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Engineering therapeutic antibodies to combat infectious diseases

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Abstract

Serum therapy fell out of favor 80 years ago, but antibodies against infectious diseases are now experiencing a renaissance. With the evolution of antibiotic-resistant bacteria, the emergence of new pathogens, and a growing population of immunocompromised individuals coupled with improvements in antibody manufacturing and biological efficacy, antibodies are an increasingly attractive therapeutic option. In this review, we highlight successful clinical strategies and discuss recent applications of advanced antibody engineering approaches to combat infectious diseases. Case studies include antibody mixtures to neutralize *Staphylococcus aureus*; bispecific antibodies promoting *Pseudomonas aeruginosa* clearance; antibody-antibiotic conjugates to eradicate *S. aureus* from protected intracellular niches; and novel anti-RSV antibodies with extended serum half-life. These new designs are powerful strategies for targeting infectious diseases due to their abilities to target multiple antigens and induce novel clearance mechanisms.

Graphical Abstract

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Conflicts of interest

The authors have received research funding from Synthetic Biologics. EKW is currently employed by Achaogen.

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Introduction

Global sales of monoclonal antibody products have grown at a rapid pace, from ~\$39 billion USD in 2008 to nearly \$75 billion in 2013, and are projected to reach ~\$94 billion in 2017 [1]. Monoclonal antibodies, already the driver of the biotech industry with 24.6% of US sales in 2012, are set to capture an even larger share of the market due to faster sales growth and higher approval rates over other pharmaceuticals [1,2]. Of the currently marketed products, most target cancer, inflammatory or autoimmune disorders, while just four target infectious diseases (Figure 1).

Although antibodies are more expensive to manufacture and harder to deliver than traditional small molecules, they also offer key advantages for treating infectious diseases. Antibodies are highly specific, allowing for selective targeting of pathogens, without disturbing the natural microbiota. Antibodies targeting pathogens can exhibit multiple mechanisms of action, including bactericidal activities, such as complement-mediated or opsonophagocytic killing, as well as more specialized anti-virulence functions. Notably, antibodies that simply block the interaction between a pathogenic protein and the relevant host receptor have demonstrated success in the clinic. Antibodies have the potential to reduce the spread of antibiotic resistance and, since the mechanisms of action are complementary, antibodies and antibiotics often exhibit additive or synergistic effects when co-administered [3].

The growing list of antibiotic-resistant bacteria, emerging pathogens and immunocompromised individuals underscores the urgent need for new anti-infective drugs to complement the antibiotic arsenal. Not only are antibodies subject to algorithmic manufacturing processes, but they are typically safe and well-tolerated, with few off-target effects, and do not interfere with other drugs. Here, we review recent clinical successes and case studies highlighting exciting new designs for the next generation of anti-infective antibodies. These include antibody cocktails, antibody variants with extended half-lives and new antibody formats, including various bispecific and linked nanobody designs, that offer access to new therapeutic mechanisms.

Anti-infective antibodies approved for human use

Anti-viral fusion antibodies

The first available anti-infective monoclonal antibody was Pavilizumab, which was approved in 1998 for the prevention of respiratory syncytial virus (RSV), and is currently indicated for use in high-risk, pre-term infants. RSV encodes 11 proteins, including the fusion F surface glycoprotein, a key therapeutic target. This protein drives the initial infection of a host cell by mediating fusion between the viral and eukaryotic membranes as it switches from a poorly stable pre-fusion to a stable post-fusion conformation. Palivizumab binds an epitope present in both conformations, physically blocking membrane fusion (Figure 1C) [4]. Monthly dosing of Pavilizumab during the RSV season has been shown to reduce the risk of infant hospitalization and the length of stay each by ~50% [5].

Anti-toxin antibodies

Monoclonal antibodies targeting bacterial toxins have been successful in treating diseases dominated by a single toxin; indeed, three of the four approved anti-infective antibodies target toxins (Table 1). These proteins are secreted during an infection and promote disease by damaging tissues at the infection site or by causing systemic effects. Neutralizing antibodies commonly act by blocking receptor-binding sites on the toxin [6], but can also prevent conformational changes essential for toxin activity [7], alter intracellular trafficking [8] or form immune complexes that facilitate toxin removal [9]. In these ways, antibodies block toxin activities, allowing antibiotics and the host immune system to clear the infection and resist other opportunistic infections [10]. For toxins that are immunosuppressive, anti-toxin antibodies can indirectly support bacterial clearance by protecting the immune system.

Two antibodies are approved to treat anthrax by targeting the anthrax toxin: Raxibacumab in 2009 [11] and Obiltoximab in 2016 [12]. Anthrax toxin is a classic AB toxin, with two enzymatically active A subunits and one receptor binding B subunit. Both antibodies bind the B subunit, protective antigen (PA), competitively inhibiting the interaction with the major PA receptor, capillary morphogenesis 2 (CMG2; Figure 1D) [13]. By blocking this initial interaction, the toxin never reaches its intracellular target and damage to cardiomyocytes and hepatocytes is prevented [14]. Antibodies blocking nearly every step in the complex anthrax intoxication process have been identified, including those that block PA cleavage by furin, subsequent PA heptamerization and association of the active subunits with PA. Many of these are protective in *in vitro* and animal models and several were subject to clinical development (for review, see [15]).

Bezlotoxumab was approved in 2016 for prevention of recurrent *Clostridium difficile* infection by neutralizing the enterotoxin TcdB [16]. *C. difficile* is a spore-forming bacterium that can colonize and cause severe infection when the normal gut microbiome is disrupted, often in response to long-term antibiotic regimens. The homologous TcdA and TcdB toxins bind unknown receptors on gut epithelial cells, enter via endocytosis and disrupt tight junctions, leading to increased gut permeability and inflammation [6]. While antibodies against both toxins contribute to protection in animal models and were developed, Bezlotoxumab demonstrated superior efficacy in clinical trials [17]. This antibody acts by binding two homologous sites in the N-terminal domain of TcdB, thereby occluding the receptor binding site [6].

Engineering strategies for anti-infective antibodies

Motivated by these successes, antibodies have been developed to treat other infectious diseases, particularly those for which no vaccine is yet available or those exhibiting high levels of antibiotic resistance. These pathogens are in general more complex, with large genomes, diverse sets of virulence factors and no clear serological correlates of protection. This led to a series of clinical failures for antibodies focused on a single target, most notably for *Staphylococcus aureus* (for review, see [18]). However, new approaches in antibody engineering, coupled with increased understanding of the clinical microbiology, sero-epidemiology and structures of neutralizing epitopes have led to promising new designs which are now entering the clinic.

Antibody cocktails

The first approach is to combine several antibodies into a cocktail targeting multiple antigens and epitopes. This strategy mimics the natural polyclonal immune response and can provide broad protection against a variety of strains using several complementary mechanisms. The key is selection of antibodies which are individually high affinity, neutralizing and typically target different conserved epitopes to reduce to risk of escape variants. While cocktails are currently more expensive to produce than monoclonal therapies, new strategies for their efficient production at manufacturing scales are being developed (for review, see [19]). Moreover, proposed FDA approval rules would no longer require separate efficacy trials for each component in addition to the combination [20].

Development of antibody cocktails is of particular interest for highly mutable pathogens such as HIV, which can evolve escape variants even during treatment with a highly potent, broadly neutralizing antibody [21]. A mixture of antibodies targeting distinct epitopes is expected to protect against a broader range of circulating strains, while simultaneously reducing the risk of escape variants. Supporting this notion, mixtures of two-to-four antibodies binding different neutralizing epitopes on the HIV envelope glycoprotein were able to neutralize 100% of viruses from a panel of 125 strains under conditions while the individual antibodies only neutralized 25–66% [22]. Similarly, a combination of two antibodies binding the Ebola glycoprotein rescued lethally infected non-human primates treated three days after exposure [23]. However, antibody escape variants did emerge from one of five non-human primates treated with a different trivalent anti-ebola cocktail, emphasizing the importance of identifying antibodies recognizing invariant epitopes [24].

Cocktails have also been explored to target multiple bacterial virulence factors simultaneously. In a well-known example, a ternary mixture of anti-botulism toxin antibodies which exhibited a 20,000-fold increase in potency compared to each individual antibody [25]. Similarly, two antibodies targeting the pertussis toxin, a major virulence factor involved in pathogenesis caused by *Bordetella pertussis*, showed efficacy in treating established disease in baboons when administered three days after infection. This cocktail included two neutralizing antibodies targeting this AB toxin: one binding the B subunit and blocking the toxin-receptor interactions and a second binding the A subunit [26]. In another case, two antibodies binding the staphylococcal enterotoxin B superantigen act via complementary mechanisms. This superantigen non-specifically activates T cells by linking the T cell receptor beta chain to a class II major histocompatibility complex on an antigen presenting cell. One antibody neutralizes the toxin binding site on the T cell receptor while the other, non-neutralizing, antibody supports formation of immune complexes involved in Fc-gamma receptor IIb (Fc γ RIIb) mediated toxin clearance [27].

Bispecific antibodies

Advances in antibody cloning, expression and purification technologies have led to a veritable lego-set of antibody parts that can be used to design new therapeutics, with nearly 100 different bispecific antibodies in development (for review, see [28]). The simplest application is a heterodimer with two heavy and two light chain sequences forming two different binding sites with distinct binding specificities (Figure 2A). In this way, a single

protein can bind two different antigens, or two different epitopes on the same antigen. This strategy was shown to retain the synergy exhibited by an antibody cocktail neutralizing pertussis toxin in mice [29], supporting the idea that bispecific antibodies offer an alternative to oligoclonal mixtures with streamlined manufacturing processes.

Bispecific antibodies can also be leveraged to increase the efficacy and effective affinity for a challenging target by co-localizing with the pathogen in sub-cellular compartments. A bispecific antibody for *Pseudomonas aeruginosa* binds to the ubiquitous exopolysaccharide Psl, and, once anchored to the bacterial surface, is better positioned to find and bind the therapeutically relevant PcrV protein [30]. This approach first targets the bacteria for phagocytosis and then blocks secretion of virulence factors from the type three secretion system, leading to enhanced bacterial destruction in the neutrophil lysosome [31]. This tetravalent construct is comprised of an anti-Psl antibody with an anti-PcrV single-chain antibody (scFv) inserted in the hinge region which was selected after empirical evaluation of multiple designs (named BiS4; Figure 2B). Despite the unusual topology of this design, the protein is sufficiently well-expressed and stable to support clinical development [32].

A similar design was created to block the initial binding event between the ebola viral glycoprotein and its receptor, an event which occurs in the endosome. A “Trojan horse” bispecific antibody was constructed in which one binding site attaches to a conserved, surface-exposed glycoprotein epitope on the virus, allowing the antibody to hitchhike during normal virus trafficking to the endosome. Once there, the second binding site attaches to the host receptor or the receptor binding site on the glycoprotein, thereby blocking viral fusion. This design is comprised of antibody constant regions with two tandem binding sites on each arm, or dual-variable domain antibody (DVD-Ig; Figure 2A). Notably, this design conferred post-exposure protection in mice, while neither parent monoclonal antibody was protective [33].

Finally, bispecific antibodies can provide access to novel therapeutic mechanisms. One approach first developed for anti-cancer therapies is to redirect any cytotoxic T cell to a tumor cell by bridging surface receptors on each cell with a bispecific formed by two linked scFvs [34]. This approach was adapted for HIV suppression with a bispecific antibody in which one arm binds the CD3 complex on the surface of a T cell, while the other binds the HIV envelope protein [35] or a peptide-MHC complex [36] on the surface of an infected cell (Figure 2C). These bispecific antibodies trigger immune synapse formation, release of pore-forming and cytotoxic molecules and, ultimately, killing of the infected target cell. A key design requirement is higher affinity for the infected cell surface protein than for CD3, to localize the therapeutic to infected cells.

Although these novel formats can be potent therapeutics, it is critical to ensure compatibility between the epitopes targeted and desired mechanisms when designing bispecific antibodies. For example, two antibodies targeting *Staphylococcus aureus* are protective individually and exhibit synergy as a mixture of monoclonal antibodies: one antibody binds the surface-bound clumping factor A (clfA) to block bacterial attachment and promote opsonophagocytosis, while the other inhibits heptamerization and receptor binding of the secreted alpha toxin, thereby protecting immune cell function [37]. However, a bispecific

combining these two antibodies afforded less protection than the binary cocktail, presumably due to reduced alpha toxin neutralization when one arm of the bispecific antibody was tethered to the bacterial cell surface [38].

Fc engineering

Antibodies are particularly valuable for their long serum half-lives (~21 days for an IgG1 isotype), which stem from pH-dependent binding between the antibody Fc region and the neonatal Fc receptor, FcRn. After endocytosis, antibodies are rescued from degradation by tight binding to FcRn at low endosomal pH (~6.0), hitchhiking as FcRn is recycled to the cell surface, where the higher serum pH of 7.4 and associated weaker antibody-FcRn binding releases the antibody back into circulation [39]. Antibodies with extended half-life could provide an increased duration of protection, while simultaneously reducing therapeutic dosages and dosing frequency.

Accordingly, antibody variants have been identified in which changes to the C_H2–C_H3 domains result in higher FcRn affinity at pH 6.0 and unchanged binding at pH 7.4. The M252Y/S254T/T256E or “YTE” changes in C_H2 confer a four-fold enhanced half-life in humans (85–117 days) [40,41]. A YTE variant of an RSV-targeting therapeutic is currently in clinical trials, and is projected to reduce dosing from five monthly doses to one per season [41]. A second set of amino acid changes, M428L/N434S or “LS” in C_H3, have been shown to confer a similar half-life extension in non-human primates with less impact on Fc γ receptor binding, but results in humans have not yet been reported [42,43].

These successes open the door for additional Fc engineering efforts to support enhanced safety and efficacy in anti-infective antibodies. Many anti-infectious disease antibodies act via Fc-independent mechanisms; for these, reduced effector functions are expected to reduce the risk of toxicity associated with antibody delivery [44,45]. Indeed, “Fc silencing” changes have been identified that prevent glycosylation of residue N297, dramatically reducing complement activation and Fc γ R binding, while retaining long serum half-life, high expression and thermostability [46]. Conversely, for antibodies that rely on Fc-mediated activities, engineering to better engage activating Fc γ receptors may be a successful strategy to improve neutralizing efficacy. For instance, limiting fucosylation of the Fc glycan increases affinity for Fc γ RIIIa, thereby improving ADCC activities [47] and protection against RSV infection in cotton rats [48].

Antibody-drug conjugates

Many of the antibodies discussed above exhibit additive or even synergistic effects when co-administered with antibiotics in animal models [30,49]. This naturally led to the concept of using an antibody-drug conjugate as a single product. First developed as a strategy to target toxic chemotherapy agents to cancerous cells, these molecules exhibit favorable pharmacokinetics as compared to the small molecule drug [50] and can potentially localize the antibiotic to the bacteria, which is inactive until the linker is cleaved to release active drug.

An antibody-antibiotic conjugate was recently reported for the treatment of *S. aureus* [51]. The authors hypothesized that an opsonizing antibody could target *S. aureus* for Fc-mediated

phagocytosis and transport to the lysosome, where phagolysosomal proteases could release the tethered antibiotic. They combined a human antibody binding the conserved cell wall teichoic acid and a rifamycin derivative with activity for non-replicating bacteria (Figure 2D). A series of *in vitro* and *in vivo* experiments demonstrated the expected mechanism of action as well as superiority to standard vancomycin treatment. This novel design allows unprecedented access to a protected reservoir of infectious bacteria, highlighting the potential for antibodies to enhance antibiotic therapy.

Targeting the right epitope with the right antibody

Implicit in the prior discussion is the identification of antibodies binding protective epitopes that are conserved and available for binding during an *in vivo* infection. However, not all neutralizing epitopes are created equal and some may be more protective than others. For instance, the RSV epitope targeted by Palivizumab (antigenic site II) is present on both pre- and post-fusion conformations of the F protein. A newer antibody, D25, targets an epitope (antigenic site Ø) present only on the pre-fusion structure with higher affinity than Palivizumab (K_d 0.07 nM versus ~1 nM), likely acting to prevent the conformational change required for membrane fusion [52]. Discovery of D25 was facilitated by herculean efforts to stabilize and crystallize the F protein in its pre-fusion conformation which have paid off: D25 is 100-fold more potent *in vitro*, nine-fold more potent than Palivizumab in the cotton rat model and is currently in phase II clinical trials [41]. Smaller antibody formats, such as nanobodies with long complementarity determining region (CDR) 3 loops, can access unique epitopes unavailable to traditional antibodies and can be readily multimerized to enhance avidity. This was done for an anti-RSV nanobody, whose epitope overlaps Palivizumab and is in phase II clinical trials, to increase the monovalent 18 nM affinity to a 0.113 nM trimeric affinity [53].

Subtle differences between antibodies binding the same or overlapping epitopes can also significantly affect efficacy. For instance, the early anti-PcrV antibody mab166 protected innate immune functions by blocking secretion of type III virulence factors from *P. aeruginosa*. This antibody provided promising pre-clinical data but did not improve symptoms in cystic fibrosis patients as a humanized and pegylated Fab (for review, [54]). However, these data provided proof-of-concept for PcrV targeting and motivated the subsequent identification of anti-PcrV antibody V2L2MD that recognizes a slightly different conformational epitope with 50-fold higher affinity (K_d of 0.04 versus 2.1 nM) [55]. This antibody is superior in animal models and is now in phase IIb clinical trials as part of the bispecific antibody described above [30].

Similarly, an early humanized antibody binding the *S. aureus* ClfA adhesin, Tefibazumab, under-performed in clinical trials [18], presumably due to insufficient blockade of ClfA-fibrinogen interactions [56]. Knowledge gained from this effort guided identification of a new anti-ClfA antibody which better inhibits fibrinogen binding (IC_{50} of 25 nM versus 330 nM) despite a worse overall affinity (K_d of 4.2 nM versus 0.8 nM). Antibody 11H10 appears clinically promising in several animal models, especially when combined with a second antibody targeting the alpha toxin [37] and improved variants with low picomolar ClfA affinities have been identified [38].

With effort and clever selection schemes, antibodies binding epitopes conserved on multiple strains or even across homologous proteins can be identified. This was shown elegantly with identification of a neutralizing antibody able to bind the *S. aureus* alpha toxin and four homologs with picomolar affinities despite sharing only ~26% overall amino acid sequence identity [57]. Lead antibodies exhibiting low levels of cross-reactivity were initially discovered from a large yeast-displayed human IgG1 library by alternating the ligand used for selection, followed by CDR mutagenesis and additional selection steps. The lead antibody blocks toxin-receptor binding and is protective in a mouse bacterial challenge model. Similarly, antibodies binding highly conserved epitopes, such as that recently identified on the influenza hemagglutinin stem [58], potentially neutralize a broad range of clinical isolates and have enhanced therapeutic potential.

Conclusions

The past few years have introduced a suite of exciting new antibodies, protein architectures and creative therapeutic mechanisms to combat infectious diseases. These efforts have been facilitated by new antibody discovery technologies, including human immune repertoire profiling [58], polyclonal immunoglobulin [59], target agnostic [60], and structure-based computational antibody design [61–63], in addition to experimental structures of virulence factors complexed with receptors and antibodies [4,6,56] and increasingly sophisticated high throughput screening schemes to discover and improve lead antibodies [57]. As a result, nearly 30 anti-infective antibodies are currently in clinical trials (Table 2). There is considerable optimism that these new approaches have addressed the short-comings of previous single component antibodies which did not meet their clinical endpoints and that some of these will ultimately be approved to treat currently challenging diseases.

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References

1. Ecker DM, Jones SD, Levine HL. The therapeutic monoclonal antibody market. *MAbs*. 2015; 7:9–14. [PubMed: 25529996]
2. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. *Nat Biotechnol*. 2014; 32:40–51. [PubMed: 24406927]
3. Hey A. History and Practice: Antibodies in Infectious Diseases. *Microbiol Spectr*. 2015; 3 AID-0026-2014.
4. McLellan JS, Chen M, Kim A, Yang Y, Graham BS, Kwong PD. Structural basis of respiratory syncytial virus neutralization by motavizumab. *Nat Struct Mol Biol*. 2010; 17:248–250. [PubMed: 20098425]
5. Meissner HC, Long SS. American Academy of Pediatrics Committee on Infectious D, Committee on F, Newborn. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. *Pediatrics*. 2003; 112:1447–1452. [PubMed: 14654628]
6. Orth P, Xiao L, Hernandez LD, Reichert P, Sheth PR, Beaumont M, Yang X, Murgolo N, Ermakov G, DiNunzio E, et al. Mechanism of action and epitopes of *Clostridium difficile* toxin B-

neutralizing antibody bezlotoxumab revealed by X-ray crystallography. *J Biol Chem.* 2014; 289:18008–18021. [PubMed: 24821719]

7. Oganessian V, Peng L, Damschroder MM, Cheng L, Sadowska A, Tkaczyk C, Sellman BR, Wu H, Dall'Acqua WF. Mechanisms of neutralization of a human anti-alpha-toxin antibody. *J Biol Chem.* 2014; 289:29874–29880. [PubMed: 25210036]
8. Yermakova A, Klock TI, Cole R, Sandvig K, Mantis NJ. Antibody-mediated inhibition of ricin toxin retrograde transport. *MBio.* 2014; 5:e00995. [PubMed: 24713323]
9. Takahashi T, Joshi SG, Al-Saleem F, Ancharski D, Singh A, Nasser Z, Simpson LL. Localization of the sites and characterization of the mechanisms by which anti-light chain antibodies neutralize the actions of the botulinum holotoxin. *Vaccine.* 2009; 27:2616–2624. [PubMed: 19428868]
- 10. Cohen TS, Hilliard JJ, Jones-Nelson O, Keller AE, O'Day T, Tkaczyk C, DiGiandomenico A, Hamilton M, Pelletier M, Wang Q, et al. Staphylococcus aureus alpha toxin potentiates opportunistic bacterial lung infections. *Sci Transl Med.* 2016; 8:329ra331. The authors report that antibody-mediated neutralization of the *S. aureus* alpha toxin can indirectly provide protection against other gram negative pathogens by protecting immune functions such as acidification of the macrophage lysosome.
11. Migone TS, Subramanian GM, Zhong J, Healey LM, Corey A, Devalaraja M, Lo L, Ullrich S, Zimmerman J, Chen A, et al. Raxibacumab for the treatment of inhalational anthrax. *N Engl J Med.* 2009; 361:135–144. [PubMed: 19587338]
12. Yamamoto BJ, Shadiack AM, Carpenter S, Sanford D, Henning LN, Gonzales N, O'Connor E, Casey LS, Serbina NV. Obiltoxaximab Prevents Disseminated Bacillus anthracis Infection and Improves Survival during Pre- and Postexposure Prophylaxis in Animal Models of Inhalational Anthrax. *Antimicrob Agents Chemother.* 2016; 60:5796–5805. [PubMed: 27431219]
13. Liu S, Crown D, Miller-Randolph S, Moayeri M, Wang H, Hu H, Morley T, Leppla SH. Capillary morphogenesis protein-2 is the major receptor mediating lethality of anthrax toxin in vivo. *Proc Natl Acad Sci U S A.* 2009; 106:12424–12429. [PubMed: 19617532]
14. Liu S, Zhang Y, Moayeri M, Liu J, Crown D, Fattah RJ, Wein AN, Yu ZX, Finkel T, Leppla SH. Key tissue targets responsible for anthrax-toxin-induced lethality. *Nature.* 2013; 501:63–68. [PubMed: 23995686]
15. Chen Z, Moayeri M, Purcell R. Monoclonal antibody therapies against anthrax. *Toxins (Basel).* 2011; 3:1004–1019. [PubMed: 22069754]
16. Lowy I, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN, Nichol G, Thomas WD Jr, Leney M, Sloan S, et al. Treatment with monoclonal antibodies against Clostridium difficile toxins. *N Engl J Med.* 2010; 362:197–205. [PubMed: 20089970]
17. Wilcox MH, Gerding DN, Poxton IR, Kelly C, Nathan R, Birch T, Cornely OA, Rahav G, Bouza E, Lee C, et al. Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection. *N Engl J Med.* 2017; 376:305–317. [PubMed: 28121498]
18. Sause WE, Buckley PT, Strohl WR, Lynch AS, Torres VJ. Antibody-Based Biologics and Their Promise to Combat Staphylococcus aureus Infections. *Trends Pharmacol Sci.* 2016; 37:231–241. [PubMed: 26719219]
19. Wang XZ, Coljee VW, Maynard JA. Back to the future: recombinant polyclonal antibody therapeutics. *Curr Opin Chem Eng.* 2013; 2:405–415. [PubMed: 24443710]
20. Proposed Rules for Fixed-Combination and Co-Packaged Drugs. Applications for Approval and Combinations of Active Ingredients Under Consideration for Inclusion in an Over-the-Counter Monograph. *Federal Register.* 2015; 80:79776–79795.
21. Bouvin-Pley M, Morgand M, Meyer L, Goujard C, Moreau A, Mouquet H, Nussenzweig M, Pace C, Ho D, Bjorkman PJ, et al. Drift of the HIV-1 envelope glycoprotein gp120 toward increased neutralization resistance over the course of the epidemic: a comprehensive study using the most potent and broadly neutralizing monoclonal antibodies. *J Virol.* 2014; 88:13910–13917. [PubMed: 25231299]
22. Kong R, Louder MK, Wagh K, Bailer RT, deCamp A, Greene K, Gao H, Taft JD, Gazumyan A, Liu C, et al. Improving neutralization potency and breadth by combining broadly reactive HIV-1 antibodies targeting major neutralization epitopes. *J Virol.* 2015; 89:2659–2671. [PubMed: 25520506]

23. Qiu X, Audet J, Lv M, He S, Wong G, Wei H, Luo L, Fernando L, Kroeker A, Fausther Bovendo H, et al. Two-mAb cocktail protects macaques against the Makona variant of Ebola virus. *Sci Transl Med*. 2016; 8:329ra333.
24. Kugelman JR, Kugelman-Tonos J, Ladner JT, Pettit J, Keeton CM, Nagle ER, Garcia KY, Froude JW, Kuehne AI, Kuhn JH, et al. Emergence of Ebola Virus Escape Variants in Infected Nonhuman Primates Treated with the MB-003 Antibody Cocktail. *Cell Rep*. 2015; 12:2111–2120. [PubMed: 26365189]
25. Nowakowski A, Wang C, Powers DB, Amersdorfer P, Smith TJ, Montgomery VA, Sheridan R, Blake R, Smith LA, Marks JD. Potent neutralization of botulinum neurotoxin by recombinant oligoclonal antibody. *Proc Natl Acad Sci U S A*. 2002; 99:11346–11350. [PubMed: 12177434]
- 26. Nguyen AW, Wagner EK, Laber JR, Goodfield LL, Smallridge WE, Harvill ET, Papin JF, Wolf RF, Padlan EA, Bristol A, et al. A cocktail of humanized anti-pertussis toxin antibodies limits disease in murine and baboon models of whooping cough. *Sci Transl Med*. 2015; 7:316ra195. This work shows that two antibodies targeting just the pertussis toxin can mitigate the symptoms of whooping cough when administered to non-human primates three days after infection, a disease with >20 virulence factor and no serological correlate of protection.
27. Dutta K, Varshney AK, Franklin MC, Goger M, Wang X, Fries BC. Mechanisms mediating enhanced neutralization efficacy of staphylococcal enterotoxin B by combinations of monoclonal antibodies. *J Biol Chem*. 2015; 290:6715–6730. [PubMed: 25572397]
28. Brinkmann U, Kontermann RE. The making of bispecific antibodies. *MAbs*. 2017; 9:182–212. [PubMed: 28071970]
29. Wagner EK, Wang X, Bui A, Maynard JA. Synergistic Neutralization of Pertussis Toxin by a Bispecific Antibody In Vitro and In Vivo. *Clin Vaccine Immunol*. 2016; 23:851–862. [PubMed: 27581436]
- 30. DiGiandomenico A, Keller AE, Gao C, Rainey GJ, Warrenner P, Camara MM, Bonnell J, Fleming R, Bezabeh B, Dimasi N, et al. A multifunctional bispecific antibody protects against *Pseudomonas aeruginosa*. *Sci Transl Med*. 2014; 6:262ra155. The bispecific antibody reported here targets the common exopolysaccharide Psl, which localizes the antibody to the bacteria and mediate phagocytosis as well as the less common PcrV protein. This supports empirical analysis of multiple bispecific antibody architectures in order to find a format that is most compatible with ligand binding and thus most protective.
- 31. Thanabalasuriar A, Surewaard BG, Willson ME, Neupane AS, Stover CK, Warrenner P, Wilson G, Keller AE, Sellman BR, DiGiandomenico A, et al. Bispecific antibody targets multiple *Pseudomonas aeruginosa* evasion mechanisms in the lung vasculature. *J Clin Invest*. 2017; 127:2249–2261. This work demonstrates the mechanism of action for a bispecific antibody targeting the Psl and PcrV antigens of *P. aeruginosa* which was not observed for the antibody mixture. This suggests that the binding sites work together to target the bacteria to neutrophil phagosomes and support enhanced killing. [PubMed: 28463232]
32. Bezabeh B, Fleming R, Fazenbaker C, Zhong H, Coffman K, Yu XQ, Leow CC, Gibson N, Wilson S, Stover CK, et al. Insertion of scFv into the hinge domain of full-length IgG1 monoclonal antibody results in tetravalent bispecific molecule with robust properties. *MAbs*. 2017; 9:240–256. [PubMed: 27981887]
- 33. Wec AZ, Nyakatura EK, Herbert AS, Howell KA, Holtsberg FW, Bakken RR, Mittler E, Christin JR, Shulenin S, Jangra RK, et al. A “Trojan horse” bispecific-antibody strategy for broad protection against ebolaviruses. *Science*. 2016; 354:350–354. The authors report a bispecific antibody able to co-localize with intracellular ebola viruses and block viral-eukaryotic membrane fusion in the endosome. [PubMed: 27608667]
34. Bargou R, Leo E, Zugmaier G, Klinger M, Goebeler M, Knop S, Noppeney R, Viardot A, Hess G, Schuler M, et al. Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. *Science*. 2008; 321:974–977. [PubMed: 18703743]
35. Sloan DD, Lam CY, Irrinki A, Liu L, Tsai A, Pace CS, Kaur J, Murry JP, Balakrishnan M, Moore PA, et al. Targeting HIV Reservoir in Infected CD4 T Cells by Dual-Affinity Re-targeting Molecules (DARTs) that Bind HIV Envelope and Recruit Cytotoxic T Cells. *PLoS Pathog*. 2015; 11:e1005233. [PubMed: 26539983]

36. Yang H, Buisson S, Bossi G, Wallace Z, Hancock G, So C, Ashfield R, Vuidepot A, Mahon T, Molloy P, et al. Elimination of Latently HIV-infected Cells from Antiretroviral Therapy-suppressed Subjects by Engineered Immune-mobilizing T-cell Receptors. *Mol Ther*. 2016; 24:1913–1925. [PubMed: 27401039]
- 37. Tkaczyk C, Hamilton MM, Sadowska A, Shi Y, Chang CS, Chowdhury P, Buonapane R, Xiao X, Warrenner P, Mediavilla J, et al. Targeting Alpha Toxin and ClfA with a Multimechanistic Monoclonal-Antibody-Based Approach for Prophylaxis of Serious *Staphylococcus aureus* Disease. *MBio*. 2016;7. Provides proof-of-concept for simultaneous treatment with antibodies targeting the *S. aureus* ClfA protein and alpha-toxin.
38. Tkaczyk C, Kasturirangan S, Minola A, Jones-Nelson O, Gunter V, Shi YY, Rosenthal K, Aleti V, Semenova E, Warrenner P, et al. Multimechanistic Monoclonal Antibodies (MAbs) Targeting *Staphylococcus aureus* Alpha-Toxin and Clumping Factor A: Activity and Efficacy Comparisons of a MAbs Combination and an Engineered Bispecific Antibody Approach. *Antimicrob Agents Chemother*. 2017:61.
39. Ward ES, Devanaboyina SC, Ober RJ. Targeting FcRn for the modulation of antibody dynamics. *Mol Immunol*. 2015; 67:131–141. [PubMed: 25766596]
40. 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.
- 41. Zhu Q, McLellan JS, Kallewaard NL, Ulbrandt ND, Palaszynski S, Zhang J, Moldt B, Khan A, Svabek C, McAuliffe JM, et al. A highly potent extended half-life antibody as a potential RSV vaccine surrogate for all infants. *Sci Transl Med*. 2017:9. The authors describe a new antibody binding a neutralizing epitope on the RSV F protein which is only present on the pre-fusion conformation. When formatted as a human IgG1 with the half-life extending YTE changes in the Fc region, it is nine-fold more effective than Palivizumab in rats and has a three-fold extended half-life in cynomolgous monkeys.
42. Ko SY, Pegu A, Rudicell RS, Yang ZY, Joyce MG, Chen X, Wang K, Bao S, Kraemer TD, Rath T, et al. Enhanced neonatal Fc receptor function improves protection against primate SHIV infection. *Nature*. 2014; 514:642–645. [PubMed: 25119033]
43. Grevys A, Bern M, Foss S, Bratlie DB, Moen A, Gunnarsen KS, Aase A, Michaelsen TE, Sandlie I, Andersen JT. Fc Engineering of Human IgG1 for Altered Binding to the Neonatal Fc Receptor Affects Fc Effector Functions. *J Immunol*. 2015; 194:5497–5508. [PubMed: 25904551]
44. Dall'Acqua WF, Kiener PA, Wu H. Properties of human IgG1s engineered for enhanced binding to the neonatal Fc receptor (FcRn). *J Biol Chem*. 2006; 281:23514–23524. [PubMed: 16793771]
45. Wang TT, Sewatanon J, Memoli MJ, Wrammert J, Bournazos S, Bhaumik SK, Pinsky BA, Chokephaibulkit K, Onlamoon N, Pattanapanyasat K, et al. IgG antibodies to dengue enhanced for FcγRIIIa binding determine disease severity. *Science*. 2017; 355:395–398. [PubMed: 28126818]
46. Lo M, Kim HS, Tong RK, Bainbridge TW, Vernes JM, Zhang Y, Lin YL, Chung S, Dennis MS, Zuchero YJ, et al. Effector-attenuating Substitutions That Maintain Antibody Stability and Reduce Toxicity in Mice. *J Biol Chem*. 2017; 292:3900–3908. [PubMed: 28077575]
47. Li T, DiLillo DJ, Bournazos S, Giddens JP, Ravetch JV, Wang LX. Modulating IgG effector function by Fc glycan engineering. *Proc Natl Acad Sci U S A*. 2017; 114:3485–3490. [PubMed: 28289219]
48. Hiatt A, Bohorova N, Bohorov O, Goodman C, Kim D, Pauly MH, Velasco J, Whaley KJ, Piedra PA, Gilbert BE, et al. Glycan variants of a respiratory syncytial virus antibody with enhanced effector function and in vivo efficacy. *Proc Natl Acad Sci U S A*. 2014; 111:5992–5997. [PubMed: 24711420]
49. Hua L, Cohen TS, Shi Y, Datta V, Hilliard JJ, Tkaczyk C, Suzich J, Stover CK, Sellman BR. MEDI4893* Promotes Survival and Extends the Antibiotic Treatment Window in a *Staphylococcus aureus* Immunocompromised Pneumonia Model. *Antimicrob Agents Chemother*. 2015; 59:4526–4532. [PubMed: 25987629]
50. Zhou C, Lehar S, Gutierrez J, Rosenberger CM, Ljumanovic N, Dinoso J, Koppada N, Hong K, Baruch A, Carrasco-Triguero M, et al. Pharmacokinetics and pharmacodynamics of DSTA4637A:

A novel THIOMAB antibody antibiotic conjugate against *Staphylococcus aureus* in mice. *MAbs*. 2016; 8:1612–1619. [PubMed: 27653831]

- 51. Lehar SM, Pillow T, Xu M, Staben L, Kajihara KK, Vandlen R, DePalatis L, Raab H, Hazenbos WL, Morisaki JH, et al. Novel antibody-antibiotic conjugate eliminates intracellular *S. aureus* Nature. 2015; 527:323–328. The authors demonstrate use of an antibody-drug conjugate to access hidden bacterial reservoirs. They identified a cell wall binding antibody to target bacteria for phagocytosis. After transport to the lysosome, endogenous proteases released a modified rifamycin antibiotic which killed bacteria.
- 52. McLellan JS, Chen M, Leung S, Graepel KW, Du X, Yang Y, Zhou T, Baxa U, Yasuda E, Beaumont T, et al. Structure of RSV fusion glycoprotein trimer bound to a prefusion-specific neutralizing antibody. *Science*. 2013; 340:1113–1117. [PubMed: 23618766]
- 53. Palomo C, Mas V, Detalle L, Depla E, Cano O, Vazquez M, Stortelers C, Melero JA. Trivalency of a Nanobody Specific for the Human Respiratory Syncytial Virus Fusion Glycoprotein Drastically Enhances Virus Neutralization and Impacts Escape Mutant Selection. *Antimicrob Agents Chemother*. 2016; 60:6498–6509. [PubMed: 27550346]
- 54. Sawa T, Ito E, Nguyen VH, Haight M. Anti-PcrV antibody strategies against virulent *Pseudomonas aeruginosa*. *Hum Vaccin Immunother*. 2014; 10:2843–2852. [PubMed: 25483637]
- 55. Warrenner P, Varkey R, Bonnell JC, DiGiandomenico A, Camara M, Cook K, Peng L, Zha J, Chowdury P, Sellman B, et al. A novel anti-PcrV antibody providing enhanced protection against *Pseudomonas aeruginosa* in multiple animal infection models. *Antimicrob Agents Chemother*. 2014; 58:4384–4391. [PubMed: 24841258]
- 56. Ganesh VK, Liang X, Geoghegan JA, Cohen ALV, Venugopalan N, Foster TJ, Hook M. Lessons from the Crystal Structure of the *S. aureus* Surface Protein Clumping Factor A in Complex With Tefibazumab, an Inhibiting Monoclonal Antibody. *EBioMedicine*. 2016; 13:328–338. [PubMed: 27789272]
- 57. Rouha H, Badarau A, Visram ZC, Battles MB, Prinz B, Magyarics Z, Nagy G, Mirkina I, Stulik L, Zerbs M, et al. Five birds, one stone: neutralization of alpha-hemolysin and 4 bi-component leukocidins of *Staphylococcus aureus* with a single human monoclonal antibody. *MAbs*. 2015; 7:243–254. The authors report identification of a single antibody able to bind and neutralize the *S. aureus* alpha toxin and four related leukocidins with picomolar affinities, despite the low level of ~26% amino acid identity among the toxins. [PubMed: 25523282]
- 58. Kallewaard NL, Corti D, Collins PJ, Neu U, McAuliffe JM, Benjamin E, Wachter-Rosati L, Palmer-Hill FJ, Yuan AQ, Walker PA, et al. Structure and Function Analysis of an Antibody Recognizing All Influenza A Subtypes. *Cell*. 2016; 166:596–608. An antibody binding a novel neutralizing epitope that is highly conserved across all influenza A subtypes is reported. [PubMed: 27453466]
- 59. Diep BA, Le VT, Badiou C, Le HN, Pinheiro MG, Duong AH, Wang X, Dip EC, Aguiar-Alves F, Basuino L, et al. IVIG-mediated protection against necrotizing pneumonia caused by MRSA. *Sci Transl Med*. 2016; 8:357ra124.
- 60. Wang Q, Chang CS, Pennini M, Pelletier M, Rajan S, Zha J, Chen Y, Cvitkovic R, Sadowska A, Heidbrink Thompson J, et al. Target-Agnostic Identification of Functional Monoclonal Antibodies Against *Klebsiella pneumoniae* Multimeric MrkA Fimbrial Subunit. *J Infect Dis*. 2016; 213:1800–1808. [PubMed: 26768253]
- 61. Fleishman SJ, Whitehead TA, Ekiert DC, Dreyfus C, Corn JE, Strauch EM, Wilson IA, Baker D. Computational design of proteins targeting the conserved stem region of influenza hemagglutinin. *Science*. 2011; 332:816–821. [PubMed: 21566186]
- 62. Entzminger KC, Hyun JM, Pantazes RJ, Patterson-Orazem AC, Qerqez AN, Frye ZP, Hughes RA, Ellington AD, Lieberman RL, Maranas CD, et al. De novo design of antibody complementarity determining regions binding a FLAG tetra-peptide. *Sci Rep*. 2017; 7:10295. [PubMed: 28860479]
- 63. Robinson LN, Tharakaraman K, Rowley KJ, Costa VV, Chan KR, Wong YH, Ong LC, Tan HC, Koch T, Cain D, et al. Structure-Guided Design of an Anti-dengue Antibody Directed to a Non-immunodominant Epitope. *Cell*. 2015; 162:493–504. [PubMed: 26189681]
- 64. Maynard JA, Maassen CB, Leppla SH, Brasky K, Patterson JL, Iverson BL, Georgiou G. Protection against anthrax toxin by recombinant antibody fragments correlates with antigen affinity. *Nat Biotechnol*. 2002; 20:597–601. [PubMed: 12042864]

Highlights

- Due to scientific advances, antibodies are increasingly viable anti-infective agents
- Antibodies that block the function of virulence factors have shown clinical success
- Antibodies complement antibiotic therapy with efficacy against resistant strains
- Novel antibody designs can access novel therapeutic mechanisms

Figure 1. Therapeutic antibodies approved in the United States

A, Approvals of therapeutic antibodies in the US by year. Solid bars indicate antibodies that are still marketed, while striped bars indicate antibodies that were subsequently withdrawn or discontinued after approval. **B**, Currently marketed antibodies organized by clinical indication. Orange denotes antibodies approved for infectious indications, blue indicates inflammatory or autoimmune indications, purple indicates cancer indications, while grey indicates other indications. The inflammatory/autoimmune category includes other diseases related to immune system hyperactivity such as transplant rejection and asthma, the cancer category includes other neoplastic diseases such as Castleman disease; the other category includes bone loss, macular degeneration, blood clot prevention and high cholesterol. **C**, Mechanism of action of Pailivizumab. This antibody binds pre- and post-fusion conformations of the fusion F protein on the surface of RSV virus particles, thereby preventing fusion of the viral and eukaryotic membranes [4]. **D**, Mechanism of action of Raxibacumab and Obiltoxaximab. Anthrax toxin activities are initiated by binding of the 83 kDa protective antigen (PA) to the major CMG2 receptor. PA is then cleaved by furin-like proteases to release a 20 kDa fragment, allowing the receptor-bound 63 kDa fragment to heptamerize and form binding sites for the enzymatically active subunits edema factor (EF) and lethal factor (LF). This large multi-protein complex is then subject to receptor-mediated endocytosis and additional steps, ultimately resulting in transport of EF and LF into the host cell cytoplasm [13]. The two approved antibodies both bind domain four of PA₈₃, blocking its ability to bind receptor and thereby preventing all subsequent events.

Figure 2. Novel protective mechanisms used by anti-infective antibodies in development

A, A sampling of recombinant antibody architectures in development for anti-infective indications. Shown are a typical human IgG1 antibody, with individual domains and binding site complementarity determining regions (CDRs) labelled; a heterodimeric bispecific antibody (bsAb) with two different heavy and two different light chains forming two distinct binding sites (indicated by red versus gray color and different binding site shapes) with heterodimerization supported by asymmetric amino acid changes in the Fc interface; a bispecific antibody formed by two linked scFvs; a dual variable domain IgG antibody (DVD-Ig) with two binding sites; and a BiS4 structure in which an scFv is inserted into the hinge region of another antibody. **B**, The bispecific antibody architecture and proposed mechanism of BiS4Pa targeting *P. aeruginosa* [28]. The Psl-specific IgG1 antibody was modified in the hinge region to present an scFv binding the type three secretion protein PcrV [30]. The protein in proposed facilitate bacterial destruction by first binding the Psl polysaccharide and targeting the bacteria for Fc receptor mediated phagocytosis. The small volume of the phagosome facilitates antibody binding to PcrV, blocking transport of immunosuppressive proteins such as ExoS into the host cell cytosol and thereby allowing acidification of the endosome. **C**, Mechanism by which linked binding domains can redirect cytotoxic T cells to kill infected cells. With one arm, the bispecific binds and activates the T cell CD3 complex while the other arm binds a cell surface protein specific for infected cells. In this way, immune synapse formation is triggered and pore forming and other cytolytic enzymes delivered to the target cell. Shown is a bispecific formed by genetic fusion of an scFv binding CD3 and a higher affinity TCR recognizing a characteristic HIV peptide bound to a major histocompatibility complex on an HIV-infected cell (*aka*, an ImmTAC) [36]. **D**, Design and proposed mechanism of the anti-*S. aureus* antibody-drug conjugate [51]. An antibody binding the β -O-linked-GlcNAc sugar modifications on wall-teichoic acid is coupled to a rifamycin derivative. The antibody binds bacteria and facilitates Fc receptor-mediated uptake into macrophages. After transport to the phagolysosome, rifamycin linker is cleaved by endogenous proteases, allowing the antibiotic to kill even non-replicating bacteria.

Table 1

Anti-infective monoclonal antibodies approved in the United States

Name	Disease	Target	Affinity (nM)	Isotype	Approval (US)	Developer	Reference
Palivizumab (Synagis)	RSV	Viral glycoprotein-RSV fusion (F) protein	2.6	Humanized IgG1	1998	Medimmune	[5]
Raxibacumab (Abthrax)	Anthrax	Bacterial toxin-protective antigen	2.8	Human IgG1	2012	GlaxoSmithKline	[12]
Obiltoxaximab (Anthim)	Anthrax	Bacterial toxin-protective antigen	0.33	Chimeric IgG1	2016	Elusys Therapeutics	[13,65]
Bezlotoxumab (Zinplava)	<i>C. difficile</i>	Bacterial toxin-enterotoxin B	0.05–0.8	Human IgG1	2016	Merck	[3]

Table 2

Anti-infective antibodies in clinical trials in the United States *

Name	Disease	Target	Source/Isotype	Clonality/Format/Fc	Status	Developer
ALX-0171	RSV	Viral glycoprotein-RSV F protein site II	Camel V _H H	Nanobody	Phase II	Ablynx
MEDI8897 (D25)	RSV	Viral glycoprotein-RSV F protein site Ø	Human IgG1	Monoclonal with extended half-life	Phase II	Medimmune
CSJ148	CMV	Viral glycoprotein-gB, pentameric complex	Human IgG1	Mixture (2)	Phase II	Novartis
GC1102	HBV	Viral glycoprotein-HBV surface antigen	Human IgG1	Monoclonal	Phase II	Green Cross
Baviximab (PGN401)	HCV	Infected cells-Phosphatidylserine	Chimeric IgG1	Monoclonal	Phase II	Peregrine Pharmaceuticals
514G3	<i>S. aureus</i> bacteremia	Bacterial surface- <i>Staphylococcus</i> protein A	Human IgG3	Monoclonal	Phase II	XBiotech
MEDI4893	<i>S. aureus</i> pneumonia	Bacterial toxin- <i>S. aureus</i> alpha toxin	Human IgG1	Monoclonal with extended half-life	Phase II	Medimmune
Salvecin (AR-301)	<i>S. aureus</i> pneumonia	Bacterial toxin- <i>S. aureus</i> alpha toxin	Human IgG1	Monoclonal	Phase II	Aridis
ASN100	<i>S. aureus</i> pneumonia	Bacterial toxin- <i>S. aureus</i> alpha toxin/leukocidins	Human IgG1	Mixture (2)	Phase II	Arsanis
DSTA4637S	<i>S. aureus</i> pneumonia	Bacterial surface- <i>Staph</i> wall teichoic acid	Human IgG1	Monoclonal ADC	Phase I	Genentech
Aerumab (panobacumab, AR-101)	<i>P. aeruginosa</i> pneumonia	Bacterial surface-LPS serotype O11	Human IgM	Monoclonal	Phase II	Aridis Pharmaceuticals
Aerucin (AR-105)	<i>P. aeruginosa</i> pneumonia	Bacterial exopolysaccharide-alginate	Human IgG1	Monoclonal	Phase II	Aridis Pharmaceuticals
MEDI3902	<i>P. aeruginosa</i> pneumonia	Bacterial exopolysaccharide-PSII, secretion system-PcrV	Human IgG1-Fab-ScFv	Bispecific	Phase II	Medimmune
Ibalizumab	HIV-1	Host viral receptor-CD4	Humanized IgG4	Monoclonal	Under Review	TaiMed Biologics
PRO 140	HIV-1	Host viral receptor-CCR5	Human IgG4	Monoclonal	Phase III	CytoDyn
UB-421	HIV-1	Host viral receptor-CD4	Humanized aglycosylated IgG1	Monoclonal	Phase II	United Biomedical Inc.
VRC01	HIV-1	Viral glycoprotein-gp120 CD4bs	Human IgG1	Monoclonal	Phase II	NIAID
VRC01-LS	HIV-1	Viral glycoprotein-gp120 CD4bs	Human IgG1	Monoclonal with extended half-life	Phase I	NIAID
3BNC117	HIV-1	Viral glycoprotein-gp120 CD4bs	Human IgG1	Monoclonal	Phase II	Rockefeller University
3BNC117-LS	HIV-1	Viral glycoprotein-Gp120 CD4bs	Human IgG1	Monoclonal with extended half-life	Phase I	Rockefeller University
10-1074	HIV-1	Viral glycoprotein-gp120 V3	Human IgG1	Monoclonal	Phase I	Rockefeller University
3BNC117 + 10-1074	HIV-1	Viral glycoprotein-gp120 CD4bs + V3	Human IgG1	Mixture (2)	Phase I	Rockefeller University
PGT121	HIV-1	Viral glycoprotein-gp120 V3	Human IgG1	Monoclonal	Phase I	International AIDS Vaccine Initiative
PGT121 + PDGM1400	HIV-1	Viral glycoprotein-Gp120 V3 + V1/V2	Human IgG1	Mixture (2)	Phase I	International AIDS Vaccine Initiative
VRC07-523LS	HIV-1	Viral glycoprotein-gp120 CD4bs	Human IgG1	Monoclonal with extended half-life	Phase I	NIAID
MB66	HIV-1/HSV-2	Viral glycoproteins-HIV-1 gp120, HSV-2 gD	Unknown	Mixture (2) vaginal film	Phase I	Mapp Biopharmaceutical

Name	Disease	Target	Source/Isotype	Clonality/Format/Fc	Status	Developer
MEDI8852	Influenza A	Viral glycoprotein-G1/G2 Hemagglutinin stalk	Human IgG1	Monoclonal	Phase II	Medimmune/Humabs Biomed
VIS410	Influenza A	Viral glycoprotein-G1/G2 Hemagglutinin stalk	Human IgG1	Monoclonal	Phase II	Visterra Inc.
CT-P27	Influenza A	Viral glycoprotein-G1/G2 Hemagglutinin stalk	Unknown	Mixture (2)	Phase II	Celltrion
REGN3470 + REGN3471 + REGN3479	Ebola	Unknown	Unknown	Mixture (3)	Phase I	Regeneron
SYN023	Rabies	Viral glycoprotein	Humanized Unknown	Mixture (2)	Phase II	Synermore Biologics
Solaris (eculizumab)	STEC-HUS	Host complement protein-C5	Humanized IgG2/4	Monoclonal	Phase III	University Hospital Toulouse/Alexion Pharmaceuticals
Pascolizumab	Tuberculosis	Host cytokine-IL-4	Humanized IgG1	Monoclonal	Phase II	National University Hospital, Singapore
Nivolumab	Sepsis	Host checkpoint inhibitor-PD-1	Human IgG4	Monoclonal	Phase I	Bristol-Myers Squibb

* Information from ClinicalTrials.gov and developer websites (Jan 2018).