeutic purposes against various viral infections. This approach has effectively combated diseases caused by viruses such as BK, Epstein-Barr, adenovirus, and cytomegalovirus [156]. Moreover, it has shown encouraging results, especially in patients who have undergone hematopoietic stem cell transplantation (HSCT) [157–159] [157–159] [157–159]. The generation of SSTs usually involves *ex vivo* expansion of circulating lymphocytes obtained from healthy convalescent COVID-19 donors. This expansion process usually takes ten to twelve days to ensure the development of a high-quality product capable of responding to different variants of SARS-CoV-2 [160]. SST therapy could be administered as a prophylactic strategy in immunocompromised individuals or as early therapy for COVID-19 in high-risk patients. The SSTs could be cryopreserved to provide an *off-the-shelf* solution with a partial HLA match [161–164]. Immunophenotypic characterization of *ex vivo* expanded SSTs reveals a predominance of $CD4^+$ T-cells specific for the SARS-CoV-2 S, M, and N proteins. These T-cells produce high levels of IL-2, IFN-γ, and TNF-α related to their cytotoxic effect against SARS-CoV-2 [165]. Clinical studies are currently evaluating the effectiveness of SST therapy in combating COVID-19. It is important to note that this strategy cannot be administered to patients with COVID-19 receiving corticosteroids [166] because these drugs induce T-cell apoptosis [167].

Furthermore, the results of a randomized, open-label, phase 1/2 clinical trial (NCT05447013) assessed the efficacy and safety of partially HLA-matched, off-the-shelf SSTs. This study was conducted during a period when the Delta variant was prevalent among high-risk hospitalized patients, involving the intravenous administration of SST to patients. The outcomes revealed no GVH reactions associated with the administration of SSTs. Moreover, preliminary findings indicated an improved recovery rate when SSTs were administered alongside dexamethasone and remdesivir, resulting in a significant 53% reduction in the risk of mortality. Furthermore, SST displayed a broader spectrum of activity against all variants of concern (VOCs), including Omicron [168]. This comprehensive coverage holds the therapeutical potential to address challenges related to immune evasion, which have been observed in various biotechnological approaches such as vaccines and monoclonal antibodies [54].

6.2. Regulatory T cell-based therapy

Regulatory T-cells, commonly referred to as Tregs, are a subset of $CD4^+$ T-cells characterized by the expression of CD25 and FOXP3 [169], which play a crucial role in immune regulation by suppressing the activation and proliferation of inflammatory cells [170]. Therefore, Tregs are involved in immune tolerance, regulation of tissue homeostasis, and tissue repair in organs such as the heart, lung, bone, liver, kidney, muscle, and central nervous system. The tissue repair functions of Tregs are associated with the expression of the epidermal growth factor receptor (EGFR), amphiregulin (AREG), CD73/CD39, and the keratinocyte growth factor [171].

The benefit of Treg-based therapy for COVID-19 remains controversial, as studies have yielded conflicting results. Studies reported higher numbers of circulating Tregs in patients with COVID-19 [172], while others have found a decrease in these cells, particularly in patients with severe disease [173]. The role of Tregs in the treatment of COVID-19 remains a matter of debate, as they have been linked to both proinflammatory effects and suppression of antiviral T-cell responses during the severe phase of the disease, strikingly similar

Table 2
Summary of ongoing NCT registered clinical trials of T regulatory Cell-based therapy for COVID-19 (updated on January 28, 2024).

NCT number	Title	Study Design	Specification of the biological product	Number of patients	Phase/Status	Location
NCT04468971	REgulatory T Cell infuSion fOr Lung Injury Due to COVID-19 PnEumonia (RESOLVE)	Randomized placebo controlled	Cryopreserved, off-the-shelf, cord blood-derived T regulatory cells	45	Phase I - completed	USA
NCT04482699	Phase I/Phase II Trial of Allogeneic Hybrid TREG/Th2 Cell (RAPA-501-ALLO) Therapy for COVID-19-Related ARDS	Randomized placebo-controlled	Allogeneic off-the-shelf RAPA-501 cells	1	Terminated. Change in an eligible patient population	USA
NCT05027815	A Phase 1/2a Study of Cryopreserved Ex Vivo Expanded Polyclonal $CD4^+CD127lo/-CD25^+$ T Regulatory Cells (cePolyTregs) for the Treatment of Acute Respiratory Distress Syndrome (ARDS) Associated With SARS-CoV-2 Infection (regARDS)	Treated arm	Cryopreserved Ex Vivo Expanded Polyclonal $CD4^+CD127^{lo/-}CD25^+$ T Regulatory Cells	7	Terminated. A decrease in COVID-19 cases made further enrollment infeasible.	USA

NCT number: National Clinical Trial Number. Data retrieved from https://clinicaltrials.gov/search?cond=tregs%20covid.

to tumor-infiltrating Tregs that suppress antitumor responses [174]. The lack of consensus suggests the need for further research to determine whether Tregs exhibit a dual role, depending on the clinical phase of COVID-19.

The tissue repair function of Tregs can be exploited to design therapies against COVID-19-related lung diseases. In murine models, adoptively transferred Tregs alleviated acute lung injury (ALI)-associated fibroproliferation by down-regulating CXCL12 expression [175].

In 2020, the first cell therapy with allogeneic Tregs was administered to two patients with COVID-19 ARDS. After receiving two to three doses of 1×10^8 umbilical cord blood (UCB)-derived Tregs, these patients showed a significant clinical improvement and no adverse events. The clinical response was primarily related to the infusion of Tregs, as evidenced by the rapid reduction in IL-6, TNF-α, and IFN-γ levels [176]. Currently, the utility of Treg-based therapy for COVID-19 is a subject of significant interest and investigation in various clinical trials (**Table 2**). One promising approach involves the use of UCB Treg off-the-shelf, cryopreserved, allogeneic cells, known as CK0802. In a randomized, multicenter, double-blinded, placebo-controlled clinical trial (NCT04468971), the administration of CK0802 in patients diagnosed with SARS-CoV-2 infection and moderate-to-severe ARDS. The patients received either 100 million Tregs (CK0802-100) or 300 million Tregs (CK0802-300) per infusion on day 0, day 3, and day 7. The results indicated an 89.7% probability of beneficial effects for CK0802-100 compared to placebo, and 28.4% for CK0802-300 compared to placebo. Importantly, the infusion of Tregs was found to be safe, as none of the patients exhibited $\geq$3 toxicity outcomes related to the therapy [177].

6.3. CAR-T cells as a model to combat SARS-CoV-2

CAR-T cells have emerged as a groundbreaking therapeutic approach, demonstrating notable success in treating certain types of cancer, particularly hematologic malignancies [178–180]. Encouraged by this success, researchers have explored the potential of CAR-T therapy as a weapon against infectious viruses, including Hepatitis C Virus, Hepatitis B Virus, and Human Immunodeficiency Virus [181,182]. Despite its promise, the use of CAR-T cell therapy against SARS-CoV-2 has been hindered by the significant side effect of Cytokine Release Syndrome (CRS) [183], introducing potential risks associated with its application and leading to a reluctance to explore this platform for COVID-19.

Nonetheless, there are ongoing technological initiatives aimed at overcoming these challenges. Guo and colleagues, for instance, presented the development of cytolytic CAR-T cells, which were tested in mice. These cells demonstrated an induced response involving key effectors such as IFN-γ, GZMB, Perforin, and FasL upon binding to the RBD peptide [184]. As CARs recognition usually relies on antibody-derived sequences, they will still be hampered by the high evasion capacity of the virus. So, Gonzalez-Garcia et al. developed a CAR-like construct with a recognition domain based on the ACE2 and one affinity-optimized ACE2 viral receptor, with the assumption that the ability to bind the virus will not wane, as Spike/ACE2 interaction is pivotal for viral entry. Both CARs drive a T cell line activation in response to SARS-CoV-2 Spike protein expressed on a pulmonary cell line [185].

In another initiative, a system was devised to replicate a SARS-CoV-2-specific immune environment, offering a valuable tool for drug screening. Thus, a SARS-CoV-2 spike protein-specific CAR (SARS-CoV-2-S CAR-T) was designed to infect human T cells and exhibit T-cell responses closely mirrored those observed in COVID-19 patients. Subsequent screening of FDA-approved drugs identified felodipine, fasudil, imatinib, and caspofungin as effective agents, capable of suppressing cytokine release by these CAR-T cells while inhibiting the NF-κB pathway *in vitro* [186]. Despite challenges, these technological advancements signal potential breakthroughs in addressing the hurdles associated with CAR-T therapy for SARS-CoV-2.

7. Natural killer cell-based therapy

Since the onset of the COVID-19 pandemic, researchers have been characterizing the role of NK cells in controlling SARS-CoV-2 infection. Notably, they have observed impaired NK cell function in COVID-19 patients [187]. In severe cases of COVID-19, there is an inverse correlation between high IL-6 levels and the expression of granzyme A by NK cells, further impairing the antiviral immune response [188]. Moreover, patients with severe COVID-19 exhibit heightened activation and signs of exhaustion in peripheral NK cells, evidenced by increased expression levels of HLA-DR, CD38, and CD69, as well as PD-1 and TIM-3, respectively [189]. Adoptive transfer of allogeneic NK cells for the treatment of COVID-19 has several advantages, such as direct antiviral activity, a less stringent requirement for donor-recipient HLA-matching [190], and the flexibility necessary to be administered in emergency scenarios. Moreover, NK cell-based therapy does not carry the risk of either graft-versus-host disease (GVHD) or cytokine release syndrome, as is the case when Ag-specific T-cell-based therapies are administered [187].

Ongoing clinical trials of NK cell-based therapies against SARS-CoV-2 are diverse. For example, the NCT04365101 trial is evaluating the potential of human placental $CD34^+$ cells-derived NK cells (CYNK-001) as an off-the-shelf, allogenic immunotherapy for patients with moderate COVID-19. In addition, the chimeric antigen receptor (CAR) platform tailored to NK cells (CAR-NK cells) has also been implemented to combat COVID-19. The CAR-NK platforms offer several advantages over CAR-T, including diminished risk of GVHD, off-the-shelf availability, and an enhanced safety profile attributed to their shorter persistence in the body. Moreover, CAR-NK cells may be better suited for effectively targeting solid tumors and overcoming immunosuppression [191]. In line with this perspective applied to viral agents, Lu et al. designed a novel approach by engineering UCB-derived NK cells to express soluble interleukin 15 (sIL15) to increase their survival and a CAR consisting of the extracellular domain of ACE2 to target the S protein (mACE2-CAR_sIL15 NK cells). These CAR-NK cells bound to the S1 subunit of a recombinant S protein and chimeric VSV-SARS-CoV-2 viral particles. Moreover, mACE2-CAR_sIL15 NK cells reduced viral load and prolonged survival of transgenic mice expressing the human ACE2 receptor (K18-hACE2) after infection with live SARS-CoV-2 [192]. In another study, NK cells engineered to express the CAR H84T-BananaLec (BanLec) directed against SARS-CoV-2 envelope mannose glycans showed antiviral activity. The H84T-BanLec CAR

construct comprises an extracellular H84T-BanLec domain, CD8α hinge and transmembrane domains, and the intracellular domains of 4-1BB (CD137) and the CD3ζ chain. The H84T-BanLec CAR-NK cells showed promising results when assayed *in vitro*: They reduced the potency of lentiviruses pseudotyped with a SARS-CoV-2 S protein envelope; significantly diminished the entry of those pseudotyped lentiviruses into ACE2-expressing 293T cells; and showed increased secretion of IFN-γ and TNF-α, indicating their capacity to eliminate infected cells [193].

Although NK cell-based therapeutics have shown promising results in laboratory settings, they must undergo rigorous evaluation in clinical trials to assess their safety and efficacy as feasible cell therapies. Clinical trials are currently in progress, according to data available at https://clinicaltrials.gov/**(Table 3)**.

7.1. Extracellular vesicle-based therapy

Extracellular vesicles (EVs) are potential therapeutic tools due to their intrinsic biological properties, such as lower immunogenicity, higher safety, flexibility to be modified *in vitro*, and immediate availability for clinical application [194,195]. Recent studies have shown that modified EVs could be helpful in the treatment of COVID-19. For example, Scott et al. developed EVs containing a CD63 receptor fused to an anti-SARS-CoV-2 nanobody (VHH72-CD63), capable of neutralizing SARS-CoV-2 by binding to the viral S-RBD domain [196]. Another approach consists of EVs carrying palmitoylated ACE2, which binds to the SARS-CoV-2 S-RBD with high affinity. These EVs effectively compete with the cell surface ACE2 receptor, block viral load, and thus protect the host against SARS-CoV-2-induced lung inflammation [197]. Furthermore, EVs derived from engineered dermal fibroblasts, known as ASTEX (activated specialized tissue effector extracellular vesicles), showed synergistic antiviral and cytoprotective effects *in vitro*, associated with suppression of the PI3K/mTOR pathway in lung epithelial cells [198].

One of the most prominent EV-based therapeutics involves mesenchymal stromal cell (MSC)-derived EVs. Compared to MSCs, MSC-derived EVs offer advantages for therapeutic use, such as lower immunogenicity and tumorigenicity and higher permeability [199]. In animal models of SARS-CoV-2-induced acute lung injury, inhalation of MSC-derived EVs has shown promising results. These EVs exhibit strong anti-inflammatory and antioxidant activities, which contribute to alleviating the inflammatory syndrome [200].

The fundamental biological functions of EVs are the subject of intense research aimed at harnessing their therapeutic potential in various diseases, including COVID-19. However, comprehensive clinical studies are needed to address critical challenges, such as standardization of protocols and evaluating EVs as carriers of biomolecules. Five ongoing clinical trials are focused on characterizing EVs derived from various sources as potential therapeutic tools against COVID-19 **(Table 4)**.

7.2. Multipotent mesenchymal/stromal cell-based therapy (MSC)

MSCs take the lead in cellular therapy strategies, constituting the focus of 72% of research studies [201]. The efficacy and safety of

Table 3
Summary of ongoing NCT registered clinical trials of Natural Killer cell-based therapies for COVID-19 (updated on January 28, 2024).

NCT number	Title	Study Design	Specification of the biological product	Number of patients	Phase/ Status	Location
NCT04634370	Phase I Clinical Trial on NK Cells for COVID-19	Single arm	Natural Killer Cells infusion	24	Unknown	Brazil
NCT04900454	Allogeneic Natural Killer (NK) Cell Therapy in Subjects Hospitalized for COVID-19	Single Group Assignment	Single infusion of DVX201, an allogeneic NK cell therapy derived from $CD34^+$ hematopoietic stem cells	18	Unknown	USA
NCT04365101	Natural Killer Cell (CYNK-001) Infusions in Adults With COVID-19 (CYNKCOVID)	Randomized-controlled	Allogeneic off-the-shelf cell therapy enriched for $CD56^+/CD3^-$ NK cells expanded from human placental $CD34^+$ cells.	86	Phase I/II	USA
NCT04280224	NK Cells Treatment for COVID-19	Randomized	NK-cells	30	Phase I - Recruiting	China
NCT04324996	A Phase I/II Study of Universal Off-the-shelf NKG2D-ACE2 CAR-NK Cells for Therapy of COVID-19	Randomized	CAR-NK cells are universal off-the-shelf NK cells enriched from umbilical cord blood and engineered genetically.	90	Phase I/II - Unknown	China
NCT04578210	Safety Infusion of NatuRal KillEr celLs or MEmory T Cells as Adoptive Therapy in COVID-19 pnEumonia or Lymphopenia (RELEASE)	Randomized	Single infusion of NK from a healthy donor recovered from COVID-19	84	Completed	Spain
NCT04363346	Study of FT516 Safety and Feasibility for the Treatment of Coronavirus Disease 2019 (COVID-19) in Hospitalized Patients With Hypoxia	Non-randomized	FT516: off-the-shelf cryopreserved NK cell product derived from an iPSC that was transduced with a high affinity, ADAM17 non-cleavable CD16 (Fc receptor) that maintains CD16 on the cell surface, which remains fully functional after NK cell activation.	5	Completed	USA

NCT number: National Clinical Trial Number. Data retrieved from https://clinicaltrials.gov/.

Table 4
Summary of ongoing NCT registered clinical trials of extracellular vesicle-based therapies for COVID-19 (updated on January 28, 2024).

NCT number	Title	Study Design	Specification of the biological product	Number of patients	Phase/Status	Location
NCT04493242	Extracellular Vesicle Infusion Treatment for COVID-19 Associated ARDS (EXIT-COVID19)	Randomized placebo-controlled	Intravenous administration of bone marrow mesenchymal stem cell-derived extracellular vesicles	102	Phase II - Completed	USA
NCT05787288	A Clinical Study on Safety and Effectiveness of Mesenchymal Stem Cell Exosomes for the Treatment of COVID-19.	Randomized	Extracellular Vesicles from Mesenchymal Stem Cells from umbilical cord blood	240	Early phase I - recruiting	China
NCT04657458	Expanded Access for Use of bmMSC-Derived Extracellular Vesicles in Patients With COVID-19 Associated ARDS	Expanded Access	ExoFlo: Intravenous administration of bone marrow mesenchymal stem cell-derived extracellular vesicles	Intermediate-size population	Phase II/ Expanded Access	Not provided
NCT05808400	Safety and Efficacy of Umbilical Cord Mesenchymal Stem Cell Exosomes in Treating Chronic Cough After COVID-19	Non-randomized	MSC-derived exosomes	80	Early Phase I - Recruiting	China
NCT04969172	A Phase II Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Exosomes Overexpressing CD24 to Prevent Clinical Deterioration in Patients with Moderate or Severe COVID-19 Infection	Randomized, Double-blind, Placebo-controlled	Exosomes overexpressing CD24	155	Phase II - Unknown	Israel
NCT05216562	Efficacy and Safety of EXOSOME-MSC Therapy to Reduce Hyper-inflammation In Moderate COVID-19 Patients (EXOMSC-COV19)	Randomized, double-blind clinical trial.	Exosome-MSC Intravenous injection	60	Phase II/ Phase III – Recruiting	Indonesia
NCT04902183	Safety and Efficacy of Exosomes Overexpressing CD24 in Two Doses for Patients with Moderate or Severe COVID-19	Randomized	Exosomes overexpressing CD24	90	Phase II -Unknown	Greece
NCT04602442	Safety and Efficiency of Method of Exosome Inhalation in COVID-19 Associated Pneumonia (COVID-19EXO2)	Randomized	Aerosol inhalation of the exosomes	90	Phase II -Unknown	Russian Federation
NCT05191381	Immune Modulation by Stem Cell Derived Exosomes in Critically Ill COVID-19	Observational	Application of exosomes in a whole blood assay	40	NA	Germany
NCT04389385	Aerosol Inhalation of the Exosomes Derived from Allogenic COVID-19 T Cell in the Treatment of Early Stage Novel Coronavirus Pneumonia	Single arm	COVID-19 Specific T Cell derived exosomes (CSTC-Exo)	60	Phase I - Unknown	Turkey
NCT05387278	Safety and Effectiveness of Placental Derived Exosomes and Umbilical Cord Mesenchymal Stem Cells in Moderate to Severe Acute Respiratory Distress Syndrome (ARDS) Associated with the novel Corona Virus Infection (COVID-19)	Randomized placebo controlled	EV-Pure™ and WJ-Pure™	20	Phase 1 – Recruiting	USA
NCT04491240	Evaluation of Safety and Efficiency of Method of Exosome Inhalation in SARS-CoV-2 Associated Pneumonia. (COVID-19EXO)	Randomized placebo controlled	aerosol inhalation of the exosomes	30	Phase I/ Phase II	Russian Federation
NCT05116761	ExoFlo™ Infusion for Post-Acute COVID-19 and Chronic Post-COVID-19 Syndrome	Randomized placebo controlled	Bone Marrow Mesenchymal Stem Cell Derived Extracellular Vesicles	60	Phase I/II	Not provided

adoptive transfer of MSC for treating COVID-19 are being evaluated in many clinical trials. As the published results are promising but inconclusive, further studies are warranted to gather convincing evidence and draw definitive conclusions.

A phase II placebo-controlled trial (NCT04288102) evaluated the long-term safety and efficacy of intravenous administration of 4.0×10^7 UC-MSCs in three total doses transfused to patients with severe COVID-19 and pulmonary lesions. After one year of treatment, the lung lesions had shrunk. Furthermore, two years after the end of treatment, MSC therapy showed sustained efficacy and long-term safety as it was non-tumorigenic in patients with COVID-19 [202].

Another clinical trial (NCT04355728) evidenced the beneficial effect of MSCs when administered to patients with COVID-19 ARDS.

Briefly, hospitalized patients with COVID-19 ARDS received two intravenous infusions at a dose of $100 \pm 20 \times 10^6$ UC-MSCs. Compared to the control group, MSC-treated patients showed a lower concentration of GM-CSF, IFN- γ, IL-5, IL-6, IL-7, TNF- α, TNF- β, and platelet-derived growth factor composed of two B-subunits (PDGF-BB) [203].

Zhu et al. conducted a randomized, single-blind, placebo-controlled phase II trial (NCT04339660) to evaluate the effects of UC-MSCs at a single dose of 1×10^6 UC-MSC/kg body-weight administered to hospitalized patients with COVID-19. This therapy was associated with a shorter hospital stay, fewer adverse events, and immunomodulatory effects. In particular, MSC infusion significantly decreased the levels of C-reactive protein and proinflammatory cytokines such as IL-18, IL-27, IL-17E, IL-25, IL-17F, CXCL-1, and IL-5. In addition, the transfer of MSCs was associated with higher levels of anti-SARS-CoV-2 antibodies and increased expression of CD19 and CD81 on B-cells [204].

The MSC-based therapy, a potential tool for treating adults, is also being investigated as a therapeutic option for children with multisystem inflammatory syndrome (MIS-C), an immune dysregulation following severe COVID-19. The NCT04456439 clinical trial described the encouraging results observed in two hospitalized patients with MIS-C who received two intravenous infusions with space of 48 h of adult bone marrow-derived MSCs (BM-MSC) at a dose of 2×10^6/kg body weight per infusion. Patients showed improved endothelial and myocardial function; in particular, the left ventricular ejection fraction normalized, and the severity of pan-valvular regurgitation reduced as evidenced by serial echocardiographic imaging. Moreover, the levels of systemic and cardiac inflammatory markers, such as the D-dimer, diminished significantly. The MSC treatment also proved safe, as no adverse reactions were observed after cell infusion. Considering the lack of therapeutic options for patients with MIS-C and the results observed in this study, the adoptive transfer of MSC could be considered a plausible therapy for children affected [205].

On the other hand, some clinical trials have shown no favorable results when administering MSC-based therapy. The placebo-controlled phase IIb study (NCT04333368) reported that patients with COVID-19 ARDS who received three intravenous infusions of UC-MSCs at a dose of 1.0×10^6/kg body-weight per infusion on D1, D3 ± 1, and D5 ± 1 showed similar results to those in the placebo group. However, it should be noted that the infusions were safe, as none of the patients experienced any serious adverse events throughout the study [206].

The MSC-based therapy is being broadly studied as a potential approach to managing different clinical conditions, with promising results in the case of COVID-19. However, further characterization of the results observed in ongoing clinical trials is imperative before this therapeutic strategy becomes available to the population. Although the data published on the https://clinicaltrials.gov/site changes daily, to date, it lists around 15 clinical studies on MSCs derived from various sources.

8. Discussion

Considering the global challenges caused by the emergence of the SARS-CoV-2 virus, exploring effective therapeutic alternatives for SARS-CoV-2 is crucial. This review aims to critically analyze the current therapeutic landscape and advancements in the fight against the virus. By delving into diverse treatment modalities, ranging from traditional immunotherapies to cutting-edge advanced therapies, we aim to provide an overview of therapeutic alternatives for SARS-CoV-2.

Omicron subvariants are exhibiting a tropism shift, primarily due to the modification of the conventional cellular entry route, which typically depends on TMPRSS2 [1]. This transition, although linked to a reduction in pathogenicity that presently manifests as milder infection symptoms, should be interpreted with caution. This is because the inherent molecular properties underlying this shift have started to be characterized and the ongoing adaptive nature of SARS-CoV-2 may continue to influence its pathogenicity. Therefore, it is essential to conduct careful and continuous monitoring is needed to assess any further developments. Tracking the mutations acquired by each subvariant and assessing its biological variation are imperative tasks. Moreover, it is essential to incorporate into the variables influencing emergence, the phenomenon of cross-species recombination of the Coronavirus that involves at least 34 species [207]. This process highlights the virus's capacity to identify and infect intermediate species, facilitating a novel route for cell entry and posing the potential risk of generating new recombinant strains capable of infecting human hosts with pandemic potential.

At the beginning of the COVID-19 pandemic, new SARS-CoV-2 variants started to be selected based on their increased affinity for the ACE2 receptor. Consequently, the prevalence of these viral variants rose in the population due to their higher infectibility. However, the increasing population immunity against SARS-CoV-2 has turned the immune response into a new selection pressure on new viral variants. The selective pressure exerted by the immune system has become relevant, as evidenced by the lack of correlation between the new RBD variants and their binding affinity to the ACE2 receptor [54], as well as the impaired response induced by vaccines against the new SARS-CoV-2 Omicron subvariants [4,55,208].

Viral evolution studies have shown that strong selection pressure should promote the protection of viral regions crucial to the viral life-cycle from host immune responses [209]. In the case of SARS-CoV-2, this protection has been achieved by the low immunogenicity of the ACE2-interacting surface (ACE2IS) located in the S-RBD domain [209]. The ACE2IS is located in the most distal part of the S-protein, *i.e.*, the most accessible to antibodies; therefore, ACE2IS is expected to be highly immunogenic. However, it is only exposed in the RBD in the "up" conformation to mediate virus entry into target cells [210]. Indeed, although most COVID-19 convalescent plasmas contain anti-S and anti-RBD antibodies, they exhibit low neutralizing activity [91,209,211].

A study by Hattory et al. [209] suggests that protein S has highly immunogenic regions outside the RBD that contribute to the enrichment of anti-non-RBD antibodies and the depletion of anti-RBD antibodies. The high immunogenicity of these non-RBD regions may be an evolutionary strategy of the SARS-CoV-2 to distract the immune system which could hinder the development of ACE2IS-targeted universal vaccines against emergent SARS-CoV-2 variants and other coronavirus. Therefore, designing new biological strategies that target immunogenic segments of SARS-CoV-2 beyond the S protein is imperative.

One crucial challenge facing next-generation vaccine platforms against SARS-CoV-2 is enhancing safety and reliability. Existing literature highlights potential, albeit rare, adverse events associated with current vaccines. For instance, cardiovascular events have been reported, particularly in connection with mRNA vaccines [212–215]. Additionally, there have been documented cases of neurological complications, such as Guillain–Barré syndrome (GBS) and Bell's palsy, linked to COVID-19 vaccination [216–218].

Addressing these concerns is necessary, as ensuring the safety and reliability of vaccines remains a top priority. While it is required to acknowledge that, in general, COVID-19 vaccines are considered safe, the occurrence of occasional adverse events, albeit infrequent, can impact public perception. It is crucial to underscore that the overall benefits of immunization far outweigh the rare adverse events. However, the existence of these events may contribute to vaccine hesitancy, potentially hindering broader vaccination efforts. Therefore, next-gen vaccine platforms must aim for heightened efficacy against SARS-CoV-2 and prioritize advancements in safety profiles that could involve refining formulations, dosages, and delivery systems to minimize the occurrence of adverse events and bolster public confidence in the vaccination process.

Importantly, immunocompromised patients are not only disproportionally affected by COVID-19 but may also be essential reservoirs and fonts of new SARS-CoV-2 variants. The impaired immune response of immunocompromised individuals favors longer viral replication, facilitating the emergence of new viral escape variants [219]. Given their increased vulnerability, immunocompromised individuals are often excluded from clinical trials due to protocol safety and efficacy guidelines. Therefore, innovations in models that can evaluate the efficacy of biotechnological tools, such as vaccines in immunocompromised individuals, are needed. In line with the development of new treatments, immunotherapeutic approaches and advanced therapies are next-generation promissory platforms for managing COVID-19 in immunocompromised populations and patients with post-acute sequelae of COVID-19 (PASC). These patients challenge healthcare systems due to the strict inclusion criteria of clinical trials [220].

Recent reports are shedding light on the role of host cell immune components in responding to Omicron infection, revealing critical findings. Notably, platelets have been observed to orchestrate the recruitment of immune cells to form aggregates, which may inhibit T-cell activation, potentially explaining the diminished immune response in hosts. Furthermore, it has been demonstrated that $CD8^{+}$ effector T cells (Teff) in re-positive patients display reduced cytotoxic signatures and heightened exhaustion signals, while NK cells exhibit increased cytotoxicity and reduced levels of apoptosis [221]. Consequently, once established, cell-based therapies have the potential to enhance cellular immunity in SARS-CoV-2 infections, providing an additional alternative to improve the outcomes for the immunocompromised population.

Although cell-based therapy traces its origins back to the experiments of the 1950s, exemplified by the successful treatment of marrow aplasia in rodent models using synergic marrow grafts [222], it has evolved into the contemporary era of market-integrated cell-based therapies. Despite the wealth of accumulated knowledge, establishing advanced treatments as a powerful tool against SARS-CoV-2 and improving its associated inflammation, immunomodulation, and tissue damage is still in its nascent stages; this is highlighted by reports from clinical studies registered at https://clinicaltrials.gov/. However, a pivotal challenge that requires attention is the harmonization of initial protocols to standardize technical concepts, including the number of doses, the number of administered events per dose, and the time necessary for evaluating efficiency parameters. The overarching objective is to assess the impact of this potential platform more objectively.

9. Limitation of the study

The review manuscript is grounded in the literature available up to January 30, 2024, and there may have been new studies or developments in the field since then. Additionally, the variability in study designs, patient populations, and treatment protocols across the reviewed studies may limit the ability to draw uniform conclusions.

10. SWOT analysis

10.1. Strengths

1. Current Relevance: Given the dynamic nature of SARS-CoV-2, the topic addresses a pressing issue, making the paper highly relevant to the current scientific and healthcare landscape.
2. Timeliness: Given the ongoing relevance of COVID-19, the manuscript addresses a pressing issue, contributing valuable insights and information that aligns with the current virus status.
3. **Informative and Educational:** The manuscript has an educational nature, offering insights into cutting-edge treatments and contributing to the scientific community's understanding of COVID-19 therapeutics.
4. **Research Rigor:** The manuscript is grounded in rigorous scientific research, encompassing diverse treatment platforms, presenting a well-supported analysis of the literature.

10.2. Weaknesses

1. **Evolving Landscape:** The evolving nature of SARS-CoV-2 virus, may result in the manuscript becoming outdated relatively quickly, necessitating periodic updates to maintain relevance.
2. **Data Gaps:** If there are limitations in the available data for specific therapies, it could hinder the manuscript's ability to provide conclusive insights into their efficacy.

10.3. Opportunities

1. **Future Research Directions:** The manuscript could guide future research endeavors by highlighting gaps in current knowledge or suggesting novel perspectives for exploration.
2. **Collaboration:** The manuscript might open avenues for collaboration between researchers.

10.4. Threats

1. **Competing Research:** Similar research topics may emerge, potentially overshadowing the paper's contributions.
2. **Public Perception:** Anticipated public expectations for the immediate implementation of advanced therapies may surface, potentially resulting in disappointment once these are not promptly in short-term.

11. Conclusion

The COVID-19 pandemic emerged as a significant health challenge in the 21st century. Extensive research and global cooperation have provided a profound understanding of the fundamental biological and molecular characteristics of SARS-CoV-2. This knowledge has proven invaluable in guiding the development of biotechnological approaches and preventive measures, particularly vaccines. These strategies have played a central role in quelling the pandemic and safeguarding human health.

Even though the state of emergency brought about by COVID-19 officially ended in May 2023 [223], the continuous emergence of new variants driven by mutation and genetic recombination mechanisms [224], has led to a wave of reinfection cases. These cases challenge the efficacy of first-generation vaccines and monoclonal antibodies, emphasizing the need for updates. Additionally, vaccine hesitancy and pandemic fatigue persist among the general population, indicating a lack of clarity regarding the dynamic course of the virus over time. Thus, it demonstrates that the challenges posed by the virus extend beyond the biological aspects, encompassing significant social difficulties that continue to impact communities in the post-pandemic era [225].

It is crucial to prioritize the development of a next-generation of vaccines equipped to efficiently thwart the potential risks posed by the rapid emergence of SARS-CoV-2 variants. Researchers actively investigate cutting-edge technical approaches to create next-

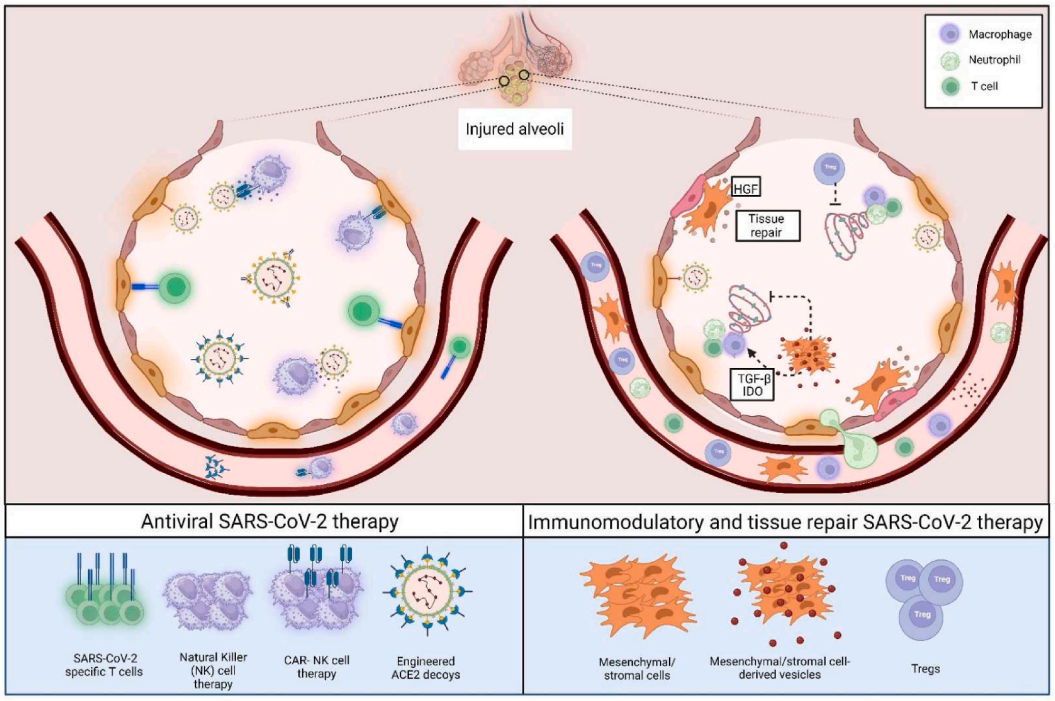


Fig. 3. Advanced therapies against COVID-19. Therapeutics for COVID-19 include antiviral and immunomodulatory-regenerative strategies. Antiviral approaches focus on the virus or virus-infected cells and include COVID-19 convalescent plasma containing anti-SARS-CoV-2 IgG and IgM antibodies or monoclonal antibodies, SARS-CoV-2 specific T-cells, natural killer (NK) cells, and CAR-NK cells. Immunomodulatory-regenerative approaches focus on modulating the immune response and promoting tissue repair. They include COVID-19 convalescent plasma containing anti-inflammatory cytokines; mesenchymal/stromal cells (MSCs) that secrete transforming growth factor beta (TGF-β) and indoleamine 2,3-Dioxygenase (IDO) that alleviate the cytokine storm syndrome, and hepatocyte growth factor (HGF) that facilitate tissue repair and regeneration of injured tissues; MSC-derived extracellular vesicles (EVs), and regulatory T-cells (Tregs).

generation vaccines, placing their bets on pan-*coronavirus* proposals. The success of these endeavors hinges on fostering international collaborations and initiatives, as they are pivotal for enabling a global-scale implementation of this initiative. This review summarizes the current technical approaches and international initiatives poised to drive this process forward in the coming years, ultimately averting a significant new threat. Vaccination is the cornerstone of preventive public health strategy because it can confer widespread immunity within a population, thereby contributing to herd immunity. The proven track record of vaccines has facilitated the development of logistically strategic campaigns to implement on a large scale.

However, the potential role of advanced therapies against SARS-CoV-2 has introduced it as a new platform to encourage the adaptation of emerging medical technologies for infectious diseases. In SARS-CoV-2, advanced therapeutic interventions aim to provide targeted treatment for infected individuals, particularly in scenarios where vaccines may have limitations. Thus, it entails modifying or enhancing the patient's immune system, presenting a versatile platform with the promise to combat the virus and regulate inflammatory responses, thereby facilitating the recovery of damaged tissues. (Fig. 3). Primary evidence suggests a therapeutic potential for MSCs in alleviating the clinical manifestations of Cytokine Storm (CS) in ARDS. CS is characterized by an overactive and dysregulated immune response, resulting in the rapid release of a large amount of pro-inflammatory cytokines, which can lead to widespread inflammation, tissue damage, multiple organ failure, and, consequently, death [226]. Studies conducted with pediatric population [227] and adult populations [170] have confirmed that treating with MSCs is associated with improved health and recovery. In addition to MSCs, using off-the-shelf SARS-CoV-2-specific T cells has shown potential for enhancing recovery rates. Pilot studies with patients experiencing severe COVID-19 suggest with caution a significant 53% reduction in the risk of mortality [168].

Although many clinical trials in cellular platforms for COVID-19 had demonstrated safety during the transition from Phase I to Phase II, the pivotal Phase III remains critical. The structural design with a larger sample size, Phase III, seeks to provide compelling evidence regarding the treatment's effectiveness. This phase plays a crucial role in obtaining approval from regulatory authorities, facilitating the progression to Phase IV. The latter phase is a post-marketing stage, ensuring continuous surveillance and treatment monitoring in real-world scenarios [228].

Considering the transition and regulatory processes observed in other scenarios, such as gene therapy for cancer and genetic diseases, a successful Phase 3 trial typically spans approximately 1–4 years. Consequently, cell therapies for COVID-19 are currently in their early phases, and it is conceivable that they could become available on the market within less than a decade. In the upcoming crucial phases of these biotechnological platforms, assessing safety and efficacy will address special populations, such as newborns, who are unsuitable for vaccination. This evaluation will also extend to include pregnant and lactating women who could develop a severe COVID-19 disease.

Studying the adaptation trajectory of SARS-CoV-2, it is crucial to anticipate possible future events rooted in the molecular mechanisms that underpin the evolutionary success of SARS-CoV-2 is essential. Such research is vital for creating broader and innovative interventions to address humanity's new challenges, and advanced therapies are poised to occupy a central role in these efforts in the near future.

CRediT authorship contribution statement

Jenny Andrea Arevalo-Romero: Writing – review & editing, Writing – original draft, Conceptualization. **Sandra M. Chingaté-López:** Resources. **Bernardo Armando Camacho:** Visualization, Resources, Conceptualization. **Carlos Javier Alméciga-Díaz:** Supervision, Conceptualization. **Cesar A. Ramirez-Segura:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

To the Ministry of Science, Technology, and Innovation of Colombia (Call 891 for Strengthening Vocations and Training in Science, Technology and Research for Economic Reactivation in the Post-Pandemic 2020 Framework). To Martha Mesa for editing and proofreading the manuscript. Some figures were prepared using BioRender.com. To the communication department of IDCBIS for the collaboration in some figures.

The *Agencia Distrital de Educación Superior, Ciencia y Tecnología* (ATENEA, Spanish acronym), Bogotá D.C., Colombia, financially supported this research (Contract 057–2022, ID 9796), as well as the work of **JAAR** and **SMCL**. **SMCL** also received a postdoctoral fellowship from the Ministry of Science, Technology, and Innovation of Colombia (grant 891-2020). The IDCBIS sponsored **BAC**. The *Pontificia Universidad Javeriana* financially supported **CJAD**. **CARS** was financed with resources transferred from the *Fondo Financiero Distrital de Salud* (FFDS, Spanish acronym) to IDCBIS (Resolution 209, 2023, issued by the District Health Secretariat).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e26423.

References

[1] M. Hoffmann, H. Kleine-Weber, S. Schroeder, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2) (2020) 271–280.e8, https://doi.org/10.1016/j.cell.2020.02.052.

[2] D.X. Liu, J.Q. Liang, T.S. Fung, Human coronavirus-229E, -OC43, -NL63, and -HKU1 (Coronaviridae), in: Encyclopedia of Virology, Elsevier, 2021, pp. 428–440, https://doi.org/10.1016/B978-0-12-809633-8.21501-X.

[3] X. Cheng, Q. Cao, S.S. Liao, An overview of literature on COVID-19, MERS and SARS: using text mining and latent Dirichlet allocation, J. Inf. Sci. 48 (3) (2022) 304–320, https://doi.org/10.1177/0165551520954674.

[4] J.J. Lau, S.M.S. Cheng, K. Leung, et al., Real-world COVID-19 vaccine effectiveness against the Omicron BA.2 variant in a SARS-CoV-2 infection-naive population, Nat. Med. 29 (2) (2023) 348–357, https://doi.org/10.1038/s41591-023-02219-5.

[5] R. Sarker, A.S.M. Roknuzzaman, Shahriar M. Nazmunnahar, MdJ. Hossain, MdR. Islam, The WHO has declared the end of pandemic phase of COVID-19: way to come back in the normal life, Health Sci Rep 6 (9) (2023) e1544, https://doi.org/10.1002/hsr2.1544.

[6] C.M. Duarte, D.I. Ketcheson, V.M. Eguíluz, et al., Rapid evolution of SARS-CoV-2 challenges human defenses, Sci. Rep. 12 (1) (2022) 6457, https://doi.org/10.1038/s41598-022-10097-z.

[7] H. Allen, E. Tessier, C. Turner, et al., Comparative transmission of SARS-CoV-2 Omicron (B.1.1.529) and Delta (B.1.617.2) variants and the impact of vaccination: national cohort study, England, Epidemiol. Infect. 151 (2023) e58, https://doi.org/10.1017/S0950268823000420.

[8] Y. Hu, J. Zou, C. Kurhade, et al., Less neutralization evasion of SARS-CoV-2 BA.2.86 than XBB sublineages and CH.1.1, Emerg. Microb. Infect. 12 (2) (2023) 2271089, https://doi.org/10.1080/22221751.2023.2271089.

[9] R.K. Mohapatra, A. Mahal, S. Mishra, V. Kandi, W.J. Obaidullah, SARS-CoV-2 variants BA.2.86 and EG.5.1 alongside scrub typhus and nipah in India during the ongoing cricket world cup 2023: threat perceptions and countermeasures, Cureus 16 (2023), https://doi.org/10.7759/cureus.48895. Published online November.

[10] C. Stein, H. Nassereldine, R.J.D. Sorensen, et al., Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis, Lancet 401 (10379) (2023) 833–842, https://doi.org/10.1016/S0140-6736(22)02465-5.

[11] D.A. Swan, C. Bracis, H. Janes, et al., COVID-19 vaccines that reduce symptoms but do not block infection need higher coverage and faster rollout to achieve population impact, Sci. Rep. 11 (1) (2021) 15531, https://doi.org/10.1038/s41598-021-94719-y.

[12] S. Cankat, M.U. Demael, L. Swadling, In search of a pan-coronavirus vaccine: next-generation vaccine design and immune mechanisms, Cell. Mol. Immunol. (2023), https://doi.org/10.1038/s41423-023-01116-8. Published online December 26.

[13] Z. Xing, M. Jeyanathan, A next-generation inhalable dry powder COVID vaccine, Nature 624 (7992) (2023) 532–534, https://doi.org/10.1038/d41586-023-03557-7.

[14] S.R. Bonam, H. Hu, Next-generation vaccines against COVID-19 variants: beyond the spike protein, Zoon 3 (1) (2023), https://doi.org/10.15212/ZOONOSES-2023-0003.

[15] X. Becerra, A. Jha, Project NextGen — defeating SARS-CoV-2 and preparing for the next pandemic, N. Engl. J. Med. 389 (9) (2023) 773–775, https://doi.org/10.1056/NEJMp2307867.

[16] A. Alakija, Leveraging lessons from the COVID-19 pandemic to strengthen low-income and middle-income country preparedness for future global health threats, Lancet Infect. Dis. 23 (8) (2023) e310–e317, https://doi.org/10.1016/S1473-3099(23)00279-7.

[17] F. El Chaer, J.J. Auletta, R.F. Chemaly, How I treat and prevent COVID-19 in patients with hematologic malignancies and recipients of cellular therapies, Blood 140 (7) (2022) 673–684, https://doi.org/10.1182/blood.2022016089.

[18] L. Gopcsa, M. Réti, H. Andrikovics, et al., Effective virus-specific T-cell therapy for high-risk SARS-CoV-2 infections in hematopoietic stem cell transplant recipients: initial case studies and literature review, GeroScience. Published online July 6 (2023), https://doi.org/10.1007/s11357-023-00858-7.

[19] A. Antinori, M. Bausch-Jurken, The burden of COVID-19 in the immunocompromised patient: implications for vaccination and needs for the future, J. Infect. Dis. 228 (Supplement_1) (2023) S4–S12, https://doi.org/10.1093/infdis/jiad181.

[20] S. Galmiche, L.B. Luong Nguyen, E. Tartour, et al., Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review, Clin. Microbiol. Infect. 28 (2) (2022) 163–177, https://doi.org/10.1016/j.cmi.2021.09.036.

[21] S. Shoham, C. Batista, Y. Ben Amor, et al., Vaccines and therapeutics for immunocompromised patients with COVID-19, eClinicalMedicine 59 (2023) 101965, https://doi.org/10.1016/j.eclinm.2023.101965.

[22] R.A. Evans, S. Dube, Y. Lu, et al., Impact of COVID-19 on immunocompromised populations during the Omicron era: insights from the observational population-based INFORM study, Lancet Reg Health - Eur. 35 (2023) 100747, https://doi.org/10.1016/j.lanepe.2023.100747.

[23] S. Nobari, M. Rezvan, F. Dashtestani, M. Gangi, H. Keshmiri Neghab, Cellular therapy: the hope for covid-19, Avicenna J. Med. Biotechnol. (AJMB) (2022), https://doi.org/10.18502/ajmb.v14i2.8883. Published online March 12.

[24] D. Mipatrini, C. Montaldo, B. Bartolini, et al., 'Disease X'—time to act now and prepare for the next pandemic threat, Eur. J. Publ. Health 32 (6) (2022) 841–842, https://doi.org/10.1093/eurpub/ckac151.

[25] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.

[26] H.L. Wells, C.M. Bonavita, I. Navarrete-Macias, B. Vilchez, A.L. Rasmussen, S.J. Anthony, The coronavirus recombination pathway, Cell Host Microbe 31 (6) (2023) 874–889, https://doi.org/10.1016/j.chom.2023.05.003.

[27] C. Wu, rong, Yin W. chao, Y. Jiang, H.E. Xu, Structure genomics of SARS-CoV-2 and its Omicron variant: drug design templates for COVID-19, Acta Pharmacol. Sin. 43 (12) (2022) 3021–3033, https://doi.org/10.1038/s41401-021-00851-w.

[28] T. Fiolet, Y. Kherabi, C.J. MacDonald, J. Ghosn, N. Peiffer-Smadja, Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review, Clin. Microbiol. Infect. 28 (2) (2022) 202–221, https://doi.org/10.1016/j.cmi.2021.10.005.

[29] Z. Zhou, Y. Zhu, M. Chu, Role of COVID-19 vaccines in SARS-CoV-2 variants, Front. Immunol. 13 (2022) 898192, https://doi.org/10.3389/fimmu.2022.898192.

[30] Y.C. Hwang, R.M. Lu, S.C. Su, et al., Monoclonal antibodies for COVID-19 therapy and SARS-CoV-2 detection, J. Biomed. Sci. 29 (1) (2022) 1, https://doi.org/10.1186/s12929-021-00784-w.

[31] D. Focosi, S. McConnell, A. Casadevall, E. Cappello, G. Valdiserra, M. Tuccori, Monoclonal antibody therapies against SARS-CoV-2, Lancet Infect. Dis. 22 (11) (2022) e311–e326, https://doi.org/10.1016/S1473-3099(22)00311-5.

[32] P.V. Markov, M. Ghafari, M. Beer, et al., The evolution of SARS-CoV-2, Nat. Rev. Microbiol. 21 (6) (2023) 361–379, https://doi.org/10.1038/s41579-023-00878-2.

[33] R.A.A. Pondé, Physicochemical effect of the N501Y, E484K/Q, K417N/T, L452R and T478K mutations on the SARS-CoV-2 spike protein RBD and its influence on agent fitness and on attributes developed by emerging variants of concern, Virology 572 (2022) 44–54, https://doi.org/10.1016/j.virol.2022.05.003.

[34] C.H.S. Costa, C.A.B. Freitas, C.N. Alves, J. Lameira, Assessment of mutations on RBD in the spike protein of SARS-CoV-2 alpha, delta and omicron variants, Review (2022), https://doi.org/10.21203/rs.3.rs-1401835/v1.

[35] J.L. Jacobs, G. Haidar, J.W. Mellors, COVID-19: challenges of viral variants, Annu. Rev. Med. 74 (1) (2023) 31–53, https://doi.org/10.1146/annurev-med-042921-020956.

[36] Nextstrain/ncov/gisaid/global/all-time. Accessed October 12, 2023. https://nextstrain.org/ncov/gisaid/global/all-time.

[37] J. Quarleri, M.V. Delpino, V. Galvan, Anticipating the future of the COVID-19 pandemic: insights into the emergence of SARS-CoV-2 variant JN.1 and its projected impact on older adults, GeroScience. Published online January 10 (2024) s11357, https://doi.org/10.1007/s11357-024-01066-7, 024-01066-01067.

[38] Qu P, Xu K, Faraone JN, et al. Immune Evasion, Infectivity, and Fusogenicity of SARS-CoV-2 BA.2.86 and FLip Variants. Cell. Published online January 2024: S0092867423014009. doi:10.1016/j.cell.2023.12.026.

[39] Zhang L, Kempf A, Nehlmeier I, et al. SARS-CoV-2 BA.2.86 enters lung cells and evades neutralizing antibodies with high efficiency. Cell. Published online January 2024:S0092867423013995. doi:10.1016/j.cell.2023.12.025.

[40] Yang S, Yu Y, Xu Y, et al. Fast evolution of SARS-CoV-2 BA.2.86 to JN.1 under heavy immune pressure. Lancet Infect. Dis.. Published online December 2023: S1473309923007442. doi:10.1016/S1473-3099(23)00744-2.

[41] Y. Kaku, K. Okumura, M. Padilla-Blanco, et al., Virological characteristics of the SARS-CoV-2 JN.1 variant, Lancet Infect Dis. Published online January (2024), https://doi.org/10.1016/S1473-3099(23)00813-7. S1473309923008137.

[42] A.M. Carabelli, T.P. Peacock, L.G. Thorne, et al., SARS-CoV-2 variant biology: immune escape, transmission and fitness, Nat Rev Microbiol. Published online January 18 (2023), https://doi.org/10.1038/s41579-022-00841-7.

[43] L.B. Shrestha, C. Foster, W. Rawlinson, N. Tedla, R.A. Bull, Evolution of the SARS-CoV-2 omicron variants BA.1 to BA.5: implications for immune escape and transmission, Rev. Med. Virol. 32 (5) (2022) e2381, https://doi.org/10.1002/rmv.2381.

[44] M.S. Alam, Insight into SARS-CoV-2 Omicron variant immune escape possibility and variant independent potential therapeutic opportunities, Heliyon 9 (2) (2023) e13285, https://doi.org/10.1016/j.heliyon.2023.e13285.

[45] K. Gangavarapu, A.A. Latif, J.L. Mullen, et al., Outbreak.info genomic reports: scalable and dynamic surveillance of SARS-CoV-2 variants and mutations, Nat. Methods 20 (4) (2023) 512–522, https://doi.org/10.1038/s41592-023-01769-3.

[46] S. Khare, C. Gurry, L. Freitas, et al., GISAID's role in pandemic response, China CDC Wkly 3 (49) (2021) 1049–1051, https://doi.org/10.46234/ccdcw2021.255.

[47] A. Telenti, E.B. Hodcroft, D.L. Robertson, The evolution and biology of SARS-CoV-2 variants, Cold Spring Harb Perspect Med 12 (5) (2022) a041390, https://doi.org/10.1101/cshperspect.a041390.

[48] D. Tian, Y. Sun, H. Xu, Q. Ye, The emergence and epidemic characteristics of the highly mutated SARS-CoV-2 Omicron variant, J. Med. Virol. 94 (6) (2022) 2376–2383, https://doi.org/10.1002/jmv.27643.

[49] J. Cai, X. Deng, J. Yang, et al., Modeling transmission of SARS-CoV-2 omicron in China, Nat. Med. 28 (7) (2022) 1468–1475, https://doi.org/10.1038/s41591-022-01855-7.

[50] S.S. Manathunga, I.A. Abeyagunawardena, S.D. Dharmaratne, A comparison of transmissibility of SARS-CoV-2 variants of concern, Virol. J. 20 (1) (2023) 59, https://doi.org/10.1186/s12985-023-02018-x.

[51] T. Tada, H. Zhou, B.M. Dcosta, et al., Increased resistance of SARS-CoV-2 Omicron variant to neutralization by vaccine-elicited and therapeutic antibodies, EBioMedicine 78 (2022) 103944, https://doi.org/10.1016/j.ebiom.2022.103944.

[52] D. Planas, T. Bruel, I. Staropoli, et al., Resistance of Omicron Subvariants BA.2.75.2, BA.4.6 and BQ.1.1 to Neutralizing Antibodies, Microbiology, 2022, https://doi.org/10.1101/2022.11.17.516888.

[53] P. Qu, J.P. Evans, J. Faraone, et al., Distinct neutralizing antibody escape of SARS-CoV-2 omicron subvariants BQ.1, BQ.1.1, BA.4.6, *BF.7 and BA.2.75.2*, Microbiology (2022), https://doi.org/10.1101/2022.10.19.512891.

[54] Q. Wang, S. Iketani, Z. Li, et al., Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants, Cell 186 (2) (2023) 279–286.e8, https://doi.org/10.1016/j.cell.2022.12.018.

[55] R. Uraki, M. Ito, Y. Furusawa, et al., Humoral immune evasion of the omicron subvariants BQ.1.1 and XBB, Lancet Infect. Dis. 23 (1) (2023) 30–32, https://doi.org/10.1016/S1473-3099(22)00816-7.

[56] P. Qu, J.P. Evans, J.N. Faraone, et al., Enhanced neutralization resistance of SARS-CoV-2 Omicron subvariants BQ.1, BQ.1.1, BA.4.6, BF.7, and BA.2.75.2, Cell Host Microbe 31 (1) (2023) 9–17.e3, https://doi.org/10.1016/j.chom.2022.11.012.

[57] B. Meng, A. Abdullahi, I.A.T.M. Ferreira, et al., Altered TMPRSS2 usage by SARS-CoV-2 Omicron impacts infectivity and fusogenicity, Nature 603 (7902) (2022) 706–714, https://doi.org/10.1038/s41586-022-04474-x.

[58] R. Strobelt, K. Broennimann, J. Adler, Y. Shaul, SARS-CoV-2 omicron specific mutations affecting infectivity, fusogenicity, and partial TMPRSS2-independency, Viruses 15 (5) (2023) 1129, https://doi.org/10.3390/v15051129.

[59] M. Wahid, A. Jawed, R.K. Mandal, et al., Role of available COVID-19 vaccines in reducing deaths and perspective for next generation vaccines and therapies to counter emerging viral variants: an update, Minerva Med. 114 (5) (2023), https://doi.org/10.23736/S0026-4806.23.08509-9.

[60] R.K. Mohapatra, S. Mishra, V. Kandi, et al., Analyzing the emerging patterns of SARS-CoV-2 Omicron subvariants for the development of next-gen vaccine: an observational study, Health Sci Rep 6 (10) (2023) e1596, https://doi.org/10.1002/hsr2.1596.

[61] R.K. Mohapatra, A. Mahal, L.S. Kutikuppala, et al., Renewed global threat by the novel SARS-CoV-2 variants 'XBB, BF.7, BQ.1, BA.2.75, BA.4.6': a discussion, Front Virol 2 (2022) 1077155, https://doi.org/10.3389/fviro.2022.1077155.

[62] A.P.S. Rathore, St John AL, Promises and challenges of mucosal COVID-19 vaccines, Vaccine 41 (27) (2023) 4042–4049, https://doi.org/10.1016/j.vaccine.2023.04.013.

[63] D. Pilapitiya, A.K. Wheatley, H.X. Tan, Mucosal vaccines for SARS-CoV-2: triumph of hope over experience, EBioMedicine 92 (2023) 104585, https://doi.org/10.1016/j.ebiom.2023.104585.

[64] C.K. Yuen, W.M. Wong, L.F. Mak, et al., An interferon-integrated mucosal vaccine provides pan-sarbecovirus protection in small animal models, Nat. Commun. 14 (1) (2023) 6762, https://doi.org/10.1038/s41467-023-42349-5.

[65] D. Lozano, V. Larraga, M. Vallet-Regí, M. Manzano, An overview of the use of nanoparticles in vaccine development, Nanomaterials 13 (12) (2023) 1828, https://doi.org/10.3390/nano13121828.

[66] A.A. Reutovich, A.K. Srivastava, P. Arosio, F. Bou-Abdallah, Ferritin nanocages as efficient nanocarriers and promising platforms for COVID-19 and other vaccines development, Biochim Biophys Acta BBA - Gen Subj 1867 (3) (2023) 130288, https://doi.org/10.1016/j.bbagen.2022.130288.

[67] J. Yu, P.V. Thomas, M. Sciacca, et al., Ad26.COV2.S and SARS-CoV-2 spike protein ferritin nanoparticle vaccine protect against SARS-CoV-2 Omicron BA.5 challenge in macaques, Cell Rep Med 4 (4) (2023) 101018, https://doi.org/10.1016/j.xcrm.2023.101018.

[68] S. Shrivastava, J.M. Carmen, Z. Lu, et al., SARS-CoV-2 spike-ferritin-nanoparticle adjuvanted with ALFQ induces long-lived plasma cells and cross-neutralizing antibodies, Npj Vaccines 8 (1) (2023) 43, https://doi.org/10.1038/s41541-023-00638-6.

[69] V.P. Chavda, R. Bezbaruah, S. Dolia, et al., Convalescent plasma (hyperimmune immunoglobulin) for COVID-19 management: an update, Process Biochem. 127 (2023) 66–81, https://doi.org/10.1016/j.procbio.2023.01.018.

[70] J.D. Roback, J. Guarner, Convalescent plasma to treat COVID-19: possibilities and challenges, JAMA 323 (16) (2020) 1561, https://doi.org/10.1001/jama.2020.4940.

[71] Y. Cheng, R. Wong, Y.O.Y. Soo, et al., Use of convalescent plasma therapy in SARS patients in Hong Kong, Eur. J. Clin. Microbiol. Infect. Dis. 24 (1) (2005) 44–46, https://doi.org/10.1007/s10096-004-1271-9.

[72] B.E. Research C for, Investigational, COVID-19 convalescent plasma. U.S. Food and drug administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-covid-19-convalescent-plasma, 2023. (Accessed 13 June 2023).

[73] M. Rojas, Y. Rodríguez, J.C. Hernández, et al., Safety and efficacy of convalescent plasma for severe COVID-19: a randomized, single blinded, parallel, controlled clinical study, BMC Infect. Dis. 22 (1) (2022) 575, https://doi.org/10.1186/s12879-022-07560-7.

[74] C. Axfors, P. Janiaud, A.M. Schmitt, et al., Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials, BMC Infect. Dis. 21 (1) (2021) 1170, https://doi.org/10.1186/s12879-021-06829-7.

[75] M. Müller-Olling, U. Vahlensieck, A. Hilger, Heterogeneity in COVID-19 convalescent plasma clinical trials, Clin. Pharmacol. Ther. 111 (5) (2022) 995–1000, https://doi.org/10.1002/cpt.2281.

[76] T.A.C. Snow, N. Saleem, G. Ambler, et al., Convalescent plasma for COVID-19: a meta-analysis, trial sequential analysis, and meta-regression, Br. J. Anaesth. 127 (6) (2021) 834–844, https://doi.org/10.1016/j.bja.2021.07.033.

[77] D.J. Sullivan, K.A. Gebo, S. Shoham, et al., Early outpatient treatment for covid-19 with convalescent plasma, N. Engl. J. Med. 386 (18) (2022) 1700–1711, https://doi.org/10.1056/NEJMoa2119657.

[78] C. Filippatos, I. Ntanasis-Stathopoulos, K. Sekeri, et al., Convalescent plasma therapy for COVID-19: a systematic review and meta-analysis on randomized controlled trials, Viruses 15 (3) (2023) 765, https://doi.org/10.3390/v15030765.
[79] A.A.R. Tobian, C.S. Cohn, B.H. Shaz, COVID-19 convalescent plasma, Blood 140 (3) (2022) 196–207, https://doi.org/10.1182/blood.2021012248.
[80] S. Körper, M. Weiss, D. Zickler, et al., Results of the CAPSID randomized trial for high-dose convalescent plasma in patients with severe COVID-19, J. Clin. Invest. 131 (20) (2021) e152264, https://doi.org/10.1172/JCI152264.
[81] D. Focosi, M. Franchini, L. Pirofski, anne, et al., COVID-19 convalescent plasma and clinical trials: understanding conflicting outcomes, Clin. Microbiol. Rev. 35 (3) (2022) e00200–e00221, https://doi.org/10.1128/cmr.00200-21.
[82] P. Pratedrat, D. Intharasongkroh, J. Chansaenroj, et al., Dynamics of cytokine, SARS-CoV-2-specific IgG, and neutralizing antibody levels in COVID-19 patients treated with convalescent plasma, Diseases 11 (3) (2023) 112, https://doi.org/10.3390/diseases11030112.
[83] E. Kampouri, J.A. Hill, V. Dioverti, COVID-19 after hematopoietic cell transplantation and chimeric antigen receptor (CAR)-T-cell therapy, Transpl Infect Dis. Published online September 28 (2023) e14144, https://doi.org/10.1111/tid.14144.
[84] L. Tomisti, F. Angelotti, M. Lenzi, et al., Efficacy of convalescent plasma to treat long-standing COVID-19 in patients with B-cell depletion, Life 13 (6) (2023) 1266, https://doi.org/10.3390/life13061266.
[85] C.M. Denkinger, M. Janssen, U. Schäkel, et al., Anti-SARS-CoV-2 antibody-containing plasma improves outcome in patients with hematologic or solid cancer and severe COVID-19: a randomized clinical trial, Nat. Can. (Ott.) 29 (2022), https://doi.org/10.1038/s43018-022-00503-w. Published online December.
[86] D.J. Sullivan, M. Franchini, M.J. Joyner, A. Casadevall, D. Focosi, Analysis of Anti-omicron Neutralizing Antibody Titers in Different Vaccinated and Unvaccinated Convalescent Plasma Sources, Infectious Diseases (except HIV/AIDS), 2021, https://doi.org/10.1101/2021.12.24.21268317.
[87] H. Natarajan, A.R. Crowley, S.E. Butler, et al., Markers of polyfunctional SARS-CoV-2 antibodies in convalescent plasma. Diamond MS, ed, mBio 12 (2) (2021) e00765-21, https://doi.org/10.1128/mBio.00765-21.
[88] M. Franchini, C. Glingani, G.M. Liumbruno, Potential mechanisms of action of convalescent plasma in COVID-19, Diagnosis 8 (4) (2021) 413–420, https://doi.org/10.1515/dx-2020-0161.
[89] A. Casadevall, D. Focosi, SARS-CoV-2 variants resistant to monoclonal antibodies in immunocompromised patients constitute a public health concern, J. Clin. Invest. 133 (6) (2023) e168603, https://doi.org/10.1172/JCI168603.
[90] Search for: Convalescent Plasma for COVID 19 | Card Results | ClinicalTrials.gov. Accessed October 12, 2023. https://clinicaltrials.gov/search?cond=Convalescent%20Plasma%20for%20COVID%2019.
[91] N.Y.L. Pang, A.S.R. Pang, V.T. Chow, D.Y. Wang, Understanding neutralising antibodies against SARS-CoV-2 and their implications in clinical practice, Mil Med Res 8 (1) (2021) 47, https://doi.org/10.1186/s40779-021-00342-3.
[92] T.F. Rogers, F. Zhao, D. Huang, et al., Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model, Science 369 (6506) (2020) 956–963, https://doi.org/10.1126/science.abc7520.
[93] W.R. Strohl, Z. Ku, Z. An, S.F. Carroll, B.A. Keyt, L.M. Strohl, Passive immunotherapy against SARS-CoV-2: from plasma-based therapy to single potent antibodies in the race to stay ahead of the variants, BioDrugs 36 (3) (2022) 231–323, https://doi.org/10.1007/s40259-022-00529-7.
[94] M. Schoof, B. Faust, R.A. Saunders, et al., An ultrapotent synthetic nanobody neutralizes SARS-CoV-2 by stabilizing inactive Spike, Science 370 (6523) (2020) 1473–1479, https://doi.org/10.1126/science.abe3255.
[95] X. Tian, C. Li, A. Huang, et al., Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody, Emerg. Microb. Infect. 9 (1) (2020) 382–385, https://doi.org/10.1080/22221751.2020.1729069.
[96] M. Shirzad, M. Nourigorji, A. Sajedi, et al., Targeted therapy in Coronavirus disease 2019 (COVID-19): implication from cell and gene therapy to immunotherapy and vaccine, Int. Immunopharm. 111 (2022) 109161, https://doi.org/10.1016/j.intimp.2022.109161.
[97] C. Yi, X. Sun, J. Ye, et al., Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies, Cell. Mol. Immunol. 17 (6) (2020) 621–630, https://doi.org/10.1038/s41423-020-0458-z.
[98] C.O. Barnes, C.A. Jette, M.E. Abernathy, et al., SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies, Nature 588 (7839) (2020) 682–687, https://doi.org/10.1038/s41586-020-2852-1.
[99] C. Kim, D.K. Ryu, J. Lee, et al., A therapeutic neutralizing antibody targeting receptor binding domain of SARS-CoV-2 spike protein, Nat. Commun. 12 (1) (2021) 288, https://doi.org/10.1038/s41467-020-20602-5.
[100] L. Liu, P. Wang, M.S. Nair, et al., Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike, Nature 584 (7821) (2020) 450–456, https://doi.org/10.1038/s41586-020-2571-7.
[101] B. Ju, Q. Zhang, J. Ge, et al., Human neutralizing antibodies elicited by SARS-CoV-2 infection, Nature 584 (7819) (2020) 115–119, https://doi.org/10.1038/s41586-020-2380-z.
[102] R. Shi, C. Shan, X. Duan, et al., A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2, Nature 584 (7819) (2020) 120–124, https://doi.org/10.1038/s41586-020-2381-y.
[103] K. Westendorf, S. Žentelis, L. Wang, et al., LY-CoV1404 (bebtelovimab) potently neutralizes SARS-CoV-2 variants, Cell Rep. 39 (7) (2022) 110812, https://doi.org/10.1016/j.celrep.2022.110812.
[104] B.E. Jones, P.L. Brown-Augsburger, K.S. Corbett, et al., The neutralizing antibody, LY-CoV555, protects against SARS-CoV-2 infection in nonhuman primates, Sci. Transl. Med. 13 (593) (2021) eabf1906, https://doi.org/10.1126/scitranslmed.abf1906.
[105] S.J. Zost, P. Gilchuk, J.B. Case, et al., Potently neutralizing and protective human antibodies against SARS-CoV-2, Nature 584 (7821) (2020) 443–449, https://doi.org/10.1038/s41586-020-2548-6.
[106] J. Hansen, A. Baum, K.E. Pascal, et al., Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail, Science 369 (6506) (2020) 1010–1014, https://doi.org/10.1126/science.abd0827.
[107] M. McCallum, N. Czudnochowski, L.E. Rosen, et al., Structural basis of SARS-CoV-2 Omicron immune evasion and receptor engagement, Science 375 (6583) (2022) 864–868, https://doi.org/10.1126/science.abn8652.
[108] D. Pinto, Y.J. Park, M. Beltramello, et al., Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody, Nature 583 (7815) (2020) 290–295, https://doi.org/10.1038/s41586-020-2349-y.
[109] M.A. Tortorici, N. Czudnochowski, T.N. Starr, et al., Broad sarbecovirus neutralization by a human monoclonal antibody, Nature 597 (7874) (2021) 103–108, https://doi.org/10.1038/s41586-021-03817-4.
[110] C.G. Rappazzo, L.V. Tse, C.I. Kaku, et al., Broad and potent activity against SARS-like viruses by an engineered human monoclonal antibody, Science 371 (6531) (2021) 823–829, https://doi.org/10.1126/science.abf4830.
[111] X. Chen, R. Li, Z. Pan, et al., Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor, Cell. Mol. Immunol. 17 (6) (2020) 647–649, https://doi.org/10.1038/s41423-020-0426-7.
[112] J.S.N. Verma, Structural insight into antibody evasion of SARS-cov-2 omicron variant, Virol Immunol J 6 (1) (2022) 1–15, https://doi.org/10.23880/vij-16000289.
[113] Q. Wang, Y. Guo, S. Iketani, et al., Antibody evasion by SARS-CoV-2 Omicron subvariants BA.2.12.1, BA.4 and BA.5, Nature 608 (7923) (2022) 603–608, https://doi.org/10.1038/s41586-022-05053-w.
[114] P. Wang, M.S. Nair, L. Liu, et al., Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7, Immunology (2021), https://doi.org/10.1101/2021.01.25.428137.
[115] S. Sridhara, A.B. Gungor, H.K. Erol, et al., Lack of effectiveness of Bebtelovimab monoclonal antibody among high-risk patients with SARS-Cov-2 Omicron during BA.2, BA.2.12.1 and BA.5 subvariants dominated era, PLoS One 18 (4) (2023) e0279326, https://doi.org/10.1371/journal.pone.0279326.
[116] Research C for DE and. FDA updates on bebtelovimab. *FDA*. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-bebtelovimab, 2022. (Accessed 15 June 2023).
[117] M. Cox, T.P. Peacock, W.T. Harvey, et al., SARS-CoV-2 variant evasion of monoclonal antibodies based on in vitro studies, Nat. Rev. Microbiol. 21 (2) (2023) 112–124, https://doi.org/10.1038/s41579-022-00809-7.

[118] H. Kim, Y.R. Jang, J.Y. Lee, et al., Effectiveness of regdanvimab treatment for SARS-CoV-2 delta variant, which exhibited decreased in vitro activity: a nationwide real-world multicenter cohort study, Front. Cell. Infect. Microbiol. 13 (2023) 1192512, https://doi.org/10.3389/fcimb.2023.1192512.

[119] L.A. VanBlargan, J.M. Errico, P.J. Halfmann, et al., An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies, Nat. Med. 28 (3) (2022) 490–495, https://doi.org/10.1038/s41591-021-01678-y.

[120] R. Rockett, K. Basile, S. Maddocks, et al., Resistance mutations in SARS-CoV-2 delta variant after sotrovimab use, N. Engl. J. Med. 386 (15) (2022) 1477–1479, https://doi.org/10.1056/NEJMc2120219.

[121] Therapeutics and COVID-19: living guideline, 13 january. https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-therapeutics-2023.1, 2023. (Accessed 15 June 2023).

[122] X. Hao, Z. Zhang, J. Ma, et al., Randomized, placebo-controlled, single-blind phase 1 studies of the safety, tolerability, and pharmacokinetics of BRII-196 and BRII-198, SARS-CoV-2 spike-targeting monoclonal antibodies with an extended half-life in healthy adults, Front. Pharmacol. 13 (2022) 983505, https://doi.org/10.3389/fphar.2022.983505.

[123] Q. Wang, Z. Li, J. Ho, et al., Resistance of SARS-CoV-2 omicron subvariant BA.4.6 *to* antibody neutralization, Microbiology (2022), https://doi.org/10.1101/2022.09.05.506628.

[124] H. Liu, P. Wei, Q. Zhang, et al., *501Y.V2 and 501Y.V3 Variants of SARS-CoV-2 lose Binding to bamlanivimab* in vitro, Biochemistry (2021), https://doi.org/10.1101/2021.02.16.431305.

[125] F. Wang, L. Li, Y. Dou, et al., Etesevimab in combination with JS026 neutralizing SARS-CoV-2 and its variants, Emerg. Microb. Infect. 11 (1) (2022) 548–551, https://doi.org/10.1080/22221751.2022.2032374.

[126] Y. Cao, A. Yisimayi, F. Jian, et al., BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection, Nature 608 (7923) (2022) 593–602, https://doi.org/10.1038/s41586-022-04980-y.

[127] D.E. Research C for, FDA announces Evusheld is not currently authorized for emergency use in the U.S. *FDA*. Published online January 25. https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-evusheld-not-currently-authorized-emergency-use-us, 2023. (Accessed 15 June 2023).

[128] E.M. Parzych, J. Du, A.R. Ali, et al., DNA-delivered antibody cocktail exhibits improved pharmacokinetics and confers prophylactic protection against SARS-CoV-2, Nat. Commun. 13 (1) (2022) 5886, https://doi.org/10.1038/s41467-022-33309-6.

[129] M.M. Lamers, B.L. Haagmans, SARS-CoV-2 pathogenesis, Nat. Rev. Microbiol. 20 (5) (2022) 270–284, https://doi.org/10.1038/s41579-022-00713-0.

[130] H. Zhang, P. Lv, J. Jiang, et al., Advances in developing ACE2 derivatives against SARS-CoV-2, Lancet Microbe 4 (5) (2023) e369–e378, https://doi.org/10.1016/S2666-5247(23)00011-3.

[131] P. Zhou, X.L. Yang, X.G. Wang, et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (7798) (2020) 270–273, https://doi.org/10.1038/s41586-020-2012-7.

[132] J. Lan, J. Ge, J. Yu, et al., Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor, Nature 581 (7807) (2020) 215–220, https://doi.org/10.1038/s41586-020-2180-5.

[133] C. Xu, Y. Wang, C. Liu, et al., Conformational dynamics of SARS-CoV-2 trimeric spike glycoprotein in complex with receptor ACE2 revealed by cryo-EM, Sci. Adv. 7 (1) (2021) eabe5575, https://doi.org/10.1126/sciadv.abe5575.

[134] C.B. Jackson, M. Farzan, B. Chen, H. Choe, Mechanisms of SARS-CoV-2 entry into cells, Nat. Rev. Mol. Cell Biol. 23 (1) (2022) 3–20, https://doi.org/10.1038/s41580-021-00418-x.

[135] H. Zhang, J.M. Penninger, Y. Li, N. Zhong, A.S. Slutsky, Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target, Intensive Care Med. 46 (4) (2020) 586–590, https://doi.org/10.1007/s00134-020-05985-9.

[136] R. Peng, L.A. Wu, Q. Wang, J. Qi, G.F. Gao, Cell entry by SARS-CoV-2, Trends Biochem. Sci. 46 (10) (2021) 848–860, https://doi.org/10.1016/j.tibs.2021.06.001.

[137] Y. Higuchi, T. Suzuki, T. Arimori, et al., Engineered ACE2 receptor therapy overcomes mutational escape of SARS-CoV-2, Nat. Commun. 12 (1) (2021) 3802, https://doi.org/10.1038/s41467-021-24013-y.

[138] N. Ikemura, S. Taminishi, T. Inaba, et al., An engineered ACE2 decoy neutralizes the SARS-CoV-2 Omicron variant and confers protection against infection in vivo, Sci. Transl. Med. 14 (650) (2022) eabn7737, https://doi.org/10.1126/scitranslmed.abn7737.

[139] V. Monteil, H. Kwon, P. Prado, et al., Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2, Cell 181 (4) (2020) 905–913.e7, https://doi.org/10.1016/j.cell.2020.04.004.

[140] A. Zoufaly, M. Poglitsch, J.H. Aberle, et al., Human recombinant soluble ACE2 in severe COVID-19, Lancet Respir. Med. 8 (11) (2020) 1154–1158, https://doi.org/10.1016/S2213-2600(20)30418-5.

[141] T.M. Abd El-Aziz, A. Al-Sabi, J.D. Stockand, Human recombinant soluble ACE2 (hrsACE2) shows promise for treating severe COVID19, Signal Transduct. Targeted Ther. 5 (1) (2020) 258, https://doi.org/10.1038/s41392-020-00374-6.

[142] K.K. Chan, D. Dorosky, P. Sharma, et al., Engineering human ACE2 to optimize binding to the spike protein of SARS coronavirus 2, Science 369 (6508) (2020) 1261–1265, https://doi.org/10.1126/science.abc0870.

[143] A. Glasgow, J. Glasgow, D. Limonta, et al., Engineered ACE2 receptor traps potently neutralize SARS-CoV-2, Proc. Natl. Acad. Sci. USA 117 (45) (2020) 28046–28055, https://doi.org/10.1073/pnas.2016093117.

[144] J.J. Sims, S. Lian, R.L. Meggersee, A. Kasimsetty, J.M. Wilson, in: V.C. Huber (Ed.), High Activity of an Affinity-Matured ACE2 Decoy against Omicron SARS-CoV-2 and Pre-emergent Coronaviruses, PLOS ONE, 2022 e0271359, https://doi.org/10.1371/journal.pone.0271359, 17(8).

[145] A. Kegler, L. Drewitz, C. Arndt, et al., A novel ACE2 decoy for both neutralization of SARS-CoV-2 variants and killing of infected cells, Front. Immunol. 14 (2023) 1204543, https://doi.org/10.3389/fimmu.2023.1204543.

[146] Y. Chen, L. Sun, I. Ullah, et al., Engineered ACE2-Fc counters murine lethal SARS-CoV-2 infection through direct neutralization and Fc-effector activities, Sci. Adv. 8 (28) (2022) eabn4188, https://doi.org/10.1126/sciadv.abn4188.

[147] Z. Zhang, E. Zeng, L. Zhang, et al., Potent prophylactic and therapeutic efficacy of recombinant human ACE2-Fc against SARS-CoV-2 infection in vivo, Cell Discov 7 (1) (2021) 65, https://doi.org/10.1038/s41421-021-00302-0.

[148] S.G. Remesh, G.E. Merz, A.F. Brilot, et al., Computational pipeline provides mechanistic understanding of Omicron variant of concern neutralizing engineered ACE2 receptor traps, Structure 31 (3) (2023) 253–264.e6, https://doi.org/10.1016/j.str.2023.01.009.

[149] K.K. Chan, T.J.C. Tan, K.K. Narayanan, E. Procko, An engineered decoy receptor for SARS-CoV-2 broadly binds protein S sequence variants, Sci. Adv. 7 (8) (2021) eabf1738, https://doi.org/10.1126/sciadv.abf1738.

[150] H. Cohen-Dvashi, J. Weinstein, M. Katz, et al., Anti-SARS-CoV-2 immunoadhesin remains effective against Omicron and other emerging variants of concern, iScience 25 (10) (2022) 105193, https://doi.org/10.1016/j.isci.2022.105193.

[151] G. Deng, M. Yin, X. Chen, F. Zeng, Clinical determinants for fatality of 44,672 patients with COVID-19, Crit. Care 24 (1) (2020) 179, https://doi.org/10.1186/s13054-020-02902-w.

[152] P. Palacios-Moguel, A. Esquivel-Pineda, X.A. Flores-Andrade, et al., Acute respiratory distress syndrome in patients with COVID-19 vs. Non-COVID-19: clinical characteristics and outcomes in a tertiary care setting in Mexico City, BMC Pulm. Med. 23 (1) (2023) 430, https://doi.org/10.1186/s12890-023-02744-6.

[153] M. Gujski, M. Jankowski, D. Rabczenko, P. Goryński, G. Juszczyk, The prevalence of acute respiratory distress syndrome (ARDS) and outcomes in hospitalized patients with COVID-19—a study based on data from the polish national hospital register, Viruses 14 (1) (2022) 76, https://doi.org/10.3390/v14010076.

[154] D. Chiumello, L. Modafferi, I. Fratti, Risk factors and mortality in elderly ARDS COVID-19 compared to patients without COVID-19, J. Clin. Med. 11 (17) (2022) 5180, https://doi.org/10.3390/jcm11175180.

[155] M.S. Qudus, M. Tian, S. Sirajuddin, et al., The roles of critical pro-inflammatory cytokines in the drive of cytokine storm during SARS-CoV-2 infection, J. Med. Virol. 95 (4) (2023) e28751, https://doi.org/10.1002/jmv.28751.

[156] T. Pfeiffer, I. Tzannou, M. Wu, et al., Posoleucel, an allogeneic, off-the-shelf multivirus-specific T-cell therapy, for the treatment of refractory viral infections in the post-HCT setting, Clin. Cancer Res. 29 (2) (2023) 324–330, https://doi.org/10.1158/1078-0432.CCR-22-2415.

[157] A.J. Barrett, S. Prockop, C.M. Bollard, Virus-specific T cells: broadening applicability, Biol. Blood Marrow Transplant. 24 (1) (2018) 13–18, https://doi.org/10.1016/j.bbmt.2017.10.004.

[158] I. Tzannou, A. Papadopoulou, S. Naik, et al., Off-the-Shelf virus-specific T cells to treat BK virus, human herpesvirus 6, cytomegalovirus, epstein-barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation, J. Clin. Oncol. 35 (31) (2017) 3547–3557, https://doi.org/10.1200/JCO.2017.73.0655.

[159] C.M. Motta, M.D. Keller, C.M. Bollard, Applications of virus-specific T cell therapies post-BMT, Semin. Hematol. 60 (1) (2023) 10–19, https://doi.org/10.1053/j.seminhematol.2022.12.002.

[160] M.D. Keller, K.M. Harris, M.A. Jensen-Wachspress, et al., SARS-CoV-2–specific T cells are rapidly expanded for therapeutic use and target conserved regions of the membrane protein, Blood 136 (25) (2020) 2905–2917, https://doi.org/10.1182/blood.2020008488.

[161] S. Vasileiou, L. Hill, M. Kuvalekar, et al., Allogeneic, Off-the-Shelf, SARS-CoV-2-specific T cells (ALVR109) for the treatment of COVID-19 in high risk patients, Haematologica. Published online November 10 (2022), https://doi.org/10.3324/haematol.2022.281946.

[162] A. Panikkar, K.E. Lineburg, J. Raju, et al., in: A.L. Hartman (Ed.), SARS-CoV-2-specific T Cells Generated for Adoptive Immunotherapy Are Capable of Recognizing Multiple SARS-CoV-2 Variants, PLOS Pathog, 2022 e1010339, https://doi.org/10.1371/journal.ppat.1010339, 18(2).

[163] G. Haidar, J.L. Jacobs, K. Hughes Kramer, et al., Therapy with allogeneic SARS-CoV-2-specific T-cells for persistent COVID-19 in immunocompromised patients, Clin. Infect. Dis. (2023) ciad233, https://doi.org/10.1093/cid/ciad233. Published online April 20.

[164] S.R. Conway, M.D. Keller, C.M. Bollard, Cellular therapies for the treatment and prevention of SARS-CoV-2 infection, Blood 140 (3) (2022) 208–221, https://doi.org/10.1182/blood.2021012249.

[165] N. Kim, J.M. Lee, E.J. Oh, et al., Off-the-Shelf partial HLA matching SARS-CoV-2 antigen specific T cell therapy: a new possibility for COVID-19 treatment, Front. Immunol. 12 (2021) 751869, https://doi.org/10.3389/fimmu.2021.751869.

[166] G. El-Saber Batiha, A.I. Al-Gareeb, H.M. Saad, H.M. Al-kuraishy, COVID-19 and corticosteroids: a narrative review, Inflammopharmacology 30 (4) (2022) 1189–1205, https://doi.org/10.1007/s10787-022-00987-z.

[167] M.B. Mazer, E. Davitt, I.R. Turnbull, et al., In vitro–administered dexamethasone suppresses T cell function with reversal by interleukin-7 in coronavirus disease 2019, Crit Care Explor 3 (4) (2021) e0378, https://doi.org/10.1097/CCE.0000000000000378.

[168] A. Papadopoulou, G. Karavalakis, E. Papadopoulou, et al., SARS-CoV-2-specific T cell therapy for severe COVID-19: a randomized phase 1/2 trial, Nat. Med. 29 (8) (2023) 2019–2029, https://doi.org/10.1038/s41591-023-02480-8.

[169] S. Hori, T. Nomura, S. Sakaguchi, Control of regulatory T cell development by the transcription factor *Foxp3*, Science 299 (5609) (2003) 1057–1061, https://doi.org/10.1126/science.1079490.

[170] M. Grumet, J. Sherman, B.S. Dorf, Efficacy of MSC in patients with severe COVID-19: analysis of the literature and a case study, Stem Cells Transl Med 11 (11) (2022) 1103–1112, https://doi.org/10.1093/stcltm/szac067.

[171] C. Zhang, L. Li, K. Feng, D. Fan, W. Xue, J. Lu, 'Repair' treg cells in tissue injury, Cell. Physiol. Biochem. 43 (6) (2017) 2155–2169, https://doi.org/10.1159/000484295.

[172] S. Ahmad, M.M. Hatmal, L. Lambuk, M.A.I. Al-Hatamleh, W. Alshaer, R. Mohamud, The role of TNFR2+ Tregs in COVID-19: an overview and a potential therapeutic strategy, Life Sci. 286 (2021) 120063, https://doi.org/10.1016/j.lfs.2021.120063.

[173] E. Stephen-Victor, M. Das, A. Karnam, B. Pitard, J.F. Gautier, J. Bayry, Potential of regulatory T-cell-based therapies in the management of severe COVID-19, Eur. Respir. J. 56 (3) (2020) 2002182, https://doi.org/10.1183/13993003.02182-2020.

[174] S. Galván-Peña, J. Leon, K. Chowdhary, et al., Profound Treg perturbations correlate with COVID-19 severity, Proc. Natl. Acad. Sci. USA 118 (37) (2021) e2111315118, https://doi.org/10.1073/pnas.2111315118.

[175] B.T. Garibaldi, F.R. D'Alessio, J.R. Mock, et al., Regulatory T cells reduce acute lung injury fibroproliferation by decreasing fibrocyte recruitment, Am. J. Respir. Cell Mol. Biol. 48 (1) (2013) 35–43, https://doi.org/10.1165/rcmb.2012-0198OC.

[176] D.E. Gladstone, B.S. Kim, K. Mooney, A.H. Karaba, F.R. D'Alessio, Regulatory T cells for treating patients with COVID-19 and acute respiratory distress syndrome: two case reports, Ann. Intern. Med. 173 (10) (2020) 852–853, https://doi.org/10.7326/L20-0681.

[177] D.E. Gladstone, F. D'Alessio, C. Howard, et al., Randomized, double-blinded, placebo-controlled trial of allogeneic cord blood T-regulatory cells for treatment of COVID-19 ARDS, Blood Adv 7 (13) (2023) 3075–3079, https://doi.org/10.1182/bloodadvances.2022009619.

[178] K.M. Cappell, J.N. Kochenderfer, Long-term outcomes following CAR T cell therapy: what we know so far, Nat. Rev. Clin. Oncol. 20 (6) (2023) 359–371, https://doi.org/10.1038/s41571-023-00754-1.

[179] J. Zarychta, A. Kowalczyk, M. Krawczyk, M. Lejman, J. Zawitkowska, CAR-T cells immunotherapies for the treatment of acute myeloid leukemia—recent advances, Cancers 15 (11) (2023) 2944, https://doi.org/10.3390/cancers15112944.

[180] S.M. Albelda, CAR T cell therapy for patients with solid tumours: key lessons to learn and unlearn, Nat. Rev. Clin. Oncol. 21 (1) (2024) 47–66, https://doi.org/10.1038/s41571-023-00832-4.

[181] M. Seif, H. Einsele, J. Löffler, CAR T cells beyond cancer: hope for immunomodulatory therapy of infectious diseases, Front. Immunol. 10 (2019) 2711, https://doi.org/10.3389/fimmu.2019.02711.

[182] M. Mohammadi, M. Akhoundi, S. Malih, A. Mohammadi, M. Sheykhhasan, Therapeutic roles of CAR T cells in infectious diseases: clinical lessons learnt from cancer, Rev. Med. Virol. 32 (4) (2022) e2325, https://doi.org/10.1002/rmv.2325.

[183] H. Ludwig, E. Terpos, N. Van De Donk, et al., Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Network, Lancet Oncol. 24 (6) (2023) e255–e269, https://doi.org/10.1016/S1470-2045(23)00159-6.

[184] X. Guo, A. Kazanova, S. Thurmond, H.U. Saragovi, C.E. Rudd, Effective chimeric antigen receptor T cells against SARS-CoV-2, iScience 24 (11) (2021) 103295, https://doi.org/10.1016/j.isci.2021.103295.

[185] P. Gonzalez-Garcia, J.P. Muñoz-Miranda, R. Fernandez-Cisnal, et al., Specific activation of T cells by an ACE2-based CAR-like receptor upon recognition of SARS-CoV-2 spike protein, Int. J. Mol. Sci. 24 (8) (2023) 7641, https://doi.org/10.3390/ijms24087641.

[186] L. Xia, L. Yuan, zhi, Y. Hu, hong, et al., A SARS-CoV-2-specific CAR-T-cell model identifies felodipine, fasudil, imatinib, and caspofungin as potential treatments for lethal COVID-19, Cell. Mol. Immunol. 20 (4) (2023) 351–364, https://doi.org/10.1038/s41423-023-00985-3.

[187] B. Krämer, R. Knoll, L. Bonaguro, et al., Early IFN-α signatures and persistent dysfunction are distinguishing features of NK cells in severe COVID-19, Immunity 54 (11) (2021) 2650, https://doi.org/10.1016/j.immuni.2021.09.002, 2669.e14.

[188] A. Mazzoni, L. Salvati, L. Maggi, et al., Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent, J. Clin. Invest. 130 (9) (2020) 4694–4703, https://doi.org/10.1172/JCI138554.

[189] M.J. Lee, C.A. Blish, Defining the role of natural killer cells in COVID-19, Nat. Immunol. 24 (10) (2023) 1628–1638, https://doi.org/10.1038/s41590-023-01560-8.

[190] F. Ahmed, D.H. Jo, S.H. Lee, Can natural killer cells Be a principal player in anti-SARS-CoV-2 immunity? Front. Immunol. 11 (2020) 586765 https://doi.org/10.3389/fimmu.2020.586765.

[191] O.K. Dagher, A.D. Posey, Forks in the road for CAR T and CAR NK cell cancer therapies, Nat. Immunol. 24 (12) (2023) 1994–2007, https://doi.org/10.1038/s41590-023-01659-y.

[192] T. Lu, R. Ma, W. Dong, et al., Off-the-shelf CAR natural killer cells secreting IL-15 target spike in treating COVID-19, Nat. Commun. 13 (1) (2022) 2576, https://doi.org/10.1038/s41467-022-30216-8.

[193] I. Christodoulou, R. Rahnama, J.W. Ravich, et al., Glycoprotein targeted CAR-NK cells for the treatment of SARS-CoV-2 infection, Front. Immunol. 12 (2021) 763460, https://doi.org/10.3389/fimmu.2021.763460.

[194] X. Zhu, M. Badawi, S. Pomeroy, et al., Comprehensive toxicity and immunogenicity studies reveal minimal effects in mice following sustained dosing of extracellular vesicles derived from HEK293T cells, J. Extracell. Vesicles 6 (1) (2017) 1324730, https://doi.org/10.1080/20013078.2017.1324730.

[195] L. Debbi, S. Guo, D. Safina, S. Levenberg, Boosting extracellular vesicle secretion, Biotechnol. Adv. 59 (2022) 107983, https://doi.org/10.1016/j.biotechadv.2022.107983.
[196] T.A. Scott, A. Supramaniam, A. Idris, et al., Engineered extracellular vesicles directed to the spike protein inhibit SARS-CoV-2, Mol Ther - Methods Clin Dev. 24 (2022) 355–366, https://doi.org/10.1016/j.omtm.2022.01.015.
[197] F. Xie, P. Su, T. Pan, et al., Engineering extracellular vesicles enriched with palmitoylated ACE2 as COVID-19 therapy, Adv. Mater. 33 (49) (2021) 2103471, https://doi.org/10.1002/adma.202103471.
[198] A.G. Ibrahim, A. Ciullo, C. Li, et al., Engineered extracellular vesicles antagonize SARS-CoV-2 infection by inhibiting mTOR signaling, Biomater Biosyst 6 (2022) 100042, https://doi.org/10.1016/j.bbiosy.2022.100042.
[199] Y. Huang, X. Li, L. Yang, Mesenchymal stem cells and their derived small extracellular vesicles for COVID-19 treatment, Stem Cell Res. Ther. 13 (1) (2022) 410, https://doi.org/10.1186/s13287-022-03034-4.
[200] R. Zhao, L. Wang, T. Wang, P. Xian, H. Wang, Q. Long, Inhalation of MSC-EVs is a noninvasive strategy for ameliorating acute lung injury, J. Contr. Release 345 (2022) 214–230, https://doi.org/10.1016/j.jconrel.2022.03.025.
[201] P.S. Couto, N. Al-Arawe, I.S. Filgueiras, et al., Systematic review and meta-analysis of cell therapy for COVID-19: global clinical trial landscape, published safety/efficacy outcomes, cell product manufacturing and clinical delivery, Front. Immunol. 14 (2023) 1200180, https://doi.org/10.3389/fimmu.2023.1200180.
[202] T.T. Li, B. Zhang, H. Fang, et al., Human mesenchymal stem cell therapy in severe COVID-19 patients: 2-year follow-up results of a randomized, double-blind, placebo-controlled trial, EBioMedicine 92 (2023) 104600, https://doi.org/10.1016/j.ebiom.2023.104600.
[203] G. Lanzoni, E. Linetsky, D. Correa, et al., Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: a double-blind, phase 1/2a, randomized controlled trial, Stem Cells Transl Med 10 (5) (2021) 660–673, https://doi.org/10.1002/sctm.20-0472.
[204] R. Zhu, T. Yan, Y. Feng, et al., Mesenchymal stem cell treatment improves outcome of COVID-19 patients via multiple immunomodulatory mechanisms, Cell Res. 31 (12) (2021) 1244–1262, https://doi.org/10.1038/s41422-021-00573-y.
[205] A.R. Eckard, K.M. Borow, E.H. Mack, E. Burke, A.M. Atz, Remestemcel-L therapy for COVID-19–associated multisystem inflammatory syndrome in children, Pediatrics 147 (5) (2021) e2020046573, https://doi.org/10.1542/peds.2020-046573.
[206] A. Monsel, C. Hauw-Berlemont, M. Mebarki, et al., Treatment of COVID-19-associated ARDS with mesenchymal stromal cells: a multicenter randomized double-blind trial, Crit. Care 26 (1) (2022) 48, https://doi.org/10.1186/s13054-022-03930-4.
[207] SARS-ANI VIS. SARS-ANI VIS. Accessed January 24, 2024. https://vis.csh.ac.at/sars-ani/.
[208] M.E. Davis-Gardner, L. Lai, B. Wali, et al., Neutralization against BA.2.75.2, BQ.1.1, and XBB from mRNA bivalent booster, N. Engl. J. Med. 388 (2) (2023) 183–185, https://doi.org/10.1056/NEJMc2214293.
[209] T. Hattori, A. Koide, M.G. Noval, et al., The ACE2-binding interface of SARS-CoV-2 spike inherently deflects immune recognition, J. Mol. Biol. 433 (3) (2021) 166748, https://doi.org/10.1016/j.jmb.2020.166748.
[210] D. Wrapp, N. Wang, K.S. Corbett, et al., Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, Science 367 (6483) (2020) 1260–1263, https://doi.org/10.1126/science.abb2507.
[211] D.F. Robbiani, C. Gaebler, F. Muecksch, et al., Convergent antibody responses to SARS-CoV-2 in convalescent individuals, Nature 584 (7821) (2020) 437–442, https://doi.org/10.1038/s41586-020-2456-9.
[212] C.A. Marschner, K.E. Shaw, F.S. Tijmes, et al., Myocarditis following COVID-19 vaccination, Heart Fail. Clin. 19 (2) (2023) 251–264, https://doi.org/10.1016/j.hfc.2022.08.012.
[213] S. Khiali, A. Rezagholizadeh, H. Behzad, H. Bannazadeh Baghi, T. Entezari-Maleki, Current evidence of COVID-19 vaccination-related cardiovascular events, Postgrad. Med. 135 (2) (2023) 102–120, https://doi.org/10.1080/00325481.2022.2161249.
[214] A.K. Sularz, A. Hua, T. Ismail, SARS-CoV-2 vaccines and myocarditis, Clin. Med. 23 (5) (2023) 495–502, https://doi.org/10.7861/clinmed.2023-0049.
[215] N.L. Altman, A.A. Berning, S.C. Mann, et al., Vaccination-associated myocarditis and myocardial injury, Circ. Res. 132 (10) (2023) 1338–1357, https://doi.org/10.1161/CIRCRESAHA.122.321881.
[216] A. Chatterjee, A. Chakravarty, Neurological complications following COVID-19 vaccination, Curr. Neurol. Neurosci. Rep. 23 (1) (2023) 1–14, https://doi.org/10.1007/s11910-022-01247-x.
[217] R.S. Tsang, M. Joy, R. Byford, et al., Adverse events following first and second dose COVID-19 vaccination in England, October 2020 to September 2021: a national vaccine surveillance platform self-controlled case series study, Euro Surveill. 28 (3) (2023), https://doi.org/10.2807/1560-7917.ES.2023.28.3.2200195.
[218] Y. Yang, L. Huang, Neurological disorders following COVID-19 vaccination, Vaccines 11 (6) (2023) 1114, https://doi.org/10.3390/vaccines11061114.
[219] M. Di Fusco, J. Lin, S. Vaghela, et al., COVID-19 vaccine effectiveness among immunocompromised populations: a targeted literature review of real-world studies, Expert Rev. Vaccines 21 (4) (2022) 435–451, https://doi.org/10.1080/14760584.2022.2035222.
[220] X. Tang, D. Xue, T. Zhang, et al., A multi-organoid platform identifies CIART as a key factor for SARS-CoV-2 infection, Nat. Cell Biol. 25 (3) (2023) 381–389, https://doi.org/10.1038/s41556-023-01095-y.
[221] H. Wang, C. Liu, X. Xie, et al., Multi-omics blood atlas reveals unique features of immune and platelet responses to SARS-CoV-2 Omicron breakthrough infection, Immunity 56 (6) (2023) 1410–1428.e8, https://doi.org/10.1016/j.immuni.2023.05.007.
[222] I. Henig, T. Zuckerman, Hematopoietic stem cell transplantation—50 Years of evolution and future perspectives, Rambam Maimonides Med J 5 (4) (2014) e0028, https://doi.org/10.5041/RMMJ.10162.
[223] E.J. Rubin, L.R. Baden, S. Morrissey, Audio interview: ending the covid-19 emergency, N. Engl. J. Med. 388 (19) (2023) e72, https://doi.org/10.1056/NEJMe2305545.
[224] A. Preska Steinberg, O.K. Silander, E. Kussell, Correlated substitutions reveal SARS-like coronaviruses recombine frequently with a diverse set of structured gene pools, Proc. Natl. Acad. Sci. USA 120 (5) (2023) e2206945119, https://doi.org/10.1073/pnas.2206945119.
[225] C. Qin, J. Deng, M. Du, et al., Pandemic fatigue and vaccine hesitancy among people who have recovered from COVID-19 infection in the post-pandemic era: cross-sectional study in China, Vaccines 11 (10) (2023) 1570, https://doi.org/10.3390/vaccines11101570.
[226] S. Montazersaheb, S.M. Hosseiniyan Khatibi, M.S. Hejazi, et al., COVID-19 infection: an overview on cytokine storm and related interventions, Virol. J. 19 (1) (2022) 92, https://doi.org/10.1186/s12985-022-01814-1.
[227] J. Kurtzberg, H. Abdel-Azim, P. Carpenter, et al., A phase 3, single-arm, prospective study of remestemcel-L, ex vivo culture-expanded adult human mesenchymal stromal cells for the treatment of pediatric patients who failed to respond to steroid treatment for acute graft-versus-host disease, Biol. Blood Marrow Transplant. 26 (5) (2020) 845–854, https://doi.org/10.1016/j.bbmt.2020.01.018.
[228] J. Le-Rademacher, H. Gunn, X. Yao, D.J. Schaid, Clinical trials overview: from explanatory to pragmatic clinical trials, Mayo Clin. Proc. 98 (8) (2023) 1241–1253, https://doi.org/10.1016/j.mayocp.2023.04.013.