Antibody Therapy: From Diphtheria to Cancer, COVID-19, and Beyond

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Abstract

The dawn of the 20th century saw the formative years of developments in immunology. In particular, immunochemistry, specifically pertaining to antibodies was extensively studied. These studies laid the foundations for employing antibodies in a variety of ways. Not surprisingly, antibodies have been used for applications ranging from biomedical research to disease diagnostics and therapeutics to evaluation of immune responses during natural infection and those elicited by vaccines. Despite recent advancements in cellular immunology and the excitement of T cell therapy, use of antibodies represents a large proportion of immunotherapeutic approaches as well as clinical interventions. Polyclonal antibodies in the form of plasma or sera continue to be used to treat a number of diseases including autoimmune disorders, cancers and infectious diseases. Historically, antisera to toxins have been the longest serving biotherapeutics. In addition, intravenous immunoglobulins (IVIg) have been extensively used to treat not only immunodeficiency conditions but also autoimmune disorders. Beyond the simplistic suppositions of their action, the IVIg have also unraveled the immune regulatory and homeostatic ramifications of their use. The advent of monoclonal antibodies (MAbs), on the other hand, have provided a clear pathway for their development of as drug molecules. MAbs have found a clear place in the treatment of cancers and extending lives and have been used in a variety of other conditions. In this review, we capture the important developments in the therapeutic applications of antibodies to alleviate disease, with a focus on some of the recent developments.

Introduction

Antibodies are indispensable components of the immune system. The tryst of antibodies with therapeutic applications began with Emil von Behring and Paul Ehrlich at the end of the 19th century into the 20th century. Combined with the seminal work of Karl Landsteiner and the exemplary contributions of a host of other scientists, the early part of the 20th century set the stage for the understanding of antibodies as biochemical molecules and their functional characteristics. Furthermore, hybridoma technology provided the much-needed impetus to take antibody to a whole new level of wide-ranging applications in medical interventions. Antibodies are now a versatile tool for diagnostics and therapy of various conditions in humans and animals.

Serum/plasma therapy

Serum or plasma therapy involves the passive transfer of pre-existing or pre-formed antibodies and serves as a ready-made armor against pathogens which have invaded the body. Plasma/serum therapy has been used against toxins, poisons & venoms, and infectious agents, including for the first time in any pandemic, the 1918 influenza pandemic, where serum from recovered patients was used to treat acutely ill patients [1]. By the early 20th century, plasma therapy was employed for the treatment of bacterial infections [2] and viral diseases such as measles [3] and polio[4]. The discovery of antibody purification through ethanol fractionation of plasma [5] was later adapted for many polyclonal antibody products.

The diphtheria antitoxin can neutralize the circulating toxin and has been used for clinical treatment since the late 1800s [6,7]. Similarly, the botulinum antitoxin effectively binds to the free toxin in the blood and prevents the progression of the symptoms, although it cannot reverse the paralysis that has already set in [8]. Antivenins were first successfully used in humans in

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1896 [9]. The antivenins are typically produced against poisons of various animal species, most commonly snakes, spiders and jellyfish, existing in the pertinent geographic regions, and are either whole IgG molecules or the F(ab')2 or Fab fragments.

Treatment with antibodies has also been employed against several viruses. The smallpox vaccine was frequently associated with a number of serious adverse events (SAE), which had to be managed by administering the vaccinia immune globulin (VIG). The VIG was also used to prevent smallpox among close contacts of patients with the disease [10]. Post-exposure prophylaxis of rabies involves a combination of active immunization and passive Ig therapy. The anti-rabies Ig is typically derived from vaccinated equines or humans, but these are gradually being replaced by monoclonal antibodies (MAbs) [11,12]. Hepatitis B immune globulin (HBIG) is used to provide short-term protection against hepatitis B infection. A combination of hepatitis B vaccine and one dose of HBIG produces immediate and sustained high levels of protective antibody against hepatitis B [13]. The HBIG is also being explored in the treatment of chronic hepatitis B [14]. Varicella zoster immunoglobulin (VZIG) is administered to reduce the severity of the disease [15,16]. Virus neutralizing antibodies (NAb) targeting the epitopes on the varicella-zoster virus (VZV) envelope fusion proteins gH or gH-gL complex, which mediate virus entry, may replace the VZIG for antibody therapy [17,18]. In the case of human cytomegalovirus (HCMV), identification of potent neutralizing antibodies against the HCMV gH/gL/pUL128-131 complex [19,20] has led to the development of therapeutic antibodies to improve transplantation outcomes [21]. For respiratory syncytial virus (RSV), various polyclonal antibody and MAb formulations are being explored for their therapeutic potential [22,23].

Specific plasma therapy received renewed attention in recent times for use against deadly infectious diseases. One such disease is the Middle Eastern Respiratory Syndrome (MERS),

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caused by MERS coronavirus (MERS-CoV), which has a case fatality rate of 35%. Owing to the small number of donors and insufficient antibody titers in convalescent plasma, establishing homo-specific plasma therapy for MERS has been difficult, and hence, equine and dromedary camel antibodies have been explored as alternatives [24,25]. Serum from dromedary camels was demonstrated to reduce the severity of the lung pathology and viral load in a mouse model [25]. Similarly, purified equine IgG and $F(ab')_2$ raised against MERS-CoV was demonstrated to neutralize the virus *in vitro*, and reduced the virus load in a mouse model [24]. However, neither have been used for treatment of humans suffering from MERS. During the Ebolavirus disease (EVD) outbreak in 2013–2016, antibody-based treatments were evaluated for their preventive or therapeutic potential. Plasma therapy for EVD was found to be safe, but no significant survival benefit was recorded [26]. Polyclonal sera produced in cattle engineered to generate human antibodies (transchromosomic cows) provided 90% protection in a mouse model of lethal EVD [27], and protected all the treated non-human primates (NHPs) when administered on 1st or 3rd day post-challenge [28]. In addition, anti-MERS-CoV antibodies produced in transchromosomic cows were found to be safe in Phase I clinical trials [29].

A major application of plasma/serum therapy against infectious disease has been during the currently on-going pandemic of coronavirus disease – 2019 (COVID-19), which is caused by severe acute respiratory syndrome CoV-2 (SARS-CoV-2). In the initial phase of the pandemic, this was the only option that was explored. This stemmed from the fact that infusion of convalescent plasma was found to provide beneficial clinical outcome against SARS [30], which is caused by the related virus, SARS-CoV-1. Several studies, including randomized controlled trials (RCTs) as well as observational studies, showed favorable trends in terms of viral load, oxygen demand, progression to intensive care, recovery time and/or death [31-33].

Mechanistically, besides the obvious effect of antibodies, the reversals in disease severity could be attributed to transient reduction in detrimental cytokines and changes in lymphocyte subpopulations [34]. However, plasma therapy could not attain the status of standard care owing to its application based on clinician's judgment of risk versus benefit to individual patients, lack of sufficient data from RCTs and uncertainties about its efficacy.

Polyclonal antibodies contained in the plasma/serum target multiple epitopes and are likely to protect even against escape mutants of pathogens. However, the disadvantages of the use of plasma/serum are batch-to-batch inconsistencies [35], low content of specific antibodies [36,37], risks of adventitious agents [38], and development of allergic reactions [8]. In addition, although robust neutralizing antibody (NAb) responses are produced against acute viral infections in the majority of individuals, some viruses such as human immunodeficiency virus (HIV) [39,40], influenza virus [41], Lassa virus [42,43], Ebola virus and SARS-CoV-2 [44] are known to induce NAb responses at much lower levels, possibly making plasma therapy ineffective for these viral infections. Variation in the structural proteins of viruses such as HIV and influenza virus could also influence the success or failure of antibody therapy. Inconsistent NAb titer in the convalescent plasma was a major drawback which limited its use against COVID-19.

Intravenous immunoglobulin (IVIg) therapy

Intravenous immunoglobulin (IVIg) is prepared from normal plasma obtained from thousands of healthy donors. It consists of IgG, IgA, traces of other Ig's, cytokines, and soluble receptors. The IVIg preparations are approved for use in immunotherapy of a variety of diseases. IVIg modulate both innate and adaptive immune systems through several mechanisms such as (a) neutralization of activated complement components [45-47]; (b) inhibition of activation and

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functions of innate immune cells such as dendritic cells [48,49], monocytes, macrophages [50-53], neutrophils [54] and NK cells [55,56]; (c) modulation of B cell functions [57,58] and its activation through toll-like receptors (TLR) [59,60], B-cell receptors [61] and IL-4 + CD40 [62]; (d) enhancing the differentiation of plasma cells [63]; and (e) reciprocal regulation of regulatory T (Treg) cells [64] and effector T cells such as Th1 and Th17 subsets, and downregulation of the production of inflammatory cytokines [65-68].

Apart from their use in immune disorders, IVIg have been used for various human infectious diseases. The beneficial effects of IVIg have been demonstrated against various bacterial infections such as severe invasive group A streptococcal disease, streptococcal toxic shock syndrome, necrotizing *Staphylococcus aureus* sepsis, recurrent bacterial infections in patients with hypogammaglobulinemia, polyneuropathy associated with *Campylobacter jejuni*, recurrent *Clostridium difficile* colitis, *Chlamydia* pneumonia and *Salmonella typhimurium* infections. The IVIg therapy has anti-inflammatory effects and can neutralize bacterial toxins with varying efficacy [69]. Higher doses of IVIg are recommended as a last resort of treatment for specific conditions like recurrent *Clostridium difficile* colitis and other bacterial diseases. IVIg were also demonstrated to be beneficial against viral infections and diseases such as West Nile, childhood HIV, parvovirus B19, HCMV-induced pneumonitis following transplantation, genital herpes, enteroviruses and VZV. Further details about the applications of IVIg in infectious diseases are reviewed elsewhere [70,71].

Monoclonal antibodies as therapeutic agents

Monoclonal antibody (MAb) therapy has gained a lot of traction in recent times. MAbs bind to specific epitopes in the target antigen. Initially, the application of MAbs was restricted to development of diagnostics; therapeutic application was constrained by the immunogenic

potential and poor efficacy due to the lack of effector function associated with murine antibodies. The United States Food and Drugs Administration (US FDA) approved the first therapeutic MAb (muromonab-CD3) of murine origin in 1986. Subsequently, modified antibodies consisting of murine variable domain and human constant domain were developed and shown to have lower side-effects without compromising the binding ability and led to the approval of the chimeric MAbs for various indications *viz.*, cancer, infectious diseases, genetic diseases, allergic conditions, etc. The MAbs were further humanized to contain only the complementary-determining region (CDR) of murine origin in a human antibody backbone, by employing the CDR grafting technique [72]. The next generation antibodies were fully human MAbs generated through phage display [73,74], transgenics [75,76] and B cell cloning techniques. MAbs produced through phage display have been used to target tumor necrosis factor α (TNFα) [77], B-lymphocyte stimulator [78], vascular endothelial growth factor receptor-2 [79], epidermal growth factor receptor [80], interleukin-23 [81], programmed cell death ligand 1 [82], plasma kallikrein [83], interferon γ (IFNγ) [84], and CD22 conjugated with a toxic fragment of *Pseudomonas* exotoxin A [85]. The pioneering work on B cell cloning and expansion from human peripheral blood mononuclear cells (PBMC's), followed by immortalization with Epstein-Barr virus [86,87] or isolation of human PBMC's or plasmablasts and cloning the antibody heavy and light chain genes [88-90] has advanced human MAb field rapidly. Numerous human anti-SARS-CoV-2 MAb candidates have been derived from PBMC's and are under various stages of development. Antibodies are also being engineered to be bi-specific, where each arm is specific to a different antigen. There are multiple therapeutic bi-specific antibody candidates under development and these are reviewed elsewhere [91].

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Immunotherapy is an emerging arena for the treatment of cancer [92-94], and encompassed vaccines, oncolytic viruses, immune checkpoint regulators and adoptive transfer of ex-vivo activated T and NK cells. In this review, we focus on MAb therapy of cancers. Antibodies can recognize specific targets on tumor cells *via* their Fab domain and engage components of the immune system *via* the Fc region to destroy the tumor cells. The IgG subclass is mostly used in these treatments due to its ability to interact with the Fcγ receptor (FcγR) on macrophages and natural killer cells which are crucial for anti-cancer immune functions. The effector mechanisms are due to receptor or ligand blocking, and antibody- or complement-mediated cytotoxicity or phagocytosis. MAbs may either directly attack the tumor cells or in can be conjugated to a toxin, drug or a radioisotope which have antitumor effects [95].

Another way to treat cancers is to target immune check point mediators, which modulate immune homeostasis and hence are necessary for self-tolerance. Tumor cells manipulate the checkpoint by binding to T-cell receptors thereby switching them "off". The immune checkpoint inhibitors (ICI) prevent inactivation of T-cells thereby allowing them to eliminate the mutant cells [96]. The targets of ICIs include cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed death protein-1 (PD-1) and its ligand PDL-1 [97,98]. The inhibitory receptor CTLA-4 prevents T-cell activation when bound to the B7 receptor on APCs [99]. Ipilimumab, the MAb against CTLA-4 was the first ICI approved by the US FDA for the treatment of melanoma. However, the use of these antibodies had resulted in immune-related adverse events (irAE) in 10-30% of the patients [100]. In case of PD-1 receptor, its binding to PDL-1 on tumor cell suppresses T-cell activation. The anti-PD-1 antibodies, Pembrolizumab and Nivolumab and the anti-PDL-1 antibodies, Atezolizumab, Avelumab and Duvalumab effectively inhibit the PD-1 and PDL-1 interaction, resulting in activation of T-cells. In clinical trials, a combination to

Ipilimumab and Nivolumab has shown good clinical outcome in patients with metastatic melanoma [101,102]. A list of MAbs approved for clinical use are provided in Table 1.

Among the infectious agents, viruses are obligate intracellular pathogens and are not inhibited by antibiotics. Several therapeutic interventions have been devised against viral infections [103]. In the case of rabies virus, cocktails consisting of two MAbs have been demonstrated to have broader virus neutralizing ability compared to formulations with only one MAb [11]. With RSV, Palivizumab, which recognizes an epitope in the fusion protein [104,105], was shown to reduce hospitalization by 55% in premature infants and in those with bronchopulmonary dysplasia [106].

Three MAb therapies have been evaluated in clinical trials against EVD. A single MAb, mAb114, which targets the receptor binding domain (RBD) of the Ebola virus glycoprotein (GP), was found to be effective [107]. REGN-EB3, a combination of three MAbs produced in humanized mice [108,109], binds to non-overlapping epitopes of GP, and neutralizes Ebola virus and triggers FcγRIIIa. Both mAb114 [110] and REGN-EB3 [111] have been found to be safe, and to significantly reduce the high fatality rate of EVD in humans [112]. ZMapp, another combination of three chimeric MAbs produced in the plant *Nicotiana benthamiana*, was superior by 91.2% when compared to the standard of care alone [113].

Various approaches were followed for the development of neutralizing MAbs against MERS-CoV. These were primarily derived from infected patients [114-118], immunized mice [119-122] or naïve human antibody libraries [123-125]. Most of these antibodies target the RBD of the MERS-CoV Spike protein and interfere in the virus entry through human dipeptidyl peptidase-4. In a marmoset model of MERS, the MAb combination of REGN3048 and

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REGN3051 proved efficacious in a prophylactic regimen [117] and the Phase I human clinical trial results are not yet published [126].

MAbs for COVID-19 therapy

Owing to the close relatedness of SARS-CoV-2 to SARS-CoV-1, initial efforts of MAb therapy against the former focused on repurposing anti-SARS-CoV-1 MAbs with cross-neutralizing activity against SARS-CoV-2 [127,128]. Later, memory B cells specific to the RBD of SARS-CoV-2 S protein were used to generate SARS-CoV-2-specific IgG1 MAbs [129]. These antibodies block the interaction between SARS-CoV-2 and its receptor, angiotensin converting enzyme – 2 (ACE2). Since then, several MAbs have been used in therapeutic intervention of COVID-19. Most of them target the RBD and interfere with the RBD-ACE2 interaction, preventing the entry of SARS-CoV-2 into cells [130-135]. The list of MAbs that are currently in various phases of clinical trial is provided in Table 2. In addition, antibodies binding to the N-terminal domain of S protein [136,137] or a distinct proteoglycan epitope [138] have been demonstrated to neutralize SARS-CoV-2, and could be developed for therapeutic purposes.

Therapeutic antibody preparations for COVID-19 with single NAb could be ineffective over time due to the emergence of escape mutants, as demonstrated for instance with hepatitis B virus [139] or RSV [104], or it can have a broader neutralizing ability as shown with rabies virus [11] or SARS-CoV-2 [138]. The emergence of SARS-CoV-2 variants such as the UK variant (SARS-CoV-2 VOC 202012/01) and the South African variant (SARS-CoV-2 501Y.V2) with the potential to escape single MAb therapy has led to the viewpoint that combinatorial MAb therapy is better for effective treatment [140].

A cocktail of REGN10933 and REGN10987, which target non-overlapping epitopes on the SARS-CoV-2 spike protein is in Phase 3 clinical trials. This combination has been shown to

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markedly reduce respiratory viral load in a non-human primate model, even when the animals were challenged with 10-fold higher virus load [141]. In Phase 1-3 clinical trial, where non-hospitalized COVID-19 positive patients were enrolled, this cocktail was able to reduce the viral load by two logs as compared to subjects who received the placebo [142].

Another example of a cocktail is AZD7442, a combination of AZD8895/Tixagevimab and AZD1061/Cilgavimab, which recognize non-overlapping epitopes on the RBD and function in synergy [143,144]. These antibodies are optimized with half-life extension and reduced Fc receptor binding and hence called Long Acting AntiBodies (LAAB). Based on the earlier studies [145-147], the half-life extension is expected to protect from COVID-19 for 6 to 12 months and the modification in the Fc region reduces the risk of antibody dependent enhancement (ADE) of the disease. This AZD7442 cocktail demonstrated prophylactic and therapeutic efficacy in mice transiently expressing ACE2 as well as in immunocompetent mice. Sotrovimab (VIR-7831) is a human MAb was isolated from SARS-CoV-1 convalescent memory B cells. It recognizes a proteoglycan motif, and its neutralization effect is due to steric interference rather than competing with receptor attachment [138]. It is currently being evaluated in Phase III clinical trial (NCT04545060).

Regdanvimab (CT-P59) is a human MAb which potently neutralizes SARS-CoV-2 isolates including the D614G variant without the ADE effect. Structural studies show that Regdanvimab binds to the receptor-binding motif within SARS-CoV-2 RBD. CT-P59 was initially shown to be effective against SARS-CoV-2 in pre-clinical studies in ferrets, hamsters and rhesus monkeys [148]. Preliminary efficacy data indicate that CT-P59 significantly reduces by >50% the proportion of patients requiring hospitalization or oxygen therapy, as compared to the placebo group [149].

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Another potential therapeutic NAb candidate named LY-CoV555 (Bamlanivimab) is not modified in the Fc region. Non-human primate challenge studies indicated that LY-CoV555 was effective in reducing the virus replication in the upper and the lower respiratory tract [150]. In Phase II clinical trials, a majority of the subjects showed viral clearance by day 11 [151]. In a randomized Phase II/III trial, however, Bamlanivimab monotherapy failed to significantly reduce viral load, but the combination therapy of Bamlanivimab and Etesevimab significantly reduced SARS-CoV-2 viral load at day 11 [152]. The clinical trial outcomes of other neutralizing MAb are yet to be published.

Another area of immunotherapy for COVID-19 has been to dampen the hyper-immune response which appears to be directly correlated with the severity of disease. Increased concentrations of granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage CSF (GM-CSF), INFγ, interleukin (IL)-1β, IL-2, IL-6, IL-7, IL-8, IL-9, IL-17, C-X-C motif chemokine 10 (CXCL10), chemokine ligand 2 (CCL2), CCL3 and CCL4 have been observed in severely affected patients. Therefore, several of these cytokines and chemokines have been targeted for mitigating the inflammatory response, and include IL-6 receptor (IL-6R), IL-6, GM-CSF and IL-1β. Summary of the status of these therapeutics are provided in Table 3.

Perspective

Antibody therapy has become pivotal against cancers and emerging pathogens, especially those pathogens that cause acute hemorrhagic fever or hyper-inflammatory conditions such as a cytokine storm. Both polyclonal (plasma/serum) and monoclonal antibody therapy have distinct advantages and disadvantages. Plasma/serum is very likely to contain multi-specific antibodies that can function through binding more than one region in an antigen or more than one antigen on a pathogen. Any inter-host variation in antigenic determinants of the pathogen is likely to be

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circumvented by polyclonal antibodies. However, standardization in terms of quantifiable levels, affinity and avidity, potency (e.g., neutralization levels) as well as freedom from adventitious agents are an issue with plasma/serum therapy, besides hypersensitivity reactions related to the use of sera from heterologous species as well as transfusion-related histo-incompatibility reactions related to heterologous individuals are a deterrent for the use of convalescent or immune plasma/sera. Additional challenges include acquiring patients, adequate availability of plasma and harvesting at an appropriate time. On the other hand, MAbs provide high specificity, consistent affinity and avidity, and antigen specificity, besides being amenable to reliable quality control during the production process. However, single MAb therapy could be ineffective in cases where the pathogen frequently mutates, or could even drive the emergence of variant strains. Hence, recent research has focused on deriving MAbs reactive to conserved epitopes or to use a combination of two or more MAbs together. And yet, clinical use of MAb has been skewed towards treating cancer or to treat inflammatory conditions, whereas only a handful of products are licensed for use against infectious diseases. However, together with the adoption of standardized procedures for the production of therapeutic antibodies, and the collaborative efforts driven by the COVID-19 pandemic, MAb therapy is likely become a benchmark for any future infectious disease outbreaks.

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critically reviewed and revised the manuscript. All the authors declare that there are no competing interests.

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Table 1: List of US FDA approved MAbs for immunotherapy of cancer

Target	Drug	Clinical use	Ref
Epidermal growth factor receptor (EGFR)	Necitumumab	Squamous non–small-cell lung cancer	[153]
	Cetuximab	Colorectal, head and neck cancer	[154]
	Panitumumab	Colorectal cancer	[155]
	Nimotuzumab	Squamous cell carcinoma, glioma	[156]
Vascular endothelial growth factor (VEGF)	Bevacizumab	Anti-angiogenic therapy	[157]
CD19-dircted CD3 T-cell engager	Blinatumomab	Acute lymphoblastic leukemia (ALL) Diffuse Large B-cell Lymphoma	[158]
CD20	Ibritumomab	Non-Hodgkin's lymphoma	[159]
	Rituximab	Non-Hodgkin's lymphoma	[160]
	Tositumomab	Non-Hodgkin's lymphoma	[161]
	Ofatumumab	Chronic lymphocyte leukemia and multiple sclerosis	[162]
	Obinutuzumab	chronic lymphocytic leukemia (in combination with chlorambucil)	[163]
CD33 (myeloid cell surface antigen on	Gemtuzumab	Acute myeloid leukaemia	[164]

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leukemia cells)			
CD38	Daratumumab	Multiple myeloma.	[165]
CD52	Alemtuzumab	Chronic lymphocytic leukemia	[166]
HeR2/neu receptor	Trastuzumab	Breast cancer	[167]
PD-1	Pembrolizumab	cervical cancer head and neck squamous cell carcinoma	[168]
	Nivolumab	Renal cell cancer Hodgkins lymphoma squamous cell carcinoma of the head and neck	[169]
PD-L1	Avelumab	Merkel cell carcinoma Non-small cell lung cancer	[170]
	Durvalumab	urothelial cancers Unresectable stage III non-small cell lung cancer	[171]
	Atezolizumab	In combination with carboplatin and etoposide for treatment of small cell lung cancer, In combination with cobimetinib and vemurafenib for patients with BRAF V600 mutation-positive	[172]

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		unresectable or metastatic melanoma.	
SLAM F7	Elotuzumab	Multiple myeloma (used in combination with lenalidomide and dexamethasone)	[173]
Disialoganglioside (GD2)	Dinutuximab	Neuroblastoma in pediatric patients	[174]
CTLA-4	Ipilimumab	Melanoma	[175]

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Table 2: MAbs against SARS-CoV-2 S protein that are in clinical trials*

Product Name	Status	Developer
REGN-COV2 (REGN10933/Casirivimab + REGN10987/Imdevimab)	Phase 3	Regeneron/NIAID
Bamlanivimab (LY3819253, LY-CoV555)	Phase 3	AbCellera/Eli Lilly/NIH
Sotrovimab (VIR-7831/GSK4182136)	Phase 3	Vir biotechnology/GSK
AZD7442 (AZD8895/Tixagevimab + AZD1061/Cilgavimab)	Phase 3	AstraZeneca/Vanderbilt University Medical Center/DARPA/BARDA
Regdanvimab (CT-P59)	Phase 3	Celltrion
DXP-593	Phase 2	Beigene/Singlomics Biopharmaceuticals/Peking University
Etesevimab (JS016, LY-CoV016, LY3832479)	Phase 2	Junshi Biosciences/Institute of Microbiology, Chinese Academy of Sciences/Eli Lilly
DZIF-10c	Phase 2	University of Cologne/The German Center for Infection Research/ BoehringerIngelheim
COVI-AMG (STI-2020)	Phase 2	Sorrento Therapeutics
STI-1499/COVI-SHIELD	Phase 1	Sorrento/Mount Sinai Health System
TY027	Phase 1	Tychan

BRII-196	Phase 1	Brii Bio/TSB Therapeutics/Tsinghua University
BRII-198	Phase 1	Brii Bio/TSB Therapeutics/Tsinghua University
SCTA01	Phase 1	Sinocelltech Ltd/Chinese Academy of Sciences
MW33	Phase 1	Mabwell (Shanghai) Bioscience Co., Ltd.
HFB30132A	Phase 1	HiFiBiO Therapeutics
HLX70	Phase 1	Hengenix Biotech Inc
ADM03820	Phase 1	Ology Bioservices

*Table modified from COVID-19 Therapeutic Antibody Tracker to include the products which are in clinical trial (https://chineseantibody.org/covid-19-track) **[109]**

Table 3: MAbs targeting the host proteins to treat COVID-19[#]

Product Name	Target	Status	Developer
Itolizumab (EQ001, H-T1, T1-h)	CD6	Approved	Biocon
Levilimab (BCD-089)	IL-6R	Approved	BIOCAD
Tocilizumab	IL-6R	Phase 4	Hoffmann-La Roche/multiple sponsors
Ravulizumab-cwvz	C5	Phase 4	Alexion Pharmaceuticals/Cambridge University Hospitals NHS Foundation Trust
Sarilumab (SAR153191, Kevzara)	IL-6R	Phase 4	Regeneron/Sanofi/multiple sponsors
Siltuximab	IL-6	Phase 3	University Hospital, Ghent/A.O. Ospedale Papa Giovanni XXIII
Lenzilumab	GM-CSF	Phase 3	Humanigen
Canakinumab	IL-1β	Phase 3	Novartis
CD24Fc (SACCOVID)	DAMPs, Siglec G/10	Phase 3	OncoImmune
Olokizumab	IL-6	Phase 3	R-Pharm JSC/Cromos Pharma
Leronlimab (PRO-140)	CCR5	Phase 3	CytoDyn

Emapalumab (Gamifant)	IFN gamma	Phase 3	Swedish Orphan Biovitrum
Bevacizumab	VEGF	Phase 3	Qilu Hospital of Shandong University/Renmin Hospital of Wuhan University/IalyMoriggiaPelasciniGravedona Hospital S.p.A/Wuhan University/Jiangbei Union Hospital of Huazhong University of science and technology/Shandong Provincial Chest Hospital
IFX-1 (BDB-001)	C5a	Phase 3	Staidson/InflaRx/Beijing Defengrei Biotechnology
Clazakizumab	IL-6	Phase 3	Medical University of Vienna/NYU Langone Health
RPH-104	IL-1	Phase 3	R-Pharm JSC, Cromos Pharma
Pamrevlumab(FG-3019)	Connective tissue growth factor (CCN2)	Phase 3	FibroGen, Inc.

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Mavrilimumab	GM-CSF receptor	Phase 3	Kiniksa Pharmaceuticals/multiple sponsors
UTTR1147A	IL-22R	Phase 2	Genentech
F-652	IL-22R	Phase 2	Generon(Shanghai) Corporation Ltd.
APG101	CD95 ligand	Phase 2	Apogenix GmbH
Crizanlizumab	P-selectin	Phase 2	Johns Hopkins University/Novartis/Socar Research SA/Brigham and Women's Hospital
Garadacimab (CSL312)	Factor XIIa	Phase 2	CSL Behring
Infliximab	TNF	Phase 2	Tufts Medical Center/NIH
APN01	SARS-CoV-2 S protein	Phase 2	APEIRON Biologics
Otilimab	GM-CSF	Phase 2	GSK
Avdoralimab	C5aR	Phase 2	Innate Pharma SA
Zansecimab (LY3127804)	Ang-2	Phase 2	Eli Lilly
Eculizumab	C5	Phase 2	Alexion Pharmaceuticals/Hudson Medical
Camrelizumab	PD-1	Phase 2	Jiangsu HengRuiMedicine/Southeast

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			University/Wuhan JinyintanHospital
Pembrolizumab	PD-1	Phase 2	MedicaScientia Innovation Research (MEDSIR)
Gimsilumab	GM-CSF	Phase 2	Roivant Sciences
Ixekizumab	IL-17A	Phase 2	Xiangya Hospital of Central South University
BMS-986253, HuMax-IL8, HuMax-Inflam/MDX018	IL-8	Phase 2	Bristol-Myers Squibb
Astegolimab	IL-33R	Phase 2	Genentech
Secukinumab (AIN457)	IL-17A	Phase 2	Lomonosov Moscow State University Medical Research and Educational Center
ATYR1923	Neuropilin-2	Phase 2	aTyr Pharma, Inc.
Axatilimab (SNDX-6352)	CSF-1R	Phase 2	Syndax Pharmaceuticals, Inc
NN8765, IPH-2201, NNC141-0100	NKG2A (CD159a)	Phase 2	Innate Pharma SA
CNTO 136	IL-6	Phase 2	Janssen
CERC-002	LIGHT	Phase 2	Cerecor
TJM2 (TJ003234)	GM-CSF	Phase 2	I-MAB
IC14	CD14	Phase 2	Implicit Bioscience
Meplazumab	CD147	Phase 2	Tang-Du Hospital
Adrecizumab(HAM8101)	Adrenomedulin	Phase 1	Adrenomed AG

CPI-006	CD73	Phase 1	Corvus Pharmaceuticals
hzVSFv13	Vimentin	Phase 1	ImmuneMed
Lanadelumab	kallikrein	Phase 1	Radboud University/Takeda
AK119	CD73	Phase 1	Akesobio
Daxdilimab (VBI7734)	ILT7	Phase 1	Viela Bio
Efineptakinalfa(GX-17)	IL-7R	Phase 1	NeoImmuneTech

[#] Table modified from COVID-19 Therapeutic Antibody Tracker to include the products which are in clinical trial (https://chineseantibody.org/covid-19-track) **[109]**.