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COMMENTARY

An update to "novel therapeutic approaches for treatment of COVID-19"

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Although the exact mechanism of pathogenesis in COVID-19 is not fully understood, cytokine storm following viral infection plays an important role in the initiation and progression of disease. SARS-CoV-2 infection induces over-activation of the immune system and massive production of inflammatory cytokines. Therefore, it is necessary to develop new strategies to modulate inflammatory responses [1]. Despite many efforts to improve therapeutic protocols for COVID-19, there is no specific approved treatment or preventable vaccine for this disease [2, 3]. However, intensive research has been conducted to both prevent and treat COVID-19. This commentary is an update for our recent paper in "Journal of Molecular Medicine, June 2020" and highlights the recent achievements in terms of preventive and therapeutic approaches in COVID-19 [4].

Development of SARS-CoV-2 preventive vaccines

- mRNA-1273 (Moderna TX, Inc.) is an mRNA vaccine that is composed of synthetic mRNA expressing the prefusion-stabilized SARS-CoV-2 spike trimer (mRNA-1273) [5, 6]. The efficacy and immunogenicity of Moderna vaccine investigated in a phase III clinical trial (NCT04470427). Moderna has announced its primary efficacy analysis (95%) and recently applied to the FDA (USA) for emergency use authorization.
- ChAdOx1 nCOV-19 is another vaccine under evaluation in phase II/III clinical trials. This vaccine has been developed by Oxford University and produced due to the technology in which an adeno-viral vector encodes SARS-CoV-2 S protein (NCT04400838) [7]. The pre-clinical investigations showed that ChAdOx1 nCOV-19 was immunogenic in vaccinated mice and rhesus macaques and triggered robust humoral and cell-mediated responses [8]. Its safety and immunogenicity were evaluated in a phase II/III trial in a prime-boost regimen in young and old adults. In 14 days after receiving the boost dose, > 99% of participants had neutralizing antibodies [9].
- BNT162b2 is a COVID-19 RNA vaccine candidate that has been announced by BioNTech/Pfizer. This vaccine encodes the receptor-binding domain (RBD) of the

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SARS-CoV-2 spike protein. Data from a phase III clinical trial showed vaccine efficiency over 95% [12, 13].

- CoronaVac is inactivated SARS-CoV-2 manufactured by Sinovac Life Sciences (Beijing, China). Its safety, tolerability, and immunogenicity have been approved in healthy adults aged 18–59 years in a phase I/II clinical trial [14]; and now it is under investigation in a phase III clinical trial (NCT04582344).
- Gam-COVID-Vac (Sputnik V) is a combined vector vaccine that consists of recombinant adenovirus type 26 (rAd26) and type 5 (rAd5) vectors. They carry the spike glycoprotein gene. Gam-COVID-Vac has been developed by Gamaleya National Research Center for Epidemiology and Microbiology (Moscow, Russia) [15]. Its safety and immunogenicity was approved in two formulations in a phase I/II clinical trial [15]. And now, the safety and efficiency of this vaccine is under assessment in a phase III clinical trial (NCT04530396).
- Using Ad5 vector to carry the spike glycoprotein gene, CanSino Biologics Inc. (China) has developed a recombinant novel coronavirus vaccine which safety and efficiency has been being evaluated in a phase III clinical trial (NCT04526990).

The progress in vaccine development is critically discussed in the following recently published reviews in detail [10, 11].

SARS-CoV-2 therapeutic approaches

In our recently published paper entitled "Novel therapeutic approaches for treatment of COVID-19," we grouped novel therapies into passive immunotherapy, cell-based therapies (including immune cell and non-immune cell therapies), monoclonal antibodies, and anti-viral drugs.

Searching terms "COVID-19" and "treatment" using https://clinicaltrials.gov/ resulted in more than 2200 clinical trials (October 29, 2020). Among these clinical trials, over 200 studies were related to cell-based therapies. They included mesenchymal stromal cell (MSC) therapies and adoptive T cell and natural killer (NK) cell therapies. Other studies applied monoclonal antibodies and nano-medicine to treat COVID-19 patients (Table 1) (Figs. 1 and 2).

Mesenchymal stromal cells in COVID-19 treatment

- Due to the immunomodulatory effects of MSCs [16, 17], clinical trials using MSCs from various sources including the umbilical cord, adipose tissue, and bone marrow have been registered for the treatment of acute respiratory distress syndrome (ARDS) caused by COVID-19 (NCT04341610, NCT04366063). Primary results showed that this strategy was safe and effective. The MSC therapy improved lung function, downregulated inflammatory cytokines, increased anti-inflammatory ones, and decreased mortality rate [18–20]. MSCs exert their anti-inflammatory properties through direct cell-cell contact, paracrine effects, and their extracellular vesicles such as exosomes [21, 22]. It seems that application of MSCs and their exosomes could be a promising approach for the management of respiratory complications in COVID-19.

Adoptive T cells in COVID-19 treatment

- Some studies reported lymphopenia and functional exhaustion due to the over-activation of the immune system during infection [23]. COVID-19 specific T and T_{CD8+} cells play an important role in the virus clearance by producing inflammatory cytokines and their cytotoxicity effects [24]. Moreover, virus-specific memory T cells were isolated from the serum of the recovered patients [25–27]. Based on this evidence, recent clinical trials designed and used the adoptive T cells in severe COVID-19 patients. Using this treatment protocol, HLA-matched T cells from fully recovered patients were transfused into newly infected individuals. This approach may help patients who are at the risk of requiring mechanical ventilation (NCT04457726, NCT04401410, and NCT04406064).

Exosomes derived from adoptive T cells in COVID-19 treatment

- In addition, another clinical trial used COVID-19-specific T cell-derived exosomes (CSTC-Exo) for the treatment of early infected patients in order to boost the IFN-γ production. Compared to the cells, CSTC-Exo does not need HLA-matching, and their administration route is an aerosol inhalation (NCT04389385). If it meets the endpoints, it could be a suitable alternative as an off-the-shelf product.
- Since regulatory T cells (Treg) are known as major anti-inflammatory T cell subsets, Treg cell therapy may be a novel regenerative and anti-inflammatory treatment strategy for COVID-19. Infusion of cord blood-derived Treg cells (CK0802) may improve the ARDS symptoms in these patients (NCT04468971). RAPA-501-ALLO is a hybrid Treg/Th2 off-the-shelf reprogrammed Treg cell product produced by the healthy donors. RAPA-501-ALLO could have a dual advantage by modulating Th1 and Th17 subpopulations and inhibiting the massive production of inflammatory cytokines, as well as regenerating the damaged alveolar tissues [28]. This product may be a useful therapeutic option for the treatment of severe COVID-19 (NCT04482699).

Table 1 SARS-CoV-2 therapeutic approaches

Therapeutic approach	Number of studies	CT number	Status	Phase	The product used
MSC	65	NCT04366063	Recruiting	II/III	MSC, MSC + MSC-EVs
		NCT04333368	Recruiting	I/II	UC-MSC
		NCT04461925	Recruiting	I/II	Placenta-derived MSC/UC-MSC
		NCT04486001	Not yet recruiting	I	Allogenic AD-MSC
		NCT04348435	Enrolling by invitation	II	AD-MSC
		NCT04473170	Completed	II	Peripheral blood stem cells
		NCT04445454	Recruiting	II	BM-MSC
		NCT04349631	Enrolling by invitation	II	Autologous AD-MSC
		NCT04525378	Recruiting	I	MSC
		NCT04392778	Recruiting	I/II	MSC
		NCT04573270	Completed	I	UC-MSC
		NCT04447833	Recruiting	I	Allogenic BM-MSC
		NCT04437823	Recruiting	II	UC-MSC
		NCT04288102	Completed	II	UC-MSC
		NCT04252118	Recruiting	I	MSC
		NCT04273646	Not yet recruiting	-	UC-MSC
		NCT04331613	Recruiting	I/II	CAStem; regulatory cells from (hESCs)
		NCT04537351	Recruiting	I/II	CYP-001(MSC from iPS)
		NCT04313322	Recruiting	I	Wj-MSC
		NCT04299152	Recruiting	II	BM-MSC
		NCT04400032	Enrolling by invitation	I	Olfactory mucosa-derived MSCs
		NCT04382547	Not yet recruiting	I/II	Cord-blood MSC
		NCT04345601	Recruiting	I	Cord-blood MSC
		NCT04565665	Recruiting	I	MSC
		NCT04361942	Not yet recruiting	II	AD-MSC
		NCT04527224	Recruiting	II	UC-MSC
		NCT04366271	Recruiting	II	UC-MSC
		NCT04339660	Active, not recruiting	I/II	WJ-MSC
		NCT04456361	Not yet recruiting	I	WJ-MSC
		NCT04390152	Not yet recruiting	I/II	MSC
		NCT04535856	Recruiting	I	UC-MSC
		NCT04457609	Not yet recruiting	I	BM-MSC
		NCT04346368	Active, not recruiting	I/II	UC-MSC
		NCT04371601	Active, not recruiting	I	AD-MSC
		NCT04362189	Not yet recruiting	II	MSC
		NCT04467047	Not yet recruiting	I	AD-MSC
		NCT04348461	Recruiting	II	MSC
		NCT04416139	Recruiting	II	DP-MSC
		NCT04336254	Not yet recruiting	I/II	UC-MSC
		NCT04452097	Not yet recruiting	I	AD-MSC
		NCT04428801	Recruiting	II	WJ-MSC
		NCT04390139	Recruiting	I/II	AD-MSC
		NCT04366323	Active, not recruiting	I/II	hCT-MSC
		NCT04355728	Recruiting	I/II	UC-MSC
		NCT04399889	Not yet recruiting	I/II	UC-LSC
		NCT04429763	Recruiting	II	UC-MSC
		NCT04494386	Recruiting	I/II	UC-MSC
		NCT04269525	Not yet recruiting	II	Remestemcel-L
		NCT04490486	Recruiting	I	BM-MSC
		NCT04371393	Not yet recruiting	III	BM-MSC
		NCT04377334	Recruiting	II	Autologous AD-MSC
		NCT04397796	Not yet recruiting	I	placental mesenchymal-like adherent stromal cells
		NCT04352803	Recruiting	I	DP-MSC
		NCT04389450	Not yet recruiting	II	MSC
		NCT04302519	Recruiting	I	MSC
		NCT04466098	Not yet recruiting	II	NestaCell®
		NCT04522986	Not yet recruiting	I	UC-MSC
		NCT04315987	Not yet recruiting	II	MSCs or MSCs RNA-engineered
		NCT04398303	Not yet recruiting	I/II	UC-MSC
		NCT04524962	Recruiting	I/II	MultiStem; BM-MSC
		NCT03042143	Recruiting		
		NCT04367077	Available		
		NCT04338347			
		NCT04451291			
		NCT04445220			
T cell	7	NCT04351659	Recruiting	I	Convalescent donor
		NCT04457726	Recruiting	I/II	Convalescent donors
		NCT04482699	Not yet recruiting	I/II	RAPA-501-ALLO (allogeneic hybrid TREG/Th2 Cells)
		NCT04389385	Active, not recruiting	I	T cell-derived exosomes
		NCT04406064	Not yet recruiting	II	Viral-specific T cells
		NCT04401410	Not yet recruiting	I	Specific T cell
		NCT04468971	Recruiting	I	cord blood-derived T regulatory cells
NK cell	5	NCT04324996	Recruiting	I/II	NKG2D-ACE2 CAR-NK
		NCT04365101	Recruiting	I/II	CYNK-001(human placental)
		NCT04280224	Recruiting	I	NK
		NCT04344548	Not yet recruiting	I/II	Allogeneic NK cell transfer
		NCT04363346	Recruiting	I	NK cell derived from an iPSC

Table 1 (continued)

Therapeutic approach	Number of studies	CT number	Status	Phase	The product used
CD34+ cells	1	NCT04522817	Not yet recruiting	I	Peripheral blood-derived autologous CD34+ cells
Acellular product	1	NCT04384445	Recruiting	I/II	Zofin; human amniotic fluid (HAF)
Monoclonal antibody	80	NCT04413838	Not yet recruiting	II	Nivolumab
		NCT04268537	Not yet recruiting	II	PD-1 blocking antibody
		NCT04464395	Recruiting	I	monoclonal antibody targeting the CD73
		NCT04334044	Recruiting	I/II	Ruxolitinib is an inhibitor of JAK1/2
		NCT04390464	Recruiting	IV	Ravulizumab/Baricitinib
		NCT04331665	Not yet recruiting	-	Ruxolitinib
		NCT04439006	Recruiting	II	Ibrutinib
		NCT04346277	Available	-	IC14, against human CD14
		NCT04441918	Recruiting	I	Anti-SARS-CoV-2
		NCT04354766	Recruiting	-	Anti-SARS-CoV-2
		NCT04425629	Recruiting	I/II	Anti-Spike (S)
		NCT04426695	Recruiting	I/II	Anti-Spike (S)
		NCT04483375	Recruiting	I	Anti-SARS-CoV-2
		NCT04409509	Recruiting	II	Garadacimab; anti-factor XIIa
		NCT04391309	Not yet recruiting	II	Antibody to CD14
		NCT04351152	Recruiting	III	Lenzilumab; anti GM-CSF
		NCT04341116	Recruiting	I/II	Anti GM-CSF
		NCT04519437	Recruiting	I	Anti-Spike (S)
		NCT04432298	Recruiting	II	Pamrevlumab; anti-Connective tissue growth factor
		NCT04545060	Recruiting	II/III	Anti-SARS-CoV-2
		NCT04452318	Recruiting	III	Anti-Spike (S)
		NCT04429529	Active, not recruiting	I	Anti-SARS-CoV-2
		NCT04324021	Recruiting	II/III	Emapalumab/anakinra
		NCT04561076	Not yet recruiting	I	Anti-Spike (S)
		NCT04351243	Recruiting	II	Gimsilumab; Anti GM-CSF
		NCT04343651	Active, not recruiting	II	Leronlimab; Anti-CCR5
		NCT04386239	Not yet recruiting	I	Sarilumab; Anti-IL-6
		NCT04357808	Recruiting	II	Sarilumab; Anti-IL-6
		NCT04305106	Recruiting	-	Bevacizumab; Anti-VEGF
		NCT04570397	Not yet recruiting	III	Ravulizumab; Anti- Complement component 5
		NCT04435184	Recruiting	II	Crizanlizumab; anti-P-selectin
		NCT04377750	Recruiting	IV	Tocilizumab; anti-IL-6R
		NCT04516564	Recruiting	I	AK119; anti-CD73
		NCT04519424	Not yet recruiting	II	CSL324; anti-GCSF
		NCT04447469	Recruiting	II/III	Mavrilimumab; anti-GM-CSF-Rα
		NCT04397497	Not yet recruiting	II	Mavrilimumab; anti-GM-CSF-Rα
		NCT04454398	Recruiting	I	Anti-Spike (S)
		NCT04476979	Recruiting	II	Tocilizumab; anti-IL-6R
		NCT04347239	Recruiting	II	Leronlimab; anti-complement component 5
		NCT04324073	Active, not recruiting	II/III	Sarilumab; anti-IL-6
		NCT04365153	Active, not recruiting	II	Canakinumab; anti-IL-1-β
		NCT04322773	Recruiting	II	Tocilizumab; anti-IL-6R
		NCT04331808	Active, not recruiting	II	Tocilizumab; anti-IL-6R
		NCT04355494	Available	-	Eculizumab; anti-complement component 5
		NCT04369469	Recruiting	III	Ravulizumab; anti-complement component 5
		NCT04445272	Recruiting	II	Tocilizumab
		NCT04479358	Recruiting	II	Tocilizumab
		NCT04317092	Recruiting	II	Tocilizumab
		NCT04345445	Not yet recruiting	III	Tocilizumab
		NCT04412772	Recruiting	III	Tocilizumab
		NCT04331795	Recruiting	II	Tocilizumab
		NCT04377659	Recruiting	II	Tocilizumab
		NCT04412291	Recruiting	II	Tocilizumab/anakinra
		NCT04359667	Not yet recruiting	II	Tocilizumab
		NCT04335071	Recruiting	II	Tocilizumab
		NCT04372186	Active, not recruiting	III	Tocilizumab
		NCT04356937	Active, not recruiting	III	Tocilizumab
		NCT04320615	Completed	III	Tocilizumab
		NCT04377503	Not yet recruiting	II	Tocilizumab
		NCT04363736	Completed	II	Tocilizumab
		NCT04363853	Recruiting	II	Tocilizumab
		NCT04361032	Not yet recruiting	III	Tocilizumab
		NCT04409262	Recruiting	III	Tocilizumab
		NCT04424056	Not yet recruiting	III	Anakinra, Tocilizumab, Ruxolitinib
		NCT04332913	Recruiting	-	Tocilizumab
		NCT04335305	Recruiting	II	Tocilizumab, Pembrolizumab
		NCT04560205	Recruiting	I	Tocilizumab
		NCT04306705	Recruiting	-	Tocilizumab
		NCT04310228	Recruiting	-	Tocilizumab
		NCT04315480	Active, not recruiting	II	Tocilizumab
		NCT04339712	Recruiting	II	Anakinra, Tocilizumab
		NCT04519385	Completed	-	Tocilizumab
		NCT04423042	Not yet recruiting	III	Tocilizumab
		NCT04492501	Completed	-	Tocilizumab
		NCT04380519	Completed	II/III	Olokizumab

Table 1 (continued)

Therapeutic approach	Number of studies	CT number	Status	Phase	The product used
		NCT04330638	Recruiting	III	Anakinra, Tocilizumab, Siltuximab
		NCT04486521	Recruiting	-	Tocilizumab
Nanoparticle	6	NCT04378244	Not yet recruiting	I	DeltaRex-G; mimic RNA virus SARS-CoV-2 by binding to viral receptors in human cells and may serve as a decoy
		NCT04517162	Recruiting	I	
		NCT04385095	Recruiting	II	
		NCT04276987	Completed	I	Polymerized-type I collagen
		NCT04491240	Enrolling by invitation	I/II	Inhaled IFN-β
		NCT04493242	Not yet recruiting	II	MSCs-derived exosomes
					MSCs-derived exosomes
					BM-derived MSC
Polyclonal antibody	1	NCT04453384	Recruiting	II	Swine glyco-humanized polyclonal antibody

NK cells in COVID-19 treatment

- NK cells are an essential part of the innate immune system and play an important role in mediating virus-induced immune responses. So, interventional therapies using NK cells have been developed for the COVID-19 treatment. Recently, the adoptive transfer of allogenic NK cells has been developed to boost the antiviral immune responses and clearance of the infected cells in COVID-19 patients (NCT04344548, NCT04280224). NKG2D-ACE2 CAR-NK is an off-the-shelf product that has been investigated in a phase I/II clinical trial (NCT04324996). These cells simultaneously target ACE2 (the main receptor for SARS-CoV-2) [29] and NKG2D on the infected cells and removed them. Therefore, they could inhibit the SARS-CoV-2 infection through ACE2 blockade.

Monoclonal antibodies in COVID-19 treatment

- It has been shown that monoclonal antibodies could be a promising treatment approach for COVID-19. Monoclonal antibodies against inflammatory cytokines such as anti-IL-1 receptor, IL-6 antagonist, anti-TNF-α,

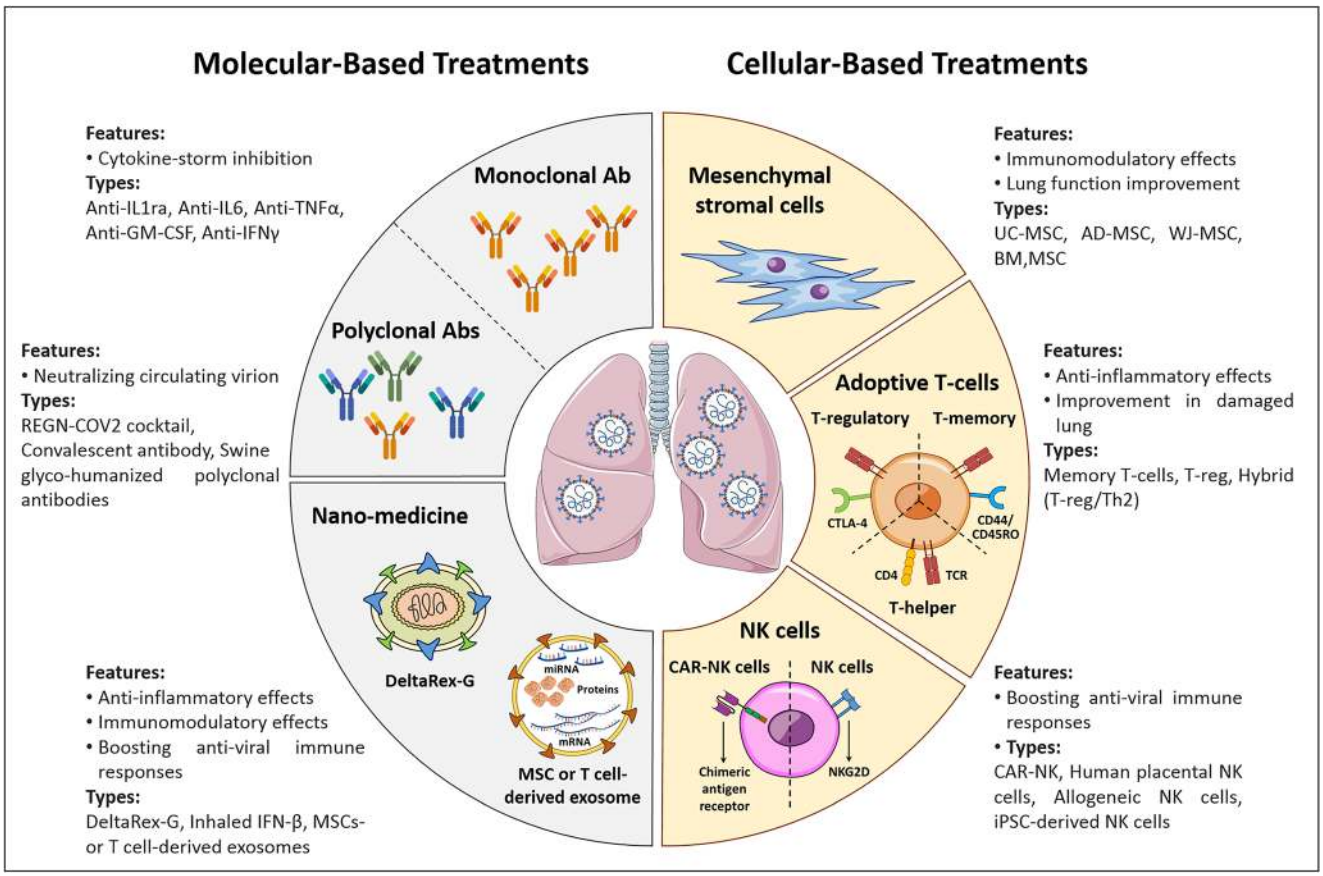
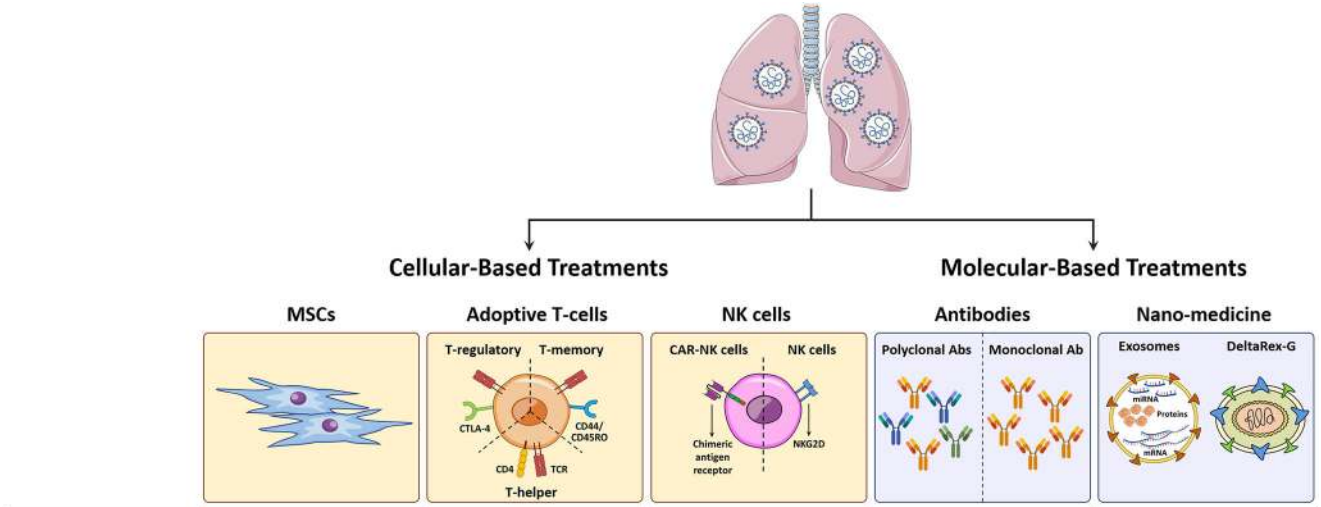


Fig. 1 Overview of molecular- and cellular-based treatments



	MSCs	Adoptive T-cells	NK cells	Antibodies	Nano-medicine
Safety	✓	✓	✓	✓	✓
Efficiency	✓	✓	✓	✓	✓
Boosting anti-viral immune responses	✗	✓	✓	✗	✓
Inflammation alleviation	✓	✓	✗	✓	✓
Lung function improvement	✓	✓	✗	✗	✓
Neutralizing circulating virion	✗	✗	✗	✓	✗

Fig. 2 Comparative analysis of therapeutic approaches to treat COVID-19

anti-GM-CSF, anti-IFN-γ, and C5a inhibitor have been studied in different clinical trials. Over 60 clinical trials have been registered to evaluate the treatment efficiency of Tocilizumab and Olokizumab (anti-IL-6 mAbs) [30–33]. The published studies showed that Tocilizumab (anti-IL-6 mAb) could improve the outcomes in COVID-19 patients and inhibit a cytokine storm [34]. Anakinra (IL-1ra) [35, 36] also showed beneficial effects for the treatment of COVID-19 patients and could decrease the mechanical ventilation need. Moreover, REGN-COV2 has been developed and consists of two neutralizing antibodies (REGN10987 + REGN10933) targeting SARS-CoV-2 spike protein [37, 38].

Nano-medicine in COVID-19 treatment

- Using nano-medicine including aerosol inhalations of therapeutic agents attracts lots of attention. Recent studies have investigated the efficiency and safety of the MSC-derived exosome (NCT04491240, NCT04276987) and interferon beta inhalation (NCT04385095).

Now, most of the mentioned studies are ongoing. The growing number of clinical trials in this field could provide more validated designs and higher quality data. In this context, the increase in international collaborations to provide larger number of patients will be helpful to obtain more definite results [39]. Identifying the exact mechanisms of the COVID-19 immunopathogenesis will ensure the development of more effective therapies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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