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Engineering the supernatural: monoclonal antibodies for challenging infectious diseases

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The COVID-19 pandemic demonstrated that monoclonal antibodies can be deployed faster than antimicrobials and vaccines. However, the majority of mAbs treat cancer and autoimmune diseases, whereas a minority treat infection. This is in part because targeting a single antigen by the antibody Fab domain is insufficient to stop the dynamic microbial life cycle. Thus, finding the 'right' antigens remains the focus of intense investigations. Equally important is the antibody-Fc domain that has the capacity to induce immune responses that enhance neutralization, and limit pathology and transmission. While Fc-effector functions have been less deeply studied, conceptual and technical advances reveal previously underappreciated antibody potential to combat diseases from microbes difficult to address with current diagnostics, therapeutics, and vaccines, including *S. aureus*, *P. aeruginosa*, *P. falciparum*, and *M. tuberculosis*. What is learned about engineering antibodies for these challenging organisms will enhance our approach to new and emerging infectious diseases.

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Introduction

Passive serum therapy was one of the main approaches to treat microbial infections. With the success of

antibiotics and vaccines, use waned. Now, the rise of antibiotic-resistant organisms, and the time required for vaccine development have renewed interest in antibodies. With the success of monoclonal antibodies (mAbs) for cancer and autoimmune diseases, the potential for infectious diseases is promising. Rapid antigen discovery and engineering antibody-Fc-domain enhancement offer new opportunities to address microbial antigen diversity, pathological virulence factors, and transmission — all of which contribute to infectious disease morbidity and mortality. As much work has focused on viruses, particularly SARS-CoV-2, HIV, influenza, and Ebola, here we discuss strategies that target persistent and growing challenges for bacteria and parasites where antibodies are less well studied. We use *Plasmodium falciparum*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Mycobacterium tuberculosis* — microbes that demonstrate the limitations of our current infectious disease armamentarium — to highlight the potential for antibodies to combat microbial diversity, pathogen evasion, and transmission.

Antibodies have the potential to directly neutralize and recruit immune responses to control infection via antibody-effector functions that target microbes specifically. Through the constant, crystallizable (Fc) domain, distinct isotypes (IgA1, IgA2, and IgM) and subclasses (IgG1, IgG2, IgG3, and IgG4) differentially engage Fc receptors (FcR) on monocytes, macrophages, neutrophils, dendritic cells (DCs), and natural killer (NK) cells to induce cellular cytotoxic and phagocytic responses (Figure 1). Thus, beyond direct neutralization or blocking initial infection, antibodies also enable immune cells to combat microbial pathogenesis and inhibit infection.

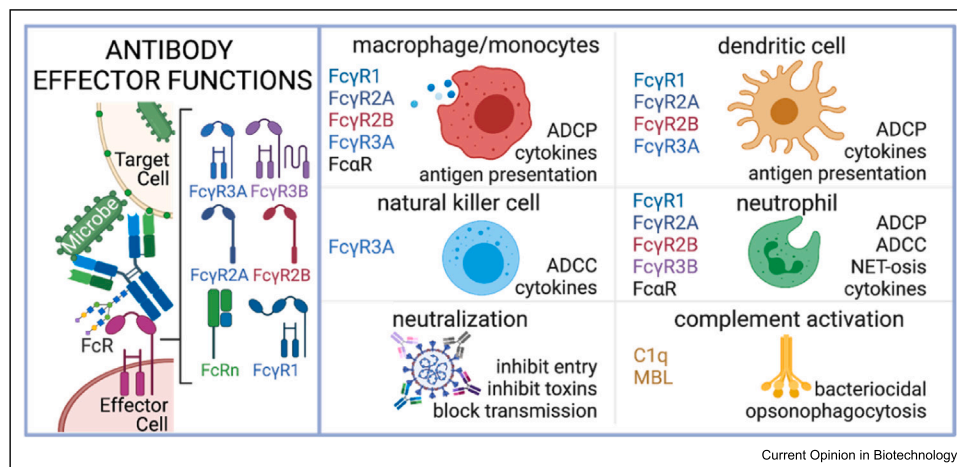
Capturing the microbe

Recent studies have demonstrated unique ways that mAbs can disrupt microbial infection: blocking entry, neutralizing microbes, and microbial effectors (i.e. toxins), disrupting biofilms, inducing innate immune-effector functions that kill microbes, and limiting vertical and horizontal transmission (Figure 2).

Blocking microbial antigens involved in entry and spread

Blocking entry into cells is a means to reduce infection and replication of a pathogen. One of the primary issues faced in developing effective mAb therapies is identifying pathogen-specific antigens critical for the life cycle within the host that are broadly applicable across

Figure 1



Antibodies function through the combination of the Fab and Fc domains. The antibody Fab domain recognizes extracellular microbes or infected host cells. Antibody–Fc interactions with FcR expressed on effector cells, including FcγRs and FcαR, induce a breadth of Fc-effector functions. High-affinity-activating FcRs (such as FcγR1 and FcRN) bind tightly to IgG. Modulation of functions is mediated by the combinatorial engagement of the low-affinity-activating FcRs (FcγR3A, FcγR3B, and FcγR2A) and the only inhibitory FcγR2B. The various subclass, isotype, and post-translational Fc glycosylation of antibodies alter Fc–FcR interactions to modulate ADCP in DCs, macrophages, monocytes, and neutrophils; ADCC on NK cells and neutrophils; inflammatory chemokine and cytokine responses; and complement activation.

multiple strains. Rapid identification and development of affinity-matured antibodies targeting pathogen-specific antigens are now possible with advances in hybridoma screening [1], barcoded antigen-baited B-cell sequencing (LIBRA-seq) [2], human single-CDR scFV library generation [3], and yeast-display technology [4–6]. Such techniques were used to identify the novel mAbs, C1S43, and L9LS, from a human malaria vaccine [7,8]. Both target a unique ‘junctional’ epitope of the circumsporozoite protein, conserved across thousands of strains, to inhibit initial entry into hepatocytes. Passive transfer of C1S43 reduces liver burden in a mouse model [7], and phase-I clinical trial data show promise with prevention of malaria [9]. However, as prophylactic use is not broadly feasible in malaria-endemic areas, mAbs targeting the later red blood cell (RBC) stage of the *Plasmodium* life cycle could be more useful. Antibodies that block binding of the *P. falciparum* reticulocyte-binding protein homolog 5 to RBCs inhibit this subsequent and critical parasite-amplification stage [10,11]. Moreover, nonneutralizing antibodies that prevent RBC invasion collaborate with these neutralizing mAbs by extending the window of opportunity for antibody action [10], broadening the use of mAbs in malaria from prophylactic to therapeutic. A similar synergy between nonneutralizing and neutralizing protective antibodies has been observed in other viral infections [12,13], indicating that this combination strategy may be applied to additional pathogens. Therefore, mAbs for pathogens with multiple life-cycle stages, such as malaria, likely require more than one antigen target to effectively block infection and disease (Figure 2a).

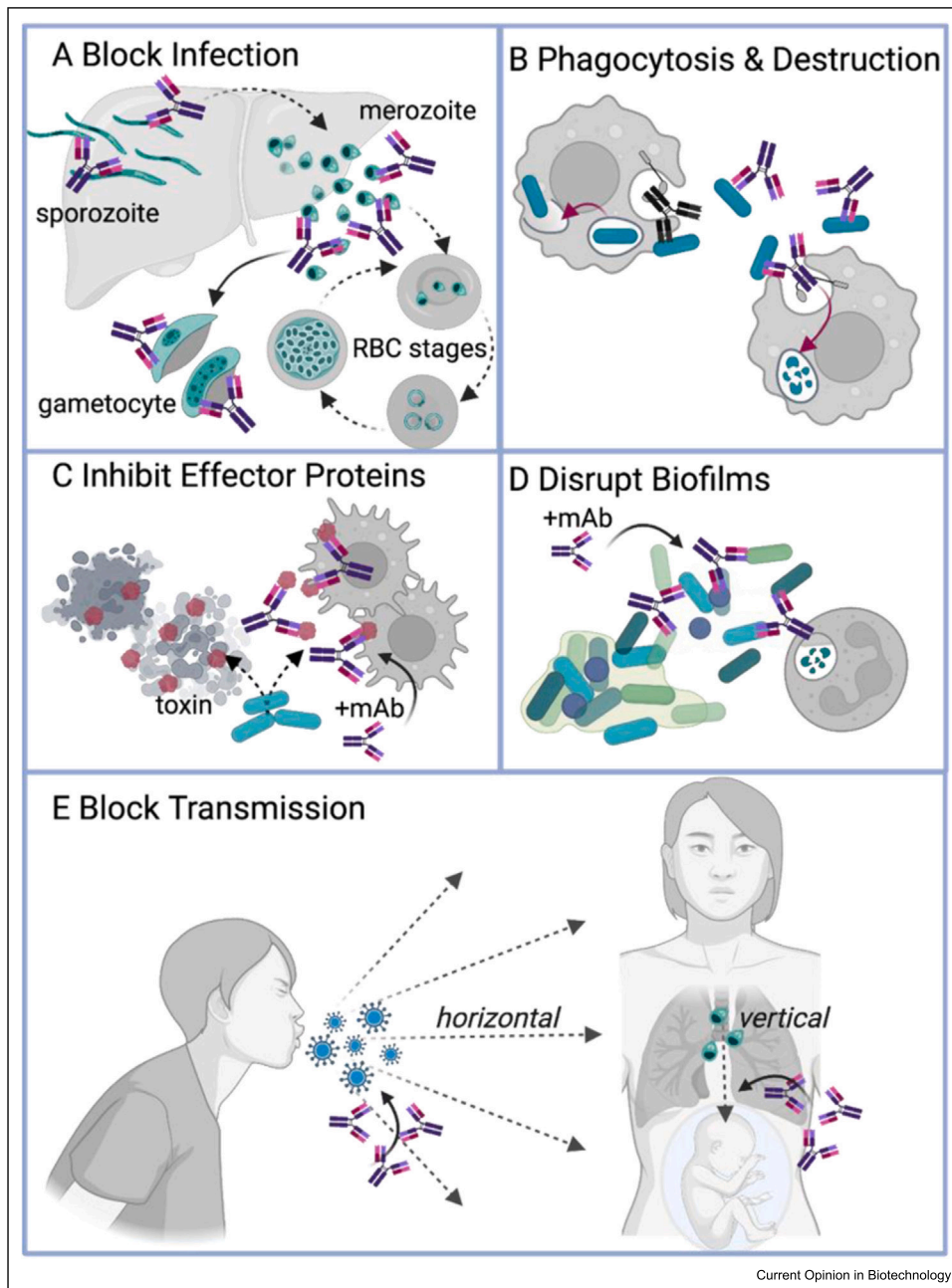
Targeting pathogens for immune-cell destruction

For bacteria that replicate in the extracellular space, enhancing uptake by neutrophils, monocytes, and macrophages via antibody-dependent cellular phagocytosis (ADCP) can limit bacterial replication and dissemination (Figure 2b). *S. aureus* employs several mechanisms to evade phagocytosis: lipoteichoic acid, SpA, and Sbi prevent antibody-mediated complement deposition and opsonophagocytic activity [14]. Antibodies targeting these evasion strategies, 3F6 and tefibazumab, have been engineered to prevent IgG binding to the SpA protein. As a result, improved opsonophagocytic activity and reduced bacterial burden in a mouse model of sepsis have been observed [15]. However, the protection seen from highly opsonophagocytic mAbs in animal models is often not recapitulated in humans [16–18], suggesting that microbial uptake alone is insufficient to improve infection outcomes. Indeed, studies with *Legionella* show that bacteria can persist inside a host cell, and only in the presence of FcR signaling is bacteria directed into lysosomal compartments for degradation [19]. These data demonstrate that antibody Fc is critical for driving bacterial destruction following phagocytosis, and engineering Fc domains (discussed below) could improve *S. aureus* mAb efficacy.

Inhibiting microbial effector proteins

Antibodies targeting toxins and secreted virulence factors of many pathogens have therapeutic and prophylactic potential (Figure 2c). Bezlotoxumab directly neutralizes *Clostridium difficile* enterotoxin B and reduces recurrent *C. difficile* infections [20,21]. For *S. aureus*, a

Figure 2



Antibodies have the potential to target a spectrum of host microbial interactions in infectious diseases. **(a)** Antibodies targeting key *P. falciparum* antigens can block infection at multiple stages of the malaria life cycle. By inhibiting liver infection, antibodies prevent sporozoite adaptation and replication within the host. Later in the *P. falciparum* life cycle, antibodies targeting blood-stage antigens block schizont and ring-stage infection of RBC. Finally, antibodies targeting gametocyte antigens decrease transfer of *P. falciparum* to the mosquito vector from the infected host. **(b)** Some but not all antibodies facilitate pathogen uptake to direct phagocytosed pathogens to lysosomal compartments for destruction. **(c)** Antibodies can bind and neutralize pathogenic toxins and virulence factors to prevent lysis of cells and tissue damage during infection. **(d)** Antibodies specific for antigens found within the matrix of microbial biofilms can disrupt their structure and recruit immune cells to eradicate bacteria. **(e)** Nebulized antibody therapy can reduce horizontal transmission of infection via aerosol. During pregnancy, antibodies can block vertical transmission to the fetus.

mAb cocktail targeting α -hemolysin and leukocidins, which lyse cells and destroy tissues, significantly decreased mortality in a model of necrotizing pneumonia

compared with monotherapy [22], showing that inhibiting multiple effector proteins simultaneously could provide clinical benefit. As such, targeting microbial

effector proteins that inhibit antibiotics could be synergistic with current antimicrobial therapies. Antibiotic resistance is one of the top-10 threats to global health. Monoclonals developed to inhibit the penicillin-binding protein PBP2a of *S. aureus* demonstrate the potential for prophylactic and therapeutic use against penicillin resistance [23]. Gram-negative bacteria, including *P. aeruginosa*, have developed β -lactamases to resist destruction of their cell membranes by the β -lactam class of antibiotics. Some individuals infected with *P. aeruginosa* develop antibodies that target β -lactamases [24], and passive transfer of these antibodies to mice can protect against infection. Strategies that employ high-throughput B-cell sequencing and screening from infected individuals could be used to discover new targets to develop into novel mAbs that combat additional mechanisms of antibiotic resistance and microbial pathogenesis.

Disrupting biofilms

As some infections progress, bacteria generate biofilms that facilitate persistence within the host [25,26]. Biofilms are extracellular matrices containing DNA, proteins, and polysaccharides that serve as a scaffold niche for microbial growth, often found on implanted medical devices. These structures resist antibiotic therapies and require prolonged treatment to prevent recrudescence [27]. One antibody-based strategy to disrupt biofilms is to target bacterial components of the biofilm (Figure 2d). Targeting the highly conserved bacterial DNAIIB with mAbs or vaccination disrupts biofilms for many Gram-negative and -positive bacteria such as *S. aureus* [28,29] and prevents recurrent ear infections from nontypeable *Haemophilus influenzae* in the preclinical chinchilla model [30]. One of these promising mAbs, TRL1068, is currently being evaluated in phase-I clinical trials for prosthetic joint infections to determine the synergistic efficacy with antibiotics against *S. aureus* biofilms [31]. If successful, these mAbs could then be used to shorten antibiotic treatments, potentially limiting the development of toxicities and resistance.

P. aeruginosa also forms biofilms but identifying effective antigen targets remains quite challenging. A mAb targeting alginate, a polysaccharide thought to be on the bacterial surface in the biofilm stage, failed to improve patient outcomes [32], despite promising preclinical animal data [33,34]. However, recent data show that neutrophil extracellular traps (an antibody-inducible effector function — Figures 1 and 2d) can disrupt *Pseudomonas* biofilm formation to prevent brain invasion in animal models [35]. Thus, further studies to identify additional antigen targets in the biofilm stage of the microbial life cycle together with the addition of Fc-effector functions may enhance the capacity of mAbs to disrupt biofilms.

Preventing transmission

Beyond treating the infected individual, preventing microbial transmission and spread is a public health concern. Intravenous and nebulized mAbs that rapidly distribute into the lungs can reduce viral burden, pathology, and production of infectious SARS-CoV-2 [36,37]. These pharmacodynamic characteristics could be leveraged for other pulmonary pathogens such as *Mycobacterium tuberculosis*, which produces sulfolipids that induce cough in an infected host [38] and could be used as an intriguing target for antibody blockade of transmission.

For vector-borne diseases such as malaria, parasites that cycle through the host must pass through the mosquito for horizontal transmission. A mAb targeting Pfs230, a highly conserved malarial antigen, can induce complement activity against *P. falciparum* gametocytes [39]. By killing these gametocytes, this mAb inhibits a critical step of the life cycle: the transfer from an infected human through a mosquito to a new human host (Figure 2a).

Finally, antibodies may also be deployed to prevent vertical transmission. In a study of malarial transmission from mother to baby, the presence of phagocytic antibodies targeting VAR2CSA, a *P. falciparum* antigen expressed on infected erythrocytes and required for placental infection, tracked with protection [40]. As IgG is the only isotype that crosses the placenta, strategies that capture these Fc functions could benefit the maternal–fetal dyad. Thus, many antibodies generated during natural infection can be leveraged to prevent not only microbial infection and virulence but also horizontal and vertical transmission (Figure 2e).

Engineering host immunity

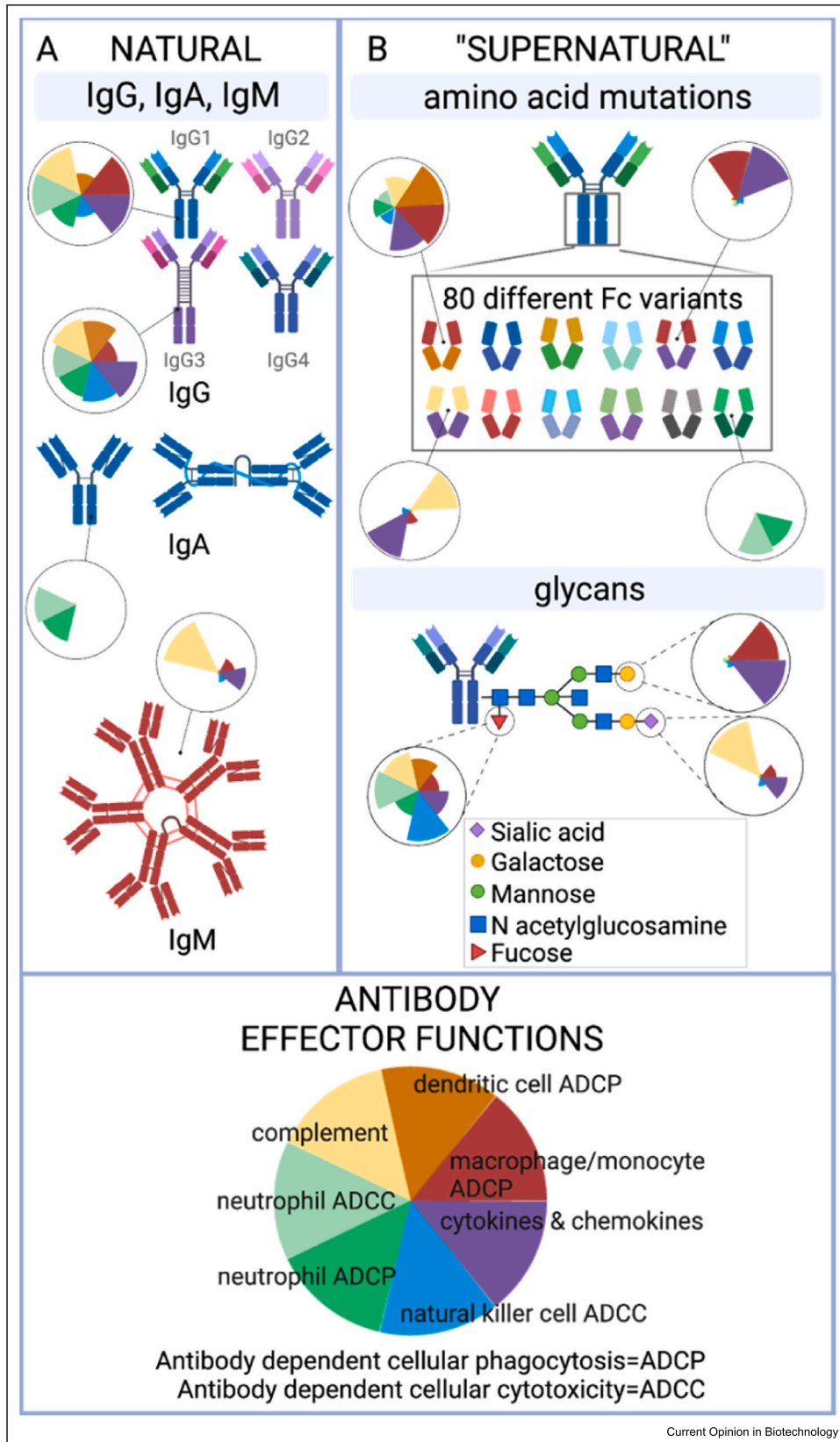
The examples highlighted above point to mechanisms and functions that may be incorporated into clinical products for use against microbial diseases. Strategies that take advantage of the diversity of antibody functions conferred by isotype, subclass, and glycosylation observed after natural infection and vaccination together with antibody molecular engineering tools broaden the possibilities for antibody-based therapeutics (Figure 3).

Leveraging different antibody isotypes

The majority of licensed mAbs are human IgG1 [41], but many protective functions arise from intrinsic properties of other isotypes and subclasses (Figure 3). Thus, IgM, IgA, and IgG3 can employ mechanisms of microbial clearance distinct from IgG1.

For IgM, multivalent binding via pentamers and hexamers enhances avidity for microbial targets and is a potent activator of complement. In an intravenous

Figure 3



Diverse antibody-Fc-effector features and functions induced during natural infection have the potential to form the basis of engineering mAbs with 'supernatural' functions. **(a)** In humans, natural diversity in subclass and isotype drives distinct antibody-effector functional profiles. IgG is the predominant isotype detected at the highest level in the blood followed by IgA and IgM. All three isotypes are also detected in the lung after many different infections and vaccinations. Classical multimerization structures are shown through additional scaffolds have been described. Of the IgG subclasses, levels of IgG1 > IgG2 > IgG3 > IgG4 in the blood with the longest hinged IgG3 having the shortest half-life but highest affinity for Fc γ R and complement. Further variation is observed with IgG alleles where amino acid changes influence CH3-CH3 interactions that impact stability and FcR binding along with downstream immune-effector functions. **(b)** Through engineering amino acid and glycosylation modifications on Fc domains, mAbs with 'supernatural' Fc-effector functional profiles that enhance protection without pathology can be generated. The combinatorial diversity from 80 amino acid and up to 36 glycan variants possible with the selective addition and subtraction of specific sugars provides a breadth of possibilities of antibody-effector functions (bottom key) for each antigen recognized by a mAb.

Bacille Calmette-Guerin vaccine study to prevent *M. tuberculosis* infection in nonhuman primates (NHP), IgM targeting a surface glycopeptidolipid tracks with sterilizing immunity. The protective nature of this isotype is corroborated by data from *in vitro* *Mtb*-restriction assays using both NHP plasma and an IgM mAb [42]. In malaria, high-avidity IgM can block *Plasmodium* invasion of RBC [43]. In COVID-19, IgM can provide superior SARS-CoV-2-neutralizing activity compared with IgG [44]. For *P. aeruginosa*, IgM can synergize with standard antimicrobials to treat pneumonia [45,46]. Thus, although IgM is usually only transiently induced at the beginning of natural infection, extending its activities through mAbs could enhance our ability to combat some pathogens.

IgA is enriched at mucosal sites and present in circulation, engaging Fc α / μ receptors on macrophages and neutrophils (Figures 1 and 3a). IgA targeting the sporozoite cloned from malaria-resistant individuals reduces liver-parasite burden in mice [47]. Superior binding to sporozoites was observed for IgA compared with the IgG isotype [47]. Similarly, mAbs targeting the *Mtb* antigens Acr/HspX [48,49], LAM and HBHA [50], are protective as IgA but not IgG. These studies suggest that the unique features of the IgA Fc domain permitting dimerization and other multimerization may contribute to better inhibitory functions.

While IgG1 is the dominant subclass, IgG3 has the highest binding affinity and is partial to Fc γ R3A (Figure 3a). The importance of this interaction and downstream effector functions is shown in studies highlighting correlates of protection in HIV [51], malaria [40,52,53], and TB [54,55]. Thus, though IgG3 has the shortest half-life of all the subclasses, augmenting these highly functional antibodies could have broad applications across microbes.

Issues with IgA, IgM, and IgG3 stability, post-translational glycosylation and pharmacokinetics limit translating these promising functions to effective therapeutics. However, modifications of antibodies on the amino acid level to prevent degradation and improve structural stability and development of large-scale cellular-production systems have addressed some of these challenges [56,57].

Engineering 'supernatural' antibodies

A parallel approach to developing IgA-, IgM-, and IgG3-based therapeutics is to adapt the human IgG1 Fc domain, crafting 'supernatural' mAbs that encompass many properties of natural antibodies in a single molecule. Amino acid [58] and post-translational glycosylation [59] modifications on the Fc domain alter Fc functions (Figure 3b). These Fc variants, such as LS for the malaria C1S43 and L9LS mAbs, increase half-life through binding to FcRn [8,9,60,61]. Additional changes drive specific Fc-mediated immune-cell functions via altered FcR affinity.

Amino acid modifications

Studies identifying amino acids within the Fc domain that mediate binding to FcRs, specifically Fc γ R2A and/or Fc γ R3A, have demonstrated its critical nature in protection [62–66]. However, the specific immune-cell functions required for protection remain unclear and are likely unique for each different pathogen. A higher-throughput engineering platform for amino acid modification, Rationally Engineered and Functionally Optimized Recombinant Monoclonal antibodies (REFORM), generates up to 80 different Fc variants for a given Fab carrying a range of functions to precisely define mechanisms of protection [67] (Figure 3b). Modification of an Ebola-specific antibody using the REFORM platform identified two Fc variants with enhanced complement activation and phagocytosis able to completely protect against death and disease in a mouse model of infection [67]. When applied to TB, REFORM of α -glucan-specific mAb found that IgG2 mediated restriction of *Mtb* in a whole-blood assay through neutrophils [68]. Because the Fab domain impacts Fc binding, the use of REFORM early in mAb-discovery pipeline for each antigen specificity could help identify unexpected Fc functions that control infection. Though these antibody functions may not naturally occur in the context of infection, through mAbs, they can be leveraged against the pathogen.

Glycans

Beyond amino acid composition, engineered cell lines and enzymes have been used to modify antibody glycans that enhance effector functions [69–71] (Figure 3b). In particular, afucosylated IgG (i.e. those lacking fucose) have significantly increased affinity for Fc γ R3A/B and its

effector functions, including antibody-dependent cellular cytotoxicity (ADCC). Afucosylated mAbs have increased protective efficacy against the highly pathogenic Ebola virus [72]. In addition, galactosylated but not sialylated *S. aureus*-specific mAb 3F6 conferred *in vivo* protection against sepsis via C1q recruitment [73]. Recent studies suggest that galactosylation increases hexamerization and subsequent complement activation [74]. Thus, enhancement of 3F6 via galactosylation could be due to enhancement of Fc-effector functions as opposed to binding to antigen. In polyclonal antibodies, sialic acid has been shown to enhance vaccine responses [75], potentially through complement activation [76]. Sialic acid may also have an anti-inflammatory effect on intravenous immunoglobulin, a polyclonal IgG pooled from thousands of human donors to treat rheumatologic disorders [77,78]. As such, hypersialylated polyclonal IgG M254 is currently in clinical trials for the autoimmune disorder immune thrombocytopenic purpura. Thus, glycan structures on the Fc domain will be important in the design of future mAbs for the treatment of infectious disease.

Potential for antibody-mediated enhancement of disease

Functions that enhance protection without pathology are critical for effective and safe therapies. Antibody-dependent enhancement (ADE) occurs in Dengue virus infection where afucosylated antibodies are linked to more severe hemorrhagic fever [79,80]. Similarly, ADE may explain increased disease associated with a 1960s formalin-inactivated respiratory syncytial virus vaccine [81] and is hypothesized to be the reason why increased mortality was observed to be associated with *S. aureus* V710 vaccination [82]. ADE has been a concern for COVID-19 based on observations that afucosylated IgG increases with severe disease [79,83] and transfer of polyclonal IgG from patients into human FcR transgenic mice leads to pathology [66]. Strikingly, there have been no reports of clinically relevant mAb-induced ADE, despite its prolific use. mAbs that mediate ADE *in vitro* paradoxically correlated with decreased microbial burden and increased protection *in vivo* [12]. Moreover, Fc engineering of potently neutralizing SARS-COV-2-specific mAbs to enhance binding to hamster and human FcRs improved therapeutic efficacy in hamster and human FcR transgenic mice [66]. As these data show the complexity of ADE, further understanding its mechanisms will aid in building supernatural mAbs to confer protection without pathology.

Where we can go

Tailoring each approach to the unique microbial life cycle and critical steps of clinically relevant disease pathology is key to harnessing the potential of antibodies. Emerging concepts and technologies are enabling us to capture these nuances and even redesign mAbs

previously thought to be ineffective into more functional therapies. In addition, capturing antibody functions that are associated with lifelong protection from childhood infection or vaccination against measles, mumps, chicken pox, yellow fever, and polio may offer mechanisms of protection that could be leveraged in mAbs. Further, immune mechanisms by which subsets of individuals are phenotypically protected from disease such as HIV-elite controllers, highly HIV-exposed seronegative, or TB resisters, could be harnessed to benefit a greater population [84–87].

The antibody functions described here are among the most well-explored. Noncanonical and newly discovered receptors that bind to the Fc domain (TRIM21, DC-SIGN, pIGR, transferrin, FcRL, etc.), report of FcR expression on immune cells not previously appreciated, such as T cells and links to additional immune activities (autophagy, inflammasome activation, and trogocytosis) expand the breadth of antibody functions beyond the scope of this review. Moreover, we are just beginning to understand how Fab antigen and Fc–FcR interact together through multiplexing to provide microbial-specific antibody-effector functions. Finally, antibodies and antibody-like proteins from chickens, camelids, lampreys, and sharks amplify the capacity to bind antigen, penetrate tissue, and maintain stability. Across all species, antibodies continue to surprise us with each new discovery bringing opportunities to build effective and safe tools against current and new pathogens alike.

Author contributions

Patricia Grace: Conceptualization, Visualization, Writing – original draft, Writing – review & editing.
Bronwyn Gunn: Conceptualization, Visualization, Writing – original draft, Writing – review & editing.
Lenette Lu: Supervision, Conceptualization, Visualization, Writing – original draft, Writing – review & editing.

Conflict of interest statement

The authors declare no conflicts of interests.

Data Availability

No data were used for the research described in the article.

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- of special interest
- of outstanding interest.

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