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

Deepak Kumar, Sulgey Gauthami, Jagadeesh Bayry, Srinivas Kaveri, Nagendra Hegde

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Deepak Kumar[1], Sulgey Gauthami[2], Jagadeesh Bayry[3,4], Srinivas V. Kaveri[3,5] Nagendra R. Hegde[2]

[1] Ella Foundation, Genome Valley, Turkapally, Shameerpet Mandal, Hyderabad – 500078, India

[2] National Institute of Animal Biotechnology, Opp. Journalist Colony, Extended Q City Road, Near Gowlidoddi, Gachibowli, Hyderabad – 500032, India

[3]Institut National de la Santé et de la Recherche Médicale (INSERM) Unite 1138, Sorbonne Université, Centre de Recherche des Cordeliers, 15, Rue de l'Ecole de Médicine, 75006 Paris, France

[4] Indian Institute of Technology Palakkad, Palakkad, Kerala – 678557, India

[5]Institut National de la Sate et de la Recherche Médicale (INSERM) Unite 872, Centre de Recherche des Cordeliers, 15, Rue de l'Ecole de Médicine, 75006 Paris, France

[5] Centre National de la Recherche Scientifique (CNRS) Bureau India, IFI, 2 Dr APJ Abdul Kalam Road, New Delhi – 110001, India

Correspondance :

Nagendra R. Hegde (hegde@niab.org.in)

Srinivas Kaveri (srini.kaveri@cnrs.fr)

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

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.

References

1 Luke TC, Kilbane EM, Jackson JL, Hoffman SL: Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med 2006;145:599-609.

2 Casadevall A, Scharff MD: Serum therapy revisited: animal models of infection and development of passive antibody therapy. Antimicrob Agents Chemother 1994;38:1695-1702.

3 Janeway CA: Use of Concentrated Human Serum gamma-Globulin in the Prevention and Attenuation of Measles. Bull N Y Acad Med 1945;21:202-222.

4 Hammon WM, Coriell LL, Wehrle PF, Stokes J, Jr.: Evaluation of Red Cross gamma globulin as a prophylactic agent for poliomyelitis. IV. Final report of results based on clinical diagnoses. J Am Med Assoc 1953;151:1272-1285.

5 Kendrick DB: Blood program in World War II, Washington, D.C. : Office of the Surgeon General, Dept. of the Army : For sale by the Supt. of Docs., U.S. G.P.O, 1964,

6 MacGregor RR: Corynebacterium diphtheriae (Diphtheria), ed 8. Elsevier, 2015.

7 Acosta PLM, Susan Hariri, and Tejpratap S.P. Tiwari: Diphtheria; in Jennifer Hamborsky AK, Charles (Skip) Wolfe (ed): Epidemiology and Prevention of Vaccine-Preventable Diseases, 2020, pp 107-118.

8 Schussler E, Sobel, J., Hsu, J., Yu, P., Meaney-Delman, D., Grammer 3rd, L.C., Nowak-Wegrzyn, A.: Workgroup Report by the Joint Task Force Involving American Academy of

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Allergy, Asthma & Immunology (AAAAI); Food Allergy, Anaphylaxis, Dermatology and Drug Allergy (FADDA) (Adverse Reactions to Foods Committee and Adverse Reactions to Drugs, Biologicals, and Latex Committee); and the Centers for Disease Control and Prevention Botulism Clinical Treatment Guidelines Workgroup-Allergic Reactions to Botulinum Antitoxin: A Systematic Review. Clin Infect Dis 2017;66:S65-S72.

9 Calmette A: Sur le venin des serpents et sur l'emploi du sérum antivenimeux dans la thérapeutique des morsures venimeuses chez l'homme et chez les animaux. Annales de l'Institut Pasteur 1897;XII:214–237.

10 Wittek R: Vaccinia immune globulin: current policies, preparedness, and product safety and efficacy. Int J Infect Dis 2006;10:193-201.

11 Ding L, Wu, M., Zhang, H., Zhu, X., Hu Y., Li, X., Liu, J., Tsao, E., Liu, M., Li C.: Safety, pharmacokinetics and pharmacodynamics of SYN023 alone or in combination with a rabies vaccine: An open, parallel, single dose, phase 1 bridging study in healthy Chinese subjects. Antiviral Res 2020;184:104956.

12 WHO: Rabies monoclonal antibodies post exposure prophylaxis World Health Organization, 2016,

13 Szmuness W, Stevens CE, Oleszko WR, Goodman A: Passive-active immunisation against hepatitis B: immunogenicity studies in adult Americans. Lancet 1981;1:575-577.

14 NIH: Hepatitis B Immune Globulin (HBIg) to Restore Immune Control in People With Chronic Hepatitis B, 2018,

15 CPS: Varicella zoster immune globulin use in neonates and infants. Can J Infect Dis 1996;7:17-18.

16 Zaia JA, Levin MJ, Preblud SR, Leszczynski J, Wright GG, Ellis RJ, Curtis AC, Valerio MA, LeGore J: Evaluation of varicella-zoster immune globulin: protection of immunosuppressed children after household exposure to varicella. J Infect Dis 1983;147:737-743.

17 Birlea M, Owens GP, Eshleman EM, Ritchie A, Traktinskiy I, Bos N, Seitz S, Azarkh Y, Mahalingam R, Gilden D, Cohrs RJ: Human anti-varicella-zoster virus (VZV) recombinant monoclonal antibody produced after Zostavax immunization recognizes the gH/gL complex and neutralizes VZV infection. J Virol 2013;87:415-421.

18 Rodriguez JE, Moninger T, Grose C: Entry and egress of varicella virus blocked by same anti-gH monoclonal antibody. Virology 1993;196:840-844.

19 Macagno A, Bernasconi NL, Vanzetta F, Dander E, Sarasini A, Revello MG, Gerna G, Sallusto F, Lanzavecchia A: Isolation of human monoclonal antibodies that potently neutralize human cytomegalovirus infection by targeting different epitopes on the gH/gL/UL128-131A complex. J Virol 2010;84:1005-1013.

20 Ha S, Li F, Troutman MC, Freed DC, Tang A, Loughney JW, Wang D, Wang IM, Vlasak J, Nickle DC, Rustandi RR, Hamm M, DePhillips PA, Zhang N, McLellan JS, Zhu H, Adler SP, McVoy MA, An Z, Fu TM: Neutralization of Diverse Human Cytomegalovirus Strains Conferred by Antibodies Targeting Viral gH/gL/pUL128-131 Pentameric Complex. J Virol 2017;91

21 Maertens J, Logan AC, Jang J, Long G, Tang JL, Hwang WYK, Koh LP, Chemaly R, Gerbitz A, Winkler J, Yeh SP, Hiemenz J, Christoph S, Lee DG, Wang PN, Holler E, Mielke S, Akard L, Yeo A, Ramachandra S, Smith K, Pertel P, Segal F: Phase 2 Study of

Anti-Human Cytomegalovirus Monoclonal Antibodies for Prophylaxis in Hematopoietic Cell Transplantation. Antimicrob Agents Chemother 2020;64

22 Soto JA, Galvez NMS, Pacheco GA, Bueno SM, Kalergis AM: Antibody development for preventing the human respiratory syncytial virus pathology. Mol Med 2020;26:35.

23 Mejias A, Garcia-Maurino C, Rodriguez-Fernandez R, Peeples ME, Ramilo O: Development and clinical applications of novel antibodies for prevention and treatment of respiratory syncytial virus infection. Vaccine 2017;35:496-502.

24 Zhao Y, Wang C, Qiu B, Li C, Wang H, Jin H, Gai W, Zheng X, Wang T, Sun W, Yan F, Gao Y, Wang Q, Yan J, Chen L, Perlman S, Zhong N, Zhao J, Yang S, Xia X: Passive immunotherapy for Middle East Respiratory Syndrome coronavirus infection with equine immunoglobulin or immunoglobulin fragments in a mouse model. Antiviral Res 2017;137:125-130.

25 Zhao J, Perera RA, Kayali G, Meyerholz D, Perlman S, Peiris M: Passive immunotherapy with dromedary immune serum in an experimental animal model for Middle East respiratory syndrome coronavirus infection. J Virol 2015;89:6117-6120.

26 van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, Horby PW, Raoul H, Magassouba N, Antierens A, Lomas C, Faye O, Sall AA, Fransen K, Buyze J, Ravinetto R, Tiberghien P, Claeys Y, De Crop M, Lynen L, Bah EI, Smith PG, Delamou A, De Weggheleire A, Haba N: Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea. N Engl J Med 2016;374:33-42.

27 Dye JM, Wu H, Hooper JW, Khurana S, Kuehne AI, Coyle EM, Ortiz RA, Fuentes S, Herbert AS, Golding H, Bakken RA, Brannan JM, Kwilas SA, Sullivan EJ, Luke TC, Smith G, Glenn G, Li W, Ye L, Yang C, Compans RW, Tripp RA, Jiao JA: Production of

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

Potent Fully Human Polyclonal Antibodies against Ebola Zaire Virus in Transchromosomal Cattle. Sci Rep 2016;6:24897.

28 Luke T, Bennett RS, Gerhardt DM, Burdette T, Postnikova E, Mazur S, Honko AN, Oberlander N, Byrum R, Ragland D, St Claire M, Janosko KB, Smith G, Glenn G, Hooper J, Dye J, Pal S, Bishop-Lilly KA, Hamilton T, Frey K, Bollinger L, Wada J, Wu H, Jiao JA, Olinger GG, Gunn B, Alter G, Khurana S, Hensley LE, Sullivan E, Jahrling PB: Fully Human Immunoglobulin G From Transchromosomic Bovines Treats Nonhuman Primates Infected With Ebola Virus Makona Isolate. J Infect Dis 2018;218:S636-S648.

29 Beigel JH, Voell J, Kumar P, Raviprakash K, Wu H, Jiao JA, Sullivan E, Luke T, Davey RT, Jr.: Safety and tolerability of a novel, polyclonal human anti-MERS coronavirus antibody produced from transchromosomic cattle: a phase 1 randomised, double-blind, single-dose-escalation study. Lancet Infect Dis 2018;18:410-418.

30 Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, Chan P, Wong KC, Leung CB, Cheng G: Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24:44-46.

31 Casadevall A, Grossman BJ, Henderson JP, Joyner MJ, Shoham S, Pirofski LA, Paneth N: The Assessment of Convalescent Plasma Efficacy against COVID-19. Med (N Y) 2020;1:66-77.

32 Devarasetti PK, Rajasekhar L, Baisya R, Sreejitha KS, Vardhan YK: A review of COVID-19 convalescent plasma use in COVID-19 with focus on proof of efficacy. Immunol Res 2021

33 Khadka S, Nisar S, Syed NI, Shrestha DB, Budhathoki P: Different aspects of convalescent plasma therapy for COVID-19 treatment; a critical review. Immunopharmacol Immunotoxicol 2021;43:30-36.

34 Acosta-Ampudia Y, Monsalve DM, Rojas M, Rodriguez Y, Gallo JE, Salazar-Uribe JC, Santander MJ, Cala MP, Zapata W, Zapata MI, Manrique R, Pardo-Oviedo JM, Camacho B, Ramirez-Santana C, Anaya JM, group C-C-: COVID-19 convalescent plasma composition and immunological effects in severe patients. J Autoimmun 2021;118:102598.

35 Felton LD: The Units of Protective Antibody in Antipneumococcus Serum and Antibody Solution. The Journal of Infectious Diseases 1928;43:531-542.

36 Weisman LE, Cruess DF, Fischer GW: Opsonic activity of commercially available standard intravenous immunoglobulin preparations. Pediatr Infect Dis J 1994;13:1122-1125.

37 Arabi YM, Hajeer AH, Luke T, Raviprakash K, Balkhy H, Johani S, Al-Dawood A, Al-Qahtani S, Al-Omari A, Al-Hameed F, Hayden FG, Fowler R, Bouchama A, Shindo N, Al-Khairy K, Carson G, Taha Y, Sadat M, Alahmadi M: Feasibility of Using Convalescent Plasma Immunotherapy for MERS-CoV Infection, Saudi Arabia. Emerg Infect Dis 2016;22:1554-1561.

38 Slade HB: Human Immunoglobulins for intravenous use and hepatitis C viral transmission. Clin Diagn Lab Immunol 1994;1:613-619.

39 Sather DN, Armann J, Ching LK, Mavrantoni A, Sellhorn G, Caldwell Z, Yu X, Wood B, Self S, Kalams S, Stamatatos L: Factors associated with the development of cross-reactive neutralizing antibodies during human immunodeficiency virus type 1 infection. J Virol 2009;83:757-769.

40 Gray ES, Madiga MC, Hermanus T, Moore PL, Wibmer CK, Tumba NL, Werner L, Mlisana K, Sibeko S, Williamson C, Abdool Karim SS, Morris L: The neutralization breadth of HIV-1 develops incrementally over four years and is associated with CD4+ T cell decline and high viral load during acute infection. J Virol 2011;85:4828-4840.

41 Andrews SF, Huang Y, Kaur K, Popova LI, Ho IY, Pauli NT, Henry Dunand CJ, Taylor WM, Lim S, Huang M, Qu X, Lee JH, Salgado-Ferrer M, Krammer F, Palese P, Wrammert J, Ahmed R, Wilson PC: Immune history profoundly affects broadly protective B cell responses to influenza. Sci Transl Med 2015;7:316ra192.

42 Sommerstein R, Flatz L, Remy MM, Malinge P, Magistrelli G, Fischer N, Sahin M, Bergthaler A, Igonet S, Ter Meulen J, Rigo D, Meda P, Rabah N, Coutard B, Bowden TA, Lambert PH, Siegrist CA, Pinschewer DD: Arenavirus Glycan Shield Promotes Neutralizing Antibody Evasion and Protracted Infection. PLoS Pathog 2015;11:e1005276.

43 Jahrling PB, Frame JD, Rhoderick JB, Monson MH: Endemic Lassa fever in Liberia. IV. Selection of optimally effective plasma for treatment by passive immunization. Trans R Soc Trop Med Hyg 1985;79:380-384.

44 Bosnjak B, Stein SC, Willenzon S, Cordes AK, Puppe W, Bernhardt G, Ravens I, Ritter C, Schultze-Florey CR, Godecke N, Martens J, Kleine-Weber H, Hoffmann M, Cossmann A, Yilmaz M, Pink I, Hoeper MM, Behrens GMN, Pohlmann S, Blasczyk R, Schulz TF, Forster R: Low serum neutralizing anti-SARS-CoV-2 S antibody levels in mildly affected COVID-19 convalescent patients revealed by two different detection methods. Cell Mol Immunol 2020

45 Basta M, Dalakas MC: High-dose intravenous immunoglobulin exerts its beneficial effect in patients with dermatomyositis by blocking endomysial deposition of activated complement fragments. J Clin Invest 1994;94:1729-1735.

46 Lutz HU, Stammler P, Bianchi V, Trueb RM, Hunziker T, Burger R, Jelezarova E, Spath PJ: Intravenously applied IgG stimulates complement attenuation in a complement-dependent autoimmune disease at the amplifying C3 convertase level. Blood 2004;103:465-472.

47 Widiapradja A, Vegh V, Lok KZ, Manzanero S, Thundyil J, Gelderblom M, Cheng YL, Pavlovski D, Tang SC, Jo DG, Magnus T, Chan SL, Sobey CG, Reutens D, Basta M, Mattson MP, Arumugam TV: Intravenous immunoglobulin protects neurons against amyloid beta-peptide toxicity and ischemic stroke by attenuating multiple cell death pathways. J Neurochem 2012;122:321-332.

48 Bayry J, Bansal K, Kazatchkine MD, Kaveri SV: DC-SIGN and alpha2,6-sialylated IgG Fc interaction is dispensable for the anti-inflammatory activity of IVIg on human dendritic cells. Proc Natl Acad Sci U S A 2009;106:E24; author reply E25.

49 Bayry J, Lacroix-Desmazes S, Carbonneil C, Misra N, Donkova V, Pashov A, Chevailler A, Mouthon L, Weill B, Bruneval P, Kazatchkine MD, Kaveri SV: Inhibition of maturation and function of dendritic cells by intravenous immunoglobulin. Blood 2003;101:758-765.

50 Ruiz de Souza V, Carreno MP, Kaveri SV, Ledur A, Sadeghi H, Cavaillon JM, Kazatchkine MD, Haeffner-Cavaillon N: Selective induction of interleukin-1 receptor antagonist and interleukin-8 in human monocytes by normal polyspecific IgG (intravenous immunoglobulin). Eur J Immunol 1995;25:1267-1273.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

51 Park-Min KH, Serbina NV, Yang W, Ma X, Krystal G, Neel BG, Nutt SL, Hu X, Ivashkiv LB: FcgammaRIII-dependent inhibition of interferon-gamma responses mediates suppressive effects of intravenous immune globulin. Immunity 2007;26:67-78.

52 Kozicky LK, Zhao ZY, Menzies SC, Fidanza M, Reid GS, Wilhelmsen K, Hellman J, Hotte N, Madsen KL, Sly LM: Intravenous immunoglobulin skews macrophages to an anti-inflammatory, IL-10-producing activation state. J Leukoc Biol 2015;98:983-994.

53 Galeotti C, Hegde P, Das M, Stephen-Victor E, Canale F, Munoz M, Sharma VK, Dimitrov JD, Kaveri SV, Bayry J: Heme oxygenase-1 is dispensable for the anti-inflammatory activity of intravenous immunoglobulin. Sci Rep 2016;6:19592.

54 Casulli S, Topcu S, Fattoum L, von Gunten S, Simon HU, Teillaud JL, Bayry J, Kaveri SV, Elbim C: A differential concentration-dependent effect of IVIg on neutrophil functions: relevance for anti-microbial and anti-inflammatory mechanisms. PLoS One 2011;6:e26469.

55 Ruiz JE, Kwak JY, Baum L, Gilman-Sachs A, Beaman KD, Kim YB, Beer AE: Intravenous immunoglobulin inhibits natural killer cell activity in vivo in women with recurrent spontaneous abortion. Am J Reprod Immunol 1996;35:370-375.

56 Finberg RW, Newburger JW, Mikati MA, Heller AH, Burns JC: Effect of high doses of intravenously administered immune globulin on natural killer cell activity in peripheral blood. J Pediatr 1992;120:376-380.

57 Paquin Proulx D, Aubin E, Lemieux R, Bazin R: Inhibition of B cell-mediated antigen presentation by intravenous immunoglobulins (IVIg). Clin Immunol 2010;135:422-429.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

58 Seite JF, Goutsmedt C, Youinou P, Pers JO, Hillion S: Intravenous immunoglobulin induces a functional silencing program similar to anergy in human B cells. J Allergy Clin Immunol 2014;133:181-188 e181-189.

59 Seite JF, Guerrier T, Cornec D, Jamin C, Youinou P, Hillion S: TLR9 responses of B cells are repressed by intravenous immunoglobulin through the recruitment of phosphatase. J Autoimmun 2011;37:190-197.

60 Kessel A, Peri R, Haj T, Snir A, Slobodin G, Sabo E, Rosner I, Shoenfeld Y, Toubi E: IVIg attenuates TLR-9 activation in B cells from SLE patients. J Clin Immunol 2011;31:30-38.

61 Seite JF, Cornec D, Renaudineau Y, Youinou P, Mageed RA, Hillion S: IVIg modulates BCR signaling through CD22 and promotes apoptosis in mature human B lymphocytes. Blood 2010;116:1698-1704.

62 Zhuang Q, Bisotto S, Fixman ED, Mazer B: Suppression of IL-4- and CD40-induced B-lymphocyte activation by intravenous immunoglobulin is not mediated through the inhibitory IgG receptor FcgammaRIIb. J Allergy Clin Immunol 2002;110:480-483.

63 de Grandmont MJ, Racine C, Roy A, Lemieux R, Neron S: Intravenous immunoglobulins induce the in vitro differentiation of human B lymphocytes and the secretion of IgG. Blood 2003;101:3065-3073.

64 Bayry J, Mouthon L, Kaveri SV: Intravenous immunoglobulin expands regulatory T cells in autoimmune rheumatic disease. J Rheumatol 2012;39:450-451.

65 Maddur MS, Vani J, Hegde P, Lacroix-Desmazes S, Kaveri SV, Bayry J: Inhibition of differentiation, amplification, and function of human TH17 cells by intravenous immunoglobulin. J Allergy Clin Immunol 2011;127:823-830 e821-827.

66 Maddur MS, Kaveri SV, Bayry J: Comparison of different IVIg preparations on IL-17 production by human Th17 cells. Autoimmun Rev 2011;10:809-810.

67 Maddur MS, Rabin M, Hegde P, Bolgert F, Guy M, Vallat JM, Magy L, Bayry J, Kaveri SV: Intravenous immunoglobulin exerts reciprocal regulation of Th1/Th17 cells and regulatory T cells in Guillain-Barre syndrome patients. Immunol Res 2014;60:320-329.

68 Saha C, Das M, Patil V, Stephen-Victor E, Sharma M, Wymann S, Jordi M, Vonarburg C, Kaveri SV, Bayry J: Monomeric Immunoglobulin A from Plasma Inhibits Human Th17 Responses In Vitro Independent of FcalphaRI and DC-SIGN. Front Immunol 2017;8:275.

69 Schrage B, Duan G, Yang LP, Fraser JD, Proft T: Different preparations of intravenous immunoglobulin vary in their efficacy to neutralize streptococcal superantigens: implications for treatment of streptococcal toxic shock syndrome. Clin Infect Dis 2006;43:743-746.

70 Bayry J, Lacroix-Desmazes S, Kazatchkine MD, Kaveri SV: Intravenous immunoglobulin for infectious diseases: back to the pre-antibiotic and passive prophylaxis era? Trends Pharmacol Sci 2004;25:306-310.

71 Bulletin: I.V. immunoglobulin therapy for infectious diseases. Drug Ther Bull 2010;48:57-60.

72 Jones PT, Dear PH, Foote J, Neuberger MS, Winter G: Replacing the complementarity-determining regions in a human antibody with those from a mouse. Nature 1986;321:522-525.

73 Smith GP: Filamentous fusion phage: novel expression vectors that display cloned antigens on the virion surface. Science 1985;228:1315-1317.

74 McCafferty J, Griffiths AD, Winter G, Chiswell DJ: Phage antibodies: filamentous phage displaying antibody variable domains. Nature 1990;348:552-554.

75 Lonberg N, Taylor LD, Harding FA, Trounstine M, Higgins KM, Schramm SR, Kuo CC, Mashayekh R, Wymore K, McCabe JG, et al.: Antigen-specific human antibodies from mice comprising four distinct genetic modifications. Nature 1994;368:856-859.

76 Mendez MJ, Green LL, Corvalan JR, Jia XC, Maynard-Currie CE, Yang XD, Gallo ML, Louie DM, Lee DV, Erickson KL, Luna J, Roy CM, Abderrahim H, Kirschenbaum F, Noguchi M, Smith DH, Fukushima A, Hales JF, Klapholz S, Finer MH, Davis CG, Zsebo KM, Jakobovits A: Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice. Nat Genet 1997;15:146-156.

77 Kempeni J: Preliminary results of early clinical trials with the fully human anti-TNFalpha monoclonal antibody D2E7. Ann Rheum Dis 1999;58 Suppl 1:I70-72.

78 Stohl W, Hilbert DM: The discovery and development of belimumab: the anti-BLyS-lupus connection. Nat Biotechnol 2012;30:69-77.

79 Spratlin JL, Cohen RB, Eadens M, Gore L, Camidge DR, Diab S, Leong S, O'Bryant C, Chow LQ, Serkova NJ, Meropol NJ, Lewis NL, Chiorean EG, Fox F, Youssoufian H, Rowinsky EK, Eckhardt SG: Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. J Clin Oncol 2010;28:780-787.

80 Dienstmann R, Tabernero J: Necitumumab, a fully human IgG1 mAb directed against the EGFR for the potential treatment of cancer. Curr Opin Investig Drugs 2010;11:1434-1441.

81 Sofen H, Smith S, Matheson RT, Leonardi CL, Calderon C, Brodmerkel C, Li K, Campbell K, Marciniak SJ, Jr., Wasfi Y, Wang Y, Szapary P, Krueger JG: Guselkumab (an IL-23-

specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. J Allergy Clin Immunol 2014;133:1032-1040.

82 Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, Shih KC, Lebbe C, Linette GP, Milella M, Brownell I, Lewis KD, Lorch JH, Chin K, Mahnke L, von Heydebreck A, Cuillerot JM, Nghiem P: Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016;17:1374-1385.

83 Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, Busse PJ, Anderson J, Magerl M, Martinez-Saguer I, Davis-Lorton M, Zanichelli A, Li HH, Craig T, Jacobs J, Johnston DT, Shapiro R, Yang WH, Lumry WR, Manning ME, Schwartz LB, Shennak M, Soteres D, Zaragoza-Urdaz RH, Gierer S, Smith AM, Tachdjian R, Wedner HJ, Hebert J, Rehman SM, Staubach P, Schranz J, Baptista J, Nothaft W, Maurer M: Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA 2018;320:2108-2121.

84 Cheloff AZ, Al-Samkari H: Emapalumab for the treatment of hemophagocytic lymphohistiocytosis. Drugs Today (Barc) 2020;56:439-446.

85 Janus A, Robak T: Moxetumomab pasudotox for the treatment of hairy cell leukemia. Expert Opin Biol Ther 2019;19:501-508.

86 Aman P, Ehlin-Henriksson B, Klein G: Epstein-Barr virus susceptibility of normal human B lymphocyte populations. J Exp Med 1984;159:208-220.

87 Traggiai E, Becker S, Subbarao K, Kolesnikova L, Uematsu Y, Gismondo MR, Murphy BR, Rappuoli R, Lanzavecchia A: An efficient method to make human monoclonal

antibodies from memory B cells: potent neutralization of SARS coronavirus. Nat Med 2004;10:871-875.

88 Smith K, Garman L, Wrammert J, Zheng NY, Capra JD, Ahmed R, Wilson PC: Rapid generation of fully human monoclonal antibodies specific to a vaccinating antigen. Nat Protoc 2009;4:372-384.

89 Obiakor H, Sehgal D, Dasso JF, Bonner RF, Malekafzali A, Mage RG: A comparison of hydraulic and laser capture microdissection methods for collection of single B cells, PCR, and sequencing of antibody VDJ. Anal Biochem 2002;306:55-62.

90 Tiller T, Meffre E, Yurasov S, Tsuiji M, Nussenzweig MC, Wardemann H: Efficient generation of monoclonal antibodies from single human B cells by single cell RT-PCR and expression vector cloning. J Immunol Methods 2008;329:112-124.

91 Labrijn AF, Janmaat ML, Reichert JM, Parren P: Bispecific antibodies: a mechanistic review of the pipeline. Nat Rev Drug Discov 2019;18:585-608.

92 Esfahani K, Roudaia L, Buhlaiga N, Del Rincon SV, Papneja N, Miller WH, Jr.: A review of cancer immunotherapy: from the past, to the present, to the future. Curr Oncol 2020;27:S87-S97.

93 Wahid B, Ali A, Rafique S, Waqar M, Wasim M, Wahid K, Idrees M: An overview of cancer immunotherapeutic strategies. Immunotherapy 2018;10:999-1010.

94 Waldman AD, Fritz JM, Lenardo MJ: A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol 2020;20:651-668.

95 Coulson A, Levy A, Gossell-Williams M: Monoclonal Antibodies in Cancer Therapy: Mechanisms, Successes and Limitations. West Indian Med J 2014;63:650-654.

96 Park R, Winnicki M, Liu E, Chu WM: Immune checkpoints and cancer in the immunogenomics era. Brief Funct Genomics 2019;18:133-139.

97 Hargadon KM, Johnson CE, Williams CJ: Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. Int Immunopharmacol 2018;62:29-39.

98 He X, Xu C: Immune checkpoint signaling and cancer immunotherapy. Cell Res 2020;30:660-669.

99 Leach DR, Krummel MF, Allison JP: Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996;271:1734-1736.

100 Das S, Johnson DB: Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. J Immunother Cancer 2019;7:306.

101 Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, Lao CD, Schadendorf D, Wagstaff J, Dummer R, Ferrucci PF, Smylie M, Hill A, Hogg D, Marquez-Rodas I, Jiang J, Rizzo J, Larkin J, Wolchok JD: Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19:1480-1492.

102 Rotte A: Combination of CTLA-4 and PD-1 blockers for treatment of cancer. J Exp Clin Cancer Res 2019;38:255.

103 Hegde NR, Rao PP, Bayry J, Kaveri SV: Immunotherapy of viral infections. Immunotherapy 2009;1:691-711.

104 Hashimoto K, Hosoya M: Neutralizing epitopes of RSV and palivizumab resistance in Japan. Fukushima J Med Sci 2017;63:127-134.

105 Schickli JH, Whitacre DC, Tang RS, Kaur J, Lawlor H, Peters CJ, Jones JE, Peterson DL, McCarthy MP, Van Nest G, Milich DR: Palivizumab epitope-displaying virus-like particles protect rodents from RSV challenge. J Clin Invest 2015;125:1637-1647.

106 IMpact-RSV-Study-Group: Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. Pediatrics 1998;102:531-537.

107 Corti D, Misasi J, Mulangu S, Stanley DA, Kanekiyo M, Wollen S, Ploquin A, Doria-Rose NA, Staupe RP, Bailey M, Shi W, Choe M, Marcus H, Thompson EA, Cagigi A, Silacci C, Fernandez-Rodriguez B, Perez L, Sallusto F, Vanzetta F, Agatic G, Cameroni E, Kisalu N, Gordon I, Ledgerwood JE, Mascola JR, Graham BS, Muyembe-Tamfun JJ, Trefry JC, Lanzavecchia A, Sullivan NJ: Protective monotherapy against lethal Ebola virus infection by a potently neutralizing antibody. Science 2016;351:1339-1342.

108 Pascal KE, Dudgeon D, Trefry JC, Anantpadma M, Sakurai Y, Murin CD, Turner HL, Fairhurst J, Torres M, Rafique A, Yan Y, Badithe A, Yu K, Potocky T, Bixler SL, Chance TB, Pratt WD, Rossi FD, Shamblin JD, Wollen SE, Zelko JM, Carrion R, Jr., Worwa G, Staples HM, Burakov D, Babb R, Chen G, Martin J, Huang TT, Erlandson K, Willis MS, Armstrong K, Dreier TM, Ward AB, Davey RA, Pitt MLM, Lipsich L, Mason P, Olson W, Stahl N, Kyratsous CA: Development of Clinical-Stage Human Monoclonal Antibodies That Treat Advanced Ebola Virus Disease in Nonhuman Primates. J Infect Dis 2018;218:S612-S626.

109 Yang L, Liu W, Yu X, Wu M, Reichert JM, Ho M: COVID-19 antibody therapeutics tracker: a global online database of antibody therapeutics for the prevention and treatment of COVID-19. Antib Ther 2020;3:205-212.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

110 Gaudinski MR, Coates EE, Novik L, Widge A, Houser KV, Burch E, Holman LA, Gordon IJ, Chen GL, Carter C, Nason M, Sitar S, Yamshchikov G, Berkowitz N, Andrews C, Vazquez S, Laurencot C, Misasi J, Arnold F, Carlton K, Lawlor H, Gall J, Bailer RT, McDermott A, Capparelli E, Koup RA, Mascola JR, Graham BS, Sullivan NJ, Ledgerwood JE: Safety, tolerability, pharmacokinetics, and immunogenicity of the therapeutic monoclonal antibody mAb114 targeting Ebola virus glycoprotein (VRC 608): an open-label phase 1 study. Lancet 2019;393:889-898.

111 Sivapalasingam S, Kamal M, Slim R, Hosain R, Shao W, Stoltz R, Yen J, Pologe LG, Cao Y, Partridge M, Sumner G, Lipsich L: Safety, pharmacokinetics, and immunogenicity of a co-formulated cocktail of three human monoclonal antibodies targeting Ebola virus glycoprotein in healthy adults: a randomised, first-in-human phase 1 study. Lancet Infect Dis 2018;18:884-893.

112 Mulangu S, Dodd LE, Davey RT, Jr., Tshiani Mbaya O, Proschan M, Mukadi D, Lusakibanza Manzo M, Nzolo D, Tshomba Oloma A, Ibanda A, Ali R, Coulibaly S, Levine AC, Grais R, Diaz J, Lane HC, Muyembe-Tamfum JJ, Sivahera B, Camara M, Kojan R, Walker R, Dighero-Kemp B, Cao H, Mukumbayi P, Mbala-Kingebeni P, Ahuka S, Albert S, Bonnett T, Crozier I, Duvenhage M, Proffitt C, Teitelbaum M, Moench T, Aboulhab J, Barrett K, Cahill K, Cone K, Eckes R, Hensley L, Herpin B, Higgs E, Ledgerwood J, Pierson J, Smolskis M, Sow Y, Tierney J, Sivapalasingam S, Holman W, Gettinger N, Vallee D, Nordwall J: A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med 2019;381:2293-2303.

113 Davey RT, Jr., Dodd L, Proschan MA, Neaton J, Neuhaus Nordwall J, Koopmeiners JS, Beigel J, Tierney J, Lane HC, Fauci AS, Massaquoi MBF, Sahr F, Malvy D: A

Randomized, Controlled Trial of ZMapp for Ebola Virus Infection. N Engl J Med 2016;375:1448-1456.

114 Choi JH, Woo HM, Lee TY, Lee SY, Shim SM, Park WJ, Yang JS, Kim JA, Yun MR, Kim DW, Kim SS, Zhang Y, Shi W, Wang L, Graham BS, Mascola JR, Wang N, McLellan JS, Lee JY, Lee H: Characterization of a human monoclonal antibody generated from a B-cell specific for a prefusion-stabilized spike protein of Middle East respiratory syndrome coronavirus. PLoS One 2020;15:e0232757.

115 Corti D, Zhao J, Pedotti M, Simonelli L, Agnihothram S, Fett C, Fernandez-Rodriguez B, Foglierini M, Agatic G, Vanzetta F, Gopal R, Langrish CJ, Barrett NA, Sallusto F, Baric RS, Varani L, Zambon M, Perlman S, Lanzavecchia A: Prophylactic and postexposure efficacy of a potent human monoclonal antibody against MERS coronavirus. Proc Natl Acad Sci U S A 2015;112:10473-10478.

116 de Wit E, Feldmann F, Horne E, Okumura A, Cameroni E, Haddock E, Saturday G, Scott D, Gopal R, Zambon M, Corti D, Feldmann H: Prophylactic efficacy of a human monoclonal antibody against MERS-CoV in the common marmoset. Antiviral Res 2019;163:70-74.

117 de Wit E, Feldmann F, Okumura A, Horne E, Haddock E, Saturday G, Scott D, Erlandson KJ, Stahl N, Lipsich L, Kyratsous CA, Feldmann H: Prophylactic and therapeutic efficacy of mAb treatment against MERS-CoV in common marmosets. Antiviral Res 2018;156:64-71.

118 Johnson RF, Bagci U, Keith L, Tang X, Mollura DJ, Zeitlin L, Qin J, Huzella L, Bartos CJ, Bohorova N, Bohorov O, Goodman C, Kim DH, Paulty MH, Velasco J, Whaley KJ, Johnson JC, Pettitt J, Ork BL, Solomon J, Oberlander N, Zhu Q, Sun J, Holbrook MR,

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

Olinger GG, Baric RS, Hensley LE, Jahrling PB, Marasco WA: 3B11-N, a monoclonal antibody against MERS-CoV, reduces lung pathology in rhesus monkeys following intratracheal inoculation of MERS-CoV Jordan-n3/2012. Virology 2016;490:49-58.

119 Du L, Zhao G, Yang Y, Qiu H, Wang L, Kou Z, Tao X, Yu H, Sun S, Tseng CT, Jiang S, Li F, Zhou Y: A conformation-dependent neutralizing monoclonal antibody specifically targeting receptor-binding domain in Middle East respiratory syndrome coronavirus spike protein. J Virol 2014;88:7045-7053.

120 Li Y, Wan Y, Liu P, Zhao J, Lu G, Qi J, Wang Q, Lu X, Wu Y, Liu W, Zhang B, Yuen KY, Perlman S, Gao GF, Yan J: A humanized neutralizing antibody against MERS-CoV targeting the receptor-binding domain of the spike protein. Cell Res 2015;25:1237-1249.

121 Pascal KE, Coleman CM, Mujica AO, Kamat V, Badithe A, Fairhurst J, Hunt C, Strein J, Berrebi A, Sisk JM, Matthews KL, Babb R, Chen G, Lai KM, Huang TT, Olson W, Yancopoulos GD, Stahl N, Frieman MB, Kyratsous CA: Pre- and postexposure efficacy of fully human antibodies against Spike protein in a novel humanized mouse model of MERS-CoV infection. Proc Natl Acad Sci U S A 2015;112:8738-8743.

122 Widjaja I, Wang C, van Haperen R, Gutierrez-Alvarez J, van Dieren B, Okba NMA, Raj VS, Li W, Fernandez-Delgado R, Grosveld F, van Kuppeveld FJM, Haagmans BL, Enjuanes L, Drabek D, Bosch BJ: Towards a solution to MERS: protective human monoclonal antibodies targeting different domains and functions of the MERS-coronavirus spike glycoprotein. Emerg Microbes Infect 2019;8:516-530.

123 Jiang L, Wang N, Zuo T, Shi X, Poon KM, Wu Y, Gao F, Li D, Wang R, Guo J, Fu L, Yuen KY, Zheng BJ, Wang X, Zhang L: Potent neutralization of MERS-CoV by human

neutralizing monoclonal antibodies to the viral spike glycoprotein. Sci Transl Med 2014;6:234ra259.

124 Tang XC, Agnihothram SS, Jiao Y, Stanhope J, Graham RL, Peterson EC, Avnir Y, Tallarico AS, Sheehan J, Zhu Q, Baric RS, Marasco WA: Identification of human neutralizing antibodies against MERS-CoV and their role in virus adaptive evolution. Proc Natl Acad Sci U S A 2014;111:E2018-2026.

125 Ying T, Du L, Ju TW, Prabakaran P, Lau CC, Lu L, Liu Q, Wang L, Feng Y, Wang Y, Zheng BJ, Yuen KY, Jiang S, Dimitrov DS: Exceptionally potent neutralization of Middle East respiratory syndrome coronavirus by human monoclonal antibodies. J Virol 2014;88:7796-7805.

126 NIH: A Safety, Tolerability, Pharmacokinetics and Immunogenicity Trial of Co-administered MERS-CoV Antibodies REGN3048 and REGN3051, 2017,

127 Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, Lu L, Jiang S, Yang Z, Wu Y, Ying T: Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg Microbes Infect 2020;9:382-385.

128 Wang C, Li W, Drabek D, Okba NMA, van Haperen R, Osterhaus A, van Kuppeveld FJM, Haagmans BL, Grosveld F, Bosch BJ: A human monoclonal antibody blocking SARS-CoV-2 infection. Nat Commun 2020;11:2251.

129 Chen X, Li R, Pan Z, Qian C, Yang Y, You R, Zhao J, Liu P, Gao L, Li Z, Huang Q, Xu L, Tang J, Tian Q, Yao W, Hu L, Yan X, Zhou X, Wu Y, Deng K, Zhang Z, Qian Z, Chen Y, Ye L: Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor. Cell Mol Immunol 2020;17:647-649.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

130 Noy-Porat T, Makdasi E, Alcalay R, Mechaly A, Levy Y, Bercovich-Kinori A, Zauberman A, Tamir H, Yahalom-Ronen Y, Israeli M, Epstein E, Achdout H, Melamed S, Chitlaru T, Weiss S, Peretz E, Rosen O, Paran N, Yitzhaki S, Shapira SC, Israely T, Mazor O, Rosenfeld R: A panel of human neutralizing mAbs targeting SARS-CoV-2 spike at multiple epitopes. Nat Commun 2020;11:4303.

131 Yuan M, Wu NC, Zhu X, Lee CD, So RTY, Lv H, Mok CKP, Wilson IA: A highly conserved cryptic epitope in the receptor binding domains of SARS-CoV-2 and SARS-CoV. Science 2020;368:630-633.

132 Shi R, Shan C, Duan X, Chen Z, Liu P, Song J, Song T, Bi X, Han C, Wu L, Gao G, Hu X, Zhang Y, Tong Z, Huang W, Liu WJ, Wu G, Zhang B, Wang L, Qi J, Feng H, Wang FS, Wang Q, Gao GF, Yuan Z, Yan J: A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. Nature 2020;584:120-124.

133 Ju B, Zhang Q, Ge J, Wang R, Sun J, Ge X, Yu J, Shan S, Zhou B, Song S, Tang X, Yu J, Lan J, Yuan J, Wang H, Zhao J, Zhang S, Wang Y, Shi X, Liu L, Zhao J, Wang X, Zhang Z, Zhang L: Human neutralizing antibodies elicited by SARS-CoV-2 infection. Nature 2020;584:115-119.

134 Lv Z, Deng YQ, Ye Q, Cao L, Sun CY, Fan C, Huang W, Sun S, Sun Y, Zhu L, Chen Q, Wang N, Nie J, Cui Z, Zhu D, Shaw N, Li XF, Li Q, Xie L, Wang Y, Rao Z, Qin CF, Wang X: Structural basis for neutralization of SARS-CoV-2 and SARS-CoV by a potent therapeutic antibody. Science 2020;369:1505-1509.

135 Iyer AS, Jones FK, Nodoushani A, Kelly M, Becker M, Slater D, Mills R, Teng E, Kamruzzaman M, Garcia-Beltran WF, Astudillo M, Yang D, Miller TE, Oliver E, Fischinger S, Atyeo C, Iafrate AJ, Calderwood SB, Lauer SA, Yu J, Li Z, Feldman J,

Hauser BM, Caradonna TM, Branda JA, Turbett SE, LaRocque RC, Mellon G, Barouch DH, Schmidt AG, Azman AS, Alter G, Ryan ET, Harris JB, Charles RC: Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. Sci Immunol 2020;5

136 Chi X, Yan R, Zhang J, Zhang G, Zhang Y, Hao M, Zhang Z, Fan P, Dong Y, Yang Y, Chen Z, Guo Y, Zhang J, Li Y, Song X, Chen Y, Xia L, Fu L, Hou L, Xu J, Yu C, Li J, Zhou Q, Chen W: A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2. Science 2020;369:650-655.

137 Liu L, Wang P, Nair MS, Yu J, Rapp M, Wang Q, Luo Y, Chan JF, Sahi V, Figueroa A, Guo XV, Cerutti G, Bimela J, Gorman J, Zhou T, Chen Z, Yuen KY, Kwong PD, Sodroski JG, Yin MT, Sheng Z, Huang Y, Shapiro L, Ho DD: Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. Nature 2020;584:450-456.

138 Pinto D, Park YJ, Beltramello M, Walls AC, Tortorici MA, Bianchi S, Jaconi S, Culap K, Zatta F, De Marco A, Peter A, Guarino B, Spreafico R, Cameroni E, Case JB, Chen RE, Havenar-Daughton C, Snell G, Telenti A, Virgin HW, Lanzavecchia A, Diamond MS, Fink K, Veesler D, Corti D: Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature 2020;583:290-295.

139 Golsaz Shirazi F, Mohammadi H, Amiri MM, Singethan K, Xia Y, Bayat AA, Bahadori M, Rabbani H, Jeddi-Tehrani M, Protzer U, Shokri F: Monoclonal antibodies to various epitopes of hepatitis B surface antigen inhibit hepatitis B virus infection. J Gastroenterol Hepatol 2014;29:1083-1091.

140 Hansen J, Baum A, Pascal KE, Russo V, Giordano S, Wloga E, Fulton BO, Yan Y, Koon K, Patel K, Chung KM, Hermann A, Ullman E, Cruz J, Rafique A, Huang T, Fairhurst J,

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

Libertiny C, Malbec M, Lee WY, Welsh R, Farr G, Pennington S, Deshpande D, Cheng J, Watty A, Bouffard P, Babb R, Levenkova N, Chen C, Zhang B, Romero Hernandez A, Saotome K, Zhou Y, Franklin M, Sivapalasingam S, Lye DC, Weston S, Logue J, Haupt R, Frieman M, Chen G, Olson W, Murphy AJ, Stahl N, Yancopoulos GD, Kyratsous CA: Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. Science 2020;369:1010-1014.

141 Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, Giordano S, Lanza K, Negron N, Ni M, Wei Y, Atwal GS, Murphy AJ, Stahl N, Yancopoulos GD, Kyratsous CA: Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science 2020;369:1014-1018.

142 Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Musser BJ, Soo Y, Rofail D, Im J, Perry C, Pan C, Hosain R, Mahmood A, Davis JD, Turner KC, Hooper AT, Hamilton JD, Baum A, Kyratsous CA, Kim Y, Cook A, Kampman W, Kohli A, Sachdeva Y, Graber X, Kowal B, DiCioccio T, Stahl N, Lipsich L, Braunstein N, Herman G, Yancopoulos GD, Trial I: REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med 2020

143 Zost SJ, Gilchuk P, Case JB, Binshtein E, Chen RE, Nkolola JP, Schafer A, Reidy JX, Trivette A, Nargi RS, Sutton RE, Suryadevara N, Martinez DR, Williamson LE, Chen EC, Jones T, Day S, Myers L, Hassan AO, Kafai NM, Winkler ES, Fox JM, Shrihari S, Mueller BK, Meiler J, Chandrashekar A, Mercado NB, Steinhardt JJ, Ren K, Loo YM, Kallewaard NL, McCune BT, Keeler SP, Holtzman MJ, Barouch DH, Gralinski LE, Baric RS, Thackray LB, Diamond MS, Carnahan RH, Crowe JE, Jr.: Potently neutralizing and protective human antibodies against SARS-CoV-2. Nature 2020;584:443-449.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

144 Zost SJ, Gilchuk P, Chen RE, Case JB, Reidy JX, Trivette A, Nargi RS, Sutton RE, Suryadevara N, Chen EC, Binshtein E, Shrihari S, Ostrowski M, Chu HY, Didier JE, MacRenaris KW, Jones T, Day S, Myers L, Eun-Hyung Lee F, Nguyen DC, Sanz I, Martinez DR, Rothlauf PW, Bloyet LM, Whelan SPJ, Baric RS, Thackray LB, Diamond MS, Carnahan RH, Crowe JE, Jr.: Rapid isolation and profiling of a diverse panel of human monoclonal antibodies targeting the SARS-CoV-2 spike protein. Nat Med 2020;26:1422-1427.

145 Robbie GJ, Criste R, Dall'acqua WF, Jensen K, Patel NK, Losonsky GA, Griffin MP: A novel investigational Fc-modified humanized monoclonal antibody, motavizumab-YTE, has an extended half-life in healthy adults. Antimicrob Agents Chemother 2013;57:6147-6153.

146 Griffin MP, Khan AA, Esser MT, Jensen K, Takas T, Kankam MK, Villafana T, Dubovsky F: Safety, Tolerability, and Pharmacokinetics of MEDI8897, the Respiratory Syncytial Virus Prefusion F-Targeting Monoclonal Antibody with an Extended Half-Life, in Healthy Adults. Antimicrob Agents Chemother 2017;61

147 Yu XQ, Robbie GJ, Wu Y, Esser MT, Jensen K, Schwartz HI, Bellamy T, Hernandez-Illas M, Jafri HS: Safety, Tolerability, and Pharmacokinetics of MEDI4893, an Investigational, Extended-Half-Life, Anti-Staphylococcus aureus Alpha-Toxin Human Monoclonal Antibody, in Healthy Adults. Antimicrob Agents Chemother 2017;61

148 Kim C, Ryu DK, Lee J, Kim YI, Seo JM, Kim YG, Jeong JH, Kim M, Kim JI, Kim P, Bae JS, Shim EY, Lee MS, Kim MS, Noh H, Park GS, Park JS, Son D, An Y, Lee JN, Kwon KS, Lee JY, Lee H, Yang JS, Kim KC, Kim SS, Woo HM, Kim JW, Park MS, Yu KM, Kim SM, Kim EH, Park SJ, Jeong ST, Yu CH, Song Y, Gu SH, Oh H, Koo BS, Hong JJ,

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

Ryu CM, Park WB, Oh MD, Choi YK, Lee SY: A therapeutic neutralizing antibody targeting receptor binding domain of SARS-CoV-2 spike protein. Nat Commun 2021;12:288.

149 Ison MG: Therapeutic Effect of Regdanvimab (CT-P59) in Patients with Mild to Moderate Symptoms of SARS CoV 2 Infection: eSymposia, Antibodies and Vaccines as Drugs for COVID-19, Virtual Key Stone Symposia, 2021,

150 Jones BE, Brown-Augsburger PL, Corbett KS, Westendorf K, Davies J, Cujec TP, Wiethoff CM, Blackbourne JL, Heinz BA, Foster D, Higgs RE, Balasubramaniam D, Wang L, Bidshahri R, Kraft L, Hwang Y, Zentelis S, Jepson KR, Goya R, Smith MA, Collins DW, Hinshaw SJ, Tycho SA, Pellacani D, Xiang P, Muthuraman K, Sobhanifar S, Piper MH, Triana FJ, Hendle J, Pustilnik A, Adams AC, Berens SJ, Baric RS, Martinez DR, Cross RW, Geisbert TW, Borisevich V, Abiona O, Belli HM, de Vries M, Mohamed A, Dittmann M, Samanovic M, Mulligan MJ, Goldsmith JA, Hsieh CL, Johnson NV, Wrapp D, McLellan JS, Barnhart BC, Graham BS, Mascola JR, Hansen CL, Falconer E: LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. bioRxiv 2020

151 Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, Shawa I, Adams AC, Van Naarden J, Custer KL, Shen L, Durante M, Oakley G, Schade AE, Sabo J, Patel DR, Klekotka P, Skovronsky DM, Investigators B-: SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med 2020

152 Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, Shawa I, Kumar P, Adams AC, Van Naarden J, Custer KL, Durante M,

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

Oakley G, Schade AE, Holzer TR, Ebert PJ, Higgs RE, Kallewaard NL, Sabo J, Patel DR, Klekotka P, Shen L, Skovronsky DM: Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA 2021

153 Fala L: Portrazza (Necitumumab), an IgG1 Monoclonal Antibody, FDA Approved for Advanced Squamous Non-Small-Cell Lung Cancer. Am Health Drug Benefits 2016;9:119-122.

154 Garcia-Foncillas J, Sunakawa Y, Aderka D, Wainberg Z, Ronga P, Witzler P, Stintzing S: Distinguishing Features of Cetuximab and Panitumumab in Colorectal Cancer and Other Solid Tumors. Front Oncol 2019;9:849.

155 Dubois EA, Cohen AF: Panitumumab. Br J Clin Pharmacol 2009;68:482-483.

156 Crombet Ramos T, Mestre Fernandez B, Mazorra Herrera Z, Iznaga Escobar NE: Nimotuzumab for Patients With Inoperable Cancer of the Head and Neck. Front Oncol 2020;10:817.

157 Kazazi-Hyseni F, Beijnen JH, Schellens JH: Bevacizumab. Oncologist 2010;15:819-825.

158 Wu J, Fu J, Zhang M, Liu D: Blinatumomab: a bispecific T cell engager (BiTE) antibody against CD19/CD3 for refractory acute lymphoid leukemia. J Hematol Oncol 2015;8:104.

159 Rizzieri D: Zevalin((R)) (ibritumomab tiuxetan): After more than a decade of treatment experience, what have we learned? Crit Rev Oncol Hematol 2016;105:5-17.

160 Weiner GJ: Rituximab: mechanism of action. Semin Hematol 2010;47:115-123.

161 Biodrugs: Iodine-131 Tositumomab: (131)I-anti-B1 antibody, (131)I-tositumomab, anti-CD20 murine monoclonal antibody-I-131, B1, Bexxar, (131)I-anti-B1 antibody, iodine-131 tositumomab, iodine-131 anti-B1 antibody, tositumomab. BioDrugs 2003;17:290-295.

162 Zhang B: Ofatumumab. MAbs 2009;1:326-331.

163 Tobinai K, Klein C, Oya N, Fingerle-Rowson G: A Review of Obinutuzumab (GA101), a Novel Type II Anti-CD20 Monoclonal Antibody, for the Treatment of Patients with B-Cell Malignancies. Adv Ther 2017;34:324-356.

164 Lambert J, Pautas C, Terre C, Raffoux E, Turlure P, Caillot D, Legrand O, Thomas X, Gardin C, Gogat-Marchant K, Rubin SD, Benner RJ, Bousset P, Preudhomme C, Chevret S, Dombret H, Castaigne S: Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. Haematologica 2019;104:113-119.

165 Sanchez L, Wang Y, Siegel DS, Wang ML: Daratumumab: a first-in-class CD38 monoclonal antibody for the treatment of multiple myeloma. J Hematol Oncol 2016;9:51.

166 Havrdova E, Horakova D, Kovarova I: Alemtuzumab in the treatment of multiple sclerosis: key clinical trial results and considerations for use. Ther Adv Neurol Disord 2015;8:31-45.

167 Gemmete JJ, Mukherji SK: Trastuzumab (herceptin). AJNR Am J Neuroradiol 2011;32:1373-1374.

168 McDermott J, Jimeno A: Pembrolizumab: PD-1 inhibition as a therapeutic strategy in cancer. Drugs Today (Barc) 2015;51:7-20.

169 Guo L, Zhang H, Chen B: Nivolumab as Programmed Death-1 (PD-1) Inhibitor for Targeted Immunotherapy in Tumor. J Cancer 2017;8:410-416.

170 Gil-Bazo I: Avelumab-a new programmed death-ligand 1 inhibitor against advanced non-small cell lung cancer. Transl Lung Cancer Res 2017;6:S35-S38.

171 Faiena I, Cummings AL, Crosetti AM, Pantuck AJ, Chamie K, Drakaki A: Durvalumab: an investigational anti-PD-L1 monoclonal antibody for the treatment of urothelial carcinoma. Drug Des Devel Ther 2018;12:209-215.

172 Lee HT, Lee JY, Lim H, Lee SH, Moon YJ, Pyo HJ, Ryu SE, Shin W, Heo YS: Molecular mechanism of PD-1/PD-L1 blockade via anti-PD-L1 antibodies atezolizumab and durvalumab. Sci Rep 2017;7:5532.

173 Magen H, Muchtar E: Elotuzumab: the first approved monoclonal antibody for multiple myeloma treatment. Ther Adv Hematol 2016;7:187-195.

174 Dhillon S: Dinutuximab: first global approval. Drugs 2015;75:923-927.

175 Tarhini A, Lo E, Minor DR: Releasing the brake on the immune system: ipilimumab in melanoma and other tumors. Cancer Biother Radiopharm 2010;25:601-613.

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

			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]**.