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MINI-REVIEW

Anti-bacterial monoclonal antibodies: next generation therapy against superbugs

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Abstract

Prior to the nineteenth century, infectious disease was one of the leading causes of death. Human life expectancy has roughly doubled over the past century as a result of the development of antibiotics and vaccines. However, the emergence of antibiotic-resistant superbugs brings new challenges. The side effects of broad-spectrum antibiotics, such as causing antimicrobial resistance and destroying the normal flora, often limit their applications. Furthermore, the development of new antibiotics has lagged far behind the emergence and spread of antibiotic resistance. On the other hand, the genome complexity of bacteria makes it difficult to create effective vaccines. Therefore, novel therapeutic agents in supplement to antibiotics and vaccines are urgently needed to improve the treatment of infections. In recent years, monoclonal antibodies (mAbs) have achieved remarkable clinical success in a variety of fields. In the treatment of infectious diseases, mAbs can play functions through multiple mechanisms, including toxins neutralization, virulence factors inhibition, complement-mediated killing activity, and opsonic phagocytosis. Toxins and bacterial surface components are good targets to generate antibodies against. The U.S. FDA has approved three monoclonal antibody drugs, and there are numerous candidates in the preclinical or clinical trial stages. This article reviews recent advances in the research and development of anti-bacterial monoclonal antibody drugs in order to provide a valuable reference for future studies in this area.

Key points

- *Novel drugs against antibiotic-resistant superbugs are urgently required*
- *Monoclonal antibodies can treat bacterial infections through multiple mechanisms*
- *There are many anti-bacterial monoclonal antibodies developed in recent years and some candidates have entered the preclinical or clinical stages of development*

Keywords Anti-bacterial · Monoclonal antibodies · Antibiotic-resistant · Infection · Toxins neutralization

Introduction

Prior to the nineteenth century, infectious disease was among the top causes of death. At the time, the average human life expectancy was only 30–40 years, which has now roughly doubled over the last century, primarily owing to the development of antibiotics and vaccines.

Alexander Fleming discovered penicillin in 1928 and started the era of antibiotics to treat bacterial infections. However, pathogens can quickly develop resistance to new antibiotics due to their ability to withstand drug pressure. The overuse of antibiotics exacerbates the problem. Nowadays, the introduction of new antibiotic molecules now lags far behind the emergence of antibiotic resistance. Antimicrobial resistance is already one of the most serious crises for health, so novel effective treatments are urgently required. Immunotherapeutic agents, such as vaccines and antibodies, have shown promise in infectious diseases treatment (Rello et al. 2019). A vaccine is a typical active immunization therapy that has made remarkable achievements in fighting viral infections such as Smallpox

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and Polio (Patel et al. 2015). Traditional inactivated or attenuated vaccines with recognized safety and protective efficacy are difficult to develop because bacteria are more complicated than viruses. Although modern vaccines, such as recombinant protein vaccines, have better safety than the traditional ones, their immunogenicity is often insufficient in the elderly or those with impaired immune function. As a result, passive immunization with antibodies has attracted a lot of attention.

Emil Adolf von Behring and Erich Wernicke developed the first diphtheria antitoxin serum in 1890 (Kaufmann 2017). The antisera, obtained by immunizing a horse with *Corynebacterium diphtheriae* or *Clostridium tetanus* toxin, were effective on patients with diphtheria or tetanus, respectively (Todoroki et al. 2018; Yamada 2011). Behring named the anti-infective substance in the immune serum "Antitoxin," which is now known as the antibody.

Monoclonal antibodies (mAbs) have lower variability, higher specificity, and less cross-reaction with host cells and normal flora than polyclonal antisera (Berry and Gaudet 2011; Luciani and Iannetti 2017; Zurawski and McLendon 2020). OKT3, the first therapeutic mAb, was approved by the U.S. FDA in 1986 to prevent renal transplant rejection. Following that, therapeutic mAbs and antibody-related products, such as Fc fusion proteins, antibody fragments, and antibody–drug conjugates (ADCs), have grown to become the biopharmaceutical market's leading product categories. Despite the enormous success of antibodies in treating cancers and autoimmune diseases, the U.S. FDA has only approved three mAbs to treat bacteria (Wagner and Maynard 2018). Anti-bacterial monoclonal antibody drug development is still in its infancy and is gaining increasing interest. The timeline of the emergence and development of treatments for bacterial infections is shown in Fig. 1. To provide the readers with up-to-date information and ideas for future research, we will conduct a comprehensive and in-depth analysis of the recent advances in the research and development of anti-bacterial antibodies, including a number of new antibody molecules and novel working mechanisms.

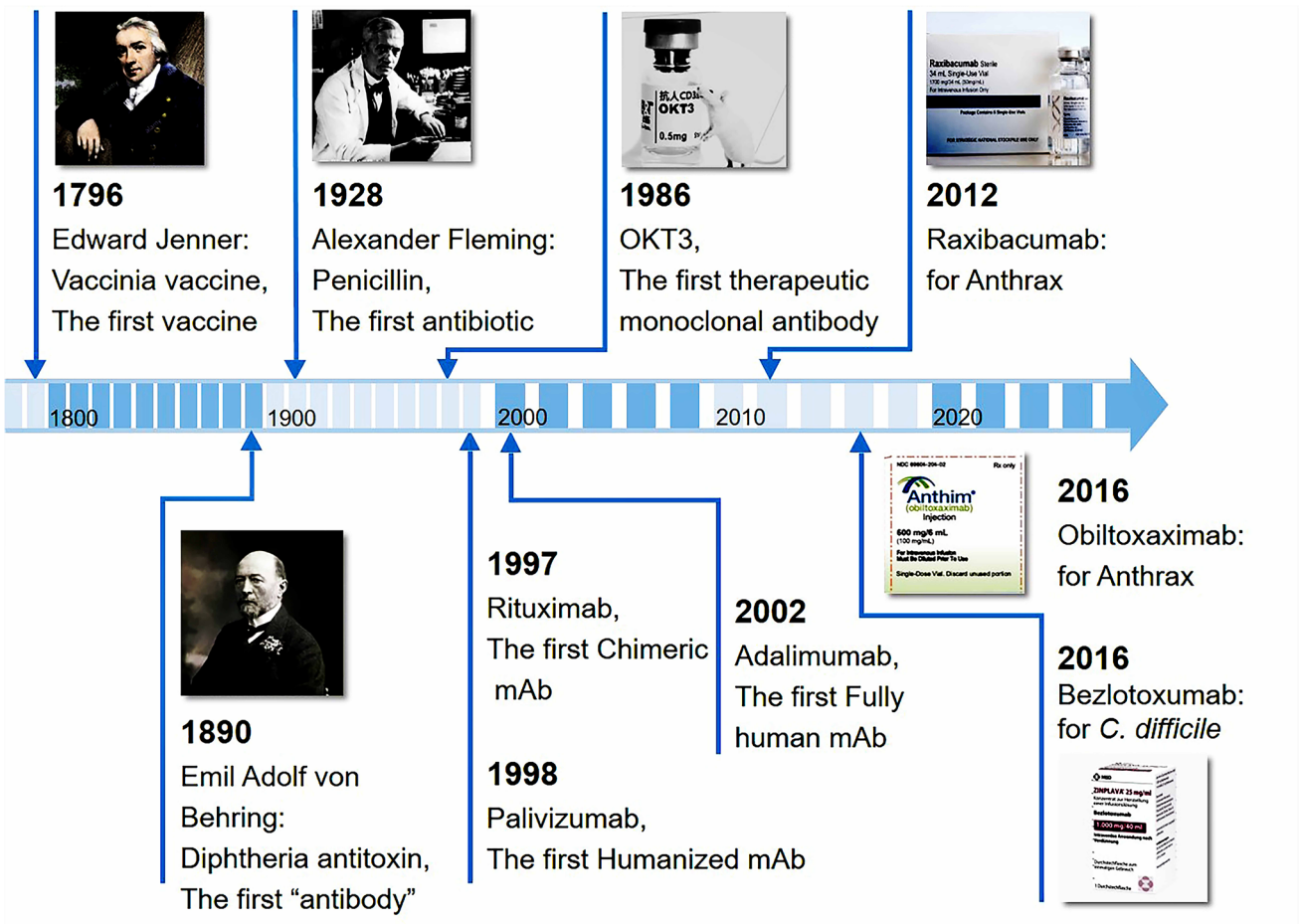

Fig. 1 Milestone timeline of the emergence and development of therapies for infectious diseases

Mechanisms of anti-bacterial monoclonal antibodies

In the process of bacterial clearance, monoclonal antibodies can directly neutralize toxins, inhibit virulence factors, and stimulate the host immune system. These functions are not exclusive but coordinate with one another, and a monoclonal antibody may eliminate pathogens through multiple modes of action, as depicted in Fig. 2.

Toxin neutralization

Antitoxin antibodies can block the binding of toxins to receptors (Sorensen and Edgar 2019), prevent the toxin's necessary structural changes for toxicity (Sadarangani 2018), and form immune complexes that assist toxin clearance (Takahashi et al. 2009). For example, Bezlotoxumab neutralizes the toxin TcdB of *Clostridium difficile* (*C. difficile*) by directly attaching to its two distinct sites, E1 and E2 (Sorensen and Edgar 2019). MEDI4893 neutralizes staphylococcal toxin AT to prevent AT-mediated cell lysis by blocking its binding to receptors and inhibiting its oligomers formation through steric hindrance (Hua et al. 2015; Tkaczyk et al. 2018).

Inhibition of specific virulence factors

Anti-bacterial mAbs can target virulence factors on the surface of bacteria to hinder pathogenicity. Both KB001-A and V2L2MD inhibit the type III secretory system (T3SS) on the surface of *Pseudomonas aeruginosa* (*P. aeruginosa*) and prevent the bacteria from injecting toxins into the cytoplasm of host cells by targeting PcrV protein (Milla et al. 2014; Warrener et al. 2014). Kenneth et al. reported that Mab69 targeting fimbrial protein EbpC effectively inhibited the adhesion of *Enterococcus faecalis* and demonstrated an outstanding therapeutic effect in a model of infectious endocarditis (Pinkston et al. 2014).

Antibody-mediated complement-dependent killing activity

The Fc region of antigen-bound antibodies can bind to C1q, thereby triggering the classical complement pathway to lyse bacteria through the formation of a membrane attack complex (MAC) (McConnell 2019; Natali et al. 2020; Ram et al. 2010). C1q needs at least two heads bound to the Fc regions to activate the complement system. Therefore, targets with high abundance or high topical density, such as polymeric carbohydrate antigens, appear beneficial for initiating the complement pathway (Nagy et al. 2017). IgM is also more potential than IgG to activate the classical pathway (Ram et al. 2010). In addition, the complement pathway is likely to be successful even in immunocompromised patients because it does not require phagocyte participation (Nagy et al. 2017).

Opsonophagocytic killing (OPK) activity

Opsonic phagocytosis is one of the primary mechanisms against systemic bacterial infection. Antibodies binding to bacteria can induce or increase phagocytosis through multiple ways. First, once the classical complement pathway is initiated, C3b deposits on the bacterial surface and binds to C3b receptors on phagocytes. Secondly, phagocytes express Fc receptors (FcRs) in order to recognize

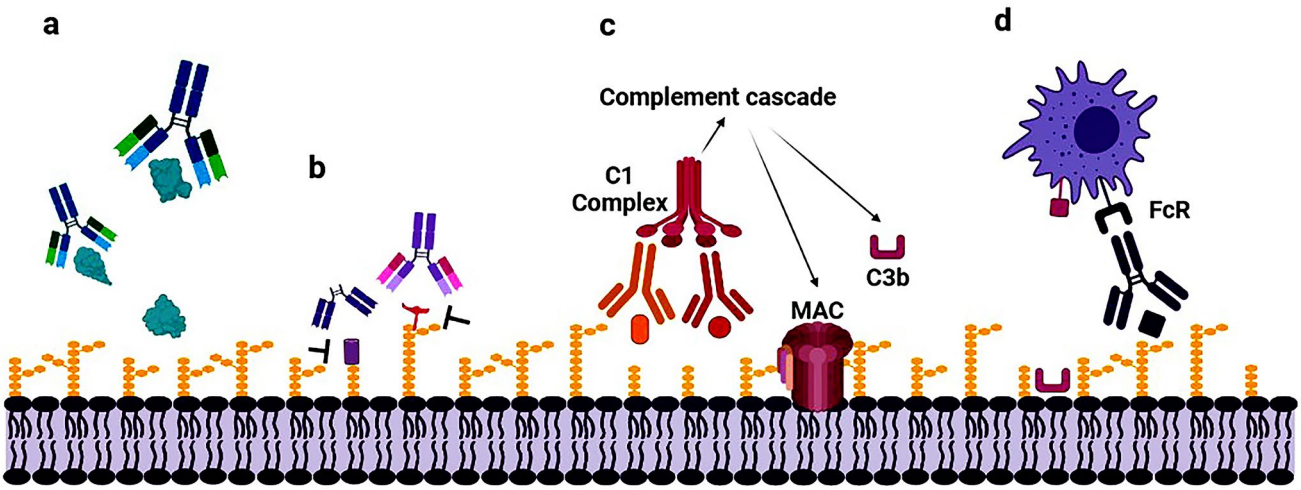

Fig. 2 Modes of actions of anti-bacterial mAbs. MAbs can (a) neutralize soluble toxins; (b) block surface associated virulence factors; (c) activate complement to lyse bacteria; or (d) opsonize bacteria for phagocytosis

various types of antibodies and antibody-formed immune complexes. Triggering FcRs may result in complement-independent phagocytosis. Activation of complement receptors and FcRs can generate synergistic effects, which are also influenced by other antibody-independent signals, such as Toll-like receptor (TLR) signals (Underhill and Ozinsky 2002).

Approved anti-bacterial monoclonal antibodies

There are now three anti-bacterial mAbs approved for clinical use, all of which neutralize exotoxins produced by gram-negative bacteria (Motley et al. 2019).

Raxibacumab (Abthrax®)

The anthrax toxin complex, the main virulence factor of *Bacillus anthracis*, is composed of lethal factor (LF), edema factor (EF), and protective antigen (PA). LF is a zinc metalloprotease that catalyzes macrophage lysis by cleaving mitogen-activated protein kinases. EF is a calmodulin-dependent adenylate cyclase, which can inhibit macrophage phagocytosis and induce neutrophil dysfunction and local edema (Liu et al. 2003; Moayeri et al. 2015). PA promotes the binding of LF and EF to the anthrax toxin receptor (ATR) or capillary morphogenesis protein 2 (CMG2) on the surface of mammalian cell, hence exerting cytotoxicity (Mazumdar 2009). Therefore, neutralizing PA can effectively avoid the toxins' pathogenic effects. Raxibacumab is a human IgG1 mAb that neutralizes PA with high affinity and blocks the entry of LF and EF into cells, thus preventing anthrax toxin-mediated cell damage (Migone et al. 2009). In addition to treating inhaled anthrax infections, Raxibacumab also demonstrated improved protection in models of fatal sepsis and gastrointestinal *Bacillus anthracis* infection (Huang et al. 2015).

Obiltoxaximab (Anthim®)

Obiltoxaximab is a chimeric IgG1 mAb derived from murine mAb 14B7 variant 1H (Leysath et al. 2009). Similar to the mechanism of Raxibacumab, Obiltoxaximab also functions by neutralizing PA. Obiltoxaximab exhibited a favorable safety and tolerability profile after intravenous or intramuscular injection. Moreover, Obiltoxaximab provided a meaningful benefit over antibiotics alone and did not impair normal immunity (Biron et al. 2015; Henning et al. 2018; Nagy et al. 2016; Yamamoto et al. 2016a, b). Overall, Obiltoxaximab demonstrated therapeutic advantages in both the early and late stages of inhalation anthrax, promoting survival, ameliorating toxemia, and inhibiting bacterial dissemination (Yamamoto et al. 2016a, b).

Bezlotoxumab (Zinplava®)

TcdA and TcdB are exotoxins secreted by *C. difficile*. These toxins could cause dysfunction of epithelial barrier by disrupting target cells' cytoskeleton structure and junction, ultimately leading to cell apoptosis (Di Bella et al. 2016).

Through its two Fab regions, a single molecule of Bezlotoxumab binds to two epitopes of the TcdB combined repetitive oligopeptide (CROP) domain, partially blocking the toxin from attaching to the host cell (Orth et al. 2014). Bezlotoxumab could prevent intestinal epithelial damage and colitis by directly neutralizing the toxin (Navalkele and Chopra 2018), facilitate intestinal microflora reconstitution, and reduce the risk of *C. difficile* infection (CDI) recurrence (Kufel et al. 2017; Navalkele and Chopra 2018; Solbach et al. 2017). Bezlotoxumab has a low immunogenicity and a favorable tolerability profile, but the high cost limits usage to patients at high risk for CDI recurrence (Chahine et al. 2018).

Anti-bacterial monoclonal antibodies in clinical research

Despite the fact that only three antimicrobial mAbs have been approved for human use, there are many candidates in clinical trials. Table 1 lists some of the candidates against drug-resistant *Staphylococcus aureus* (*S. aureus*) and *P. aeruginosa*.

Staphylococcus aureus

S. aureus is one of the most prevalent gram-positive opportunistic pathogens, which can cause diseases such as local suppurative infection, pneumonia, pericarditis, and sepsis (Saeed et al. 2018). *S. aureus* is among the most common causes of nosocomial infection, especially medical device-related infections. Since the discovery of the first case of methicillin-resistant *Staphylococcus aureus* (MRSA) in 1968, the incidence of MRSA infections has increased rapidly. Many antibodies against *S. aureus* virulence factors have been generated.

DSTA4637S

DSTA4637S is an antibody-antibiotic conjugate (AAC) that combines genetically engineered human IgG1 with antibiotics. The antibody component specifically binds to N-acetylglucosamine (GlcNAc) of wall teichoic acid (WTA), a key factor for bacteria colonization, peptidoglycan synthesis, and antibiotic resistance (Sewell and Brown 2014). The antibiotic component dmDNA31 (dimethyl DNA31, 4-dimethylaminopiperidino-hydroxybenzoxazino rifamycin)

Table 1 Anti-bacterial monoclonal antibodies in clinical research

Name	Disease	Target	Source	Format	Developer	Status	Last update	NCT number
DSTA4637S	*S. aureus* pneumonia	Bacterial surface-Staph wall teichoic acid	Human IgG1	Monoclonal AAC	Genentech	Phase I	2020.01 Completed	NCT03162250
AR-301	*S. aureus* pneumonia	Bacterial toxin-*S. aureus* alpha toxin	Human IgG1	Monoclonal	Aridis Pharmaceuticals	Phase III	2020.01 Recruiting	NCT03816956
MEDI4893	*S. aureus* pneumonia	Bacterial toxin-*S. aureus* alpha toxin	Human IgG1	Monoclonal with extended half-life	Medimmune	Phase II	2019.10 Completed	NCT02296320
ASN100	*S. aureus* pneumonia	Bacterial toxin-*S. aureus* alpha toxin/ leukocidins	Human IgG1	Mixture of ASN-1 and ASN-2	Arsanis	Phase II	2019.07 Terminated	NCT02940626
F598	*S. aureus, N. gonorrhoeae*, et al.; *N. gonorrhoeae* urethritis	Poly-N-acetyl-D-glucosamine (PNAG)	Human Fab	Monoclonal	Alopexx Pharmaceuticals, LLC	Phase II	2019.02 Terminated	NCT03222401
514G3	*S. aureus* bacteremia	Bacterial surface-Staphylococcus protein A	Human IgG3	Monoclonal	XBiotech	Phase II	2017.02 Completed	NCT02357966
MEDI3902	*P. aeruginosa* pneumonia	Bacterial exopolysaccharide-Psl; secretion system-PcrV	Human IgG1-Fab-ScFv	Bispecific	Medimmune	Phase II	2019.12 Completed	NCT02696902
AR-105	*P. aeruginosa* pneumonia	Bacterial Exopolysaccharide-alginate	Human IgG1	Monoclonal	Aridis Pharmaceuticals	Phase II	2019.02 Completed	NCT03027609
KB001-A	*P. aeruginosa* pneumonia	T3SS-PcrV	PEGylated Fab	Monoclonal	Humanigen	Phase II	2015.01 Completed	NCT01695343
KB001	*P. aeruginosa* pneumonia	T3SS-PcrV	Human Fab	Monoclonal	Humanigen	Phase II	2014.07 Completed	NCT00638365

is a rifamycin-class antibiotic that inhibits DNA-dependent RNA polymerase with bactericidal potency. Antibodies and antibiotics are linked by a protease-cleavable valine-citrulline (VC) junction with a 2:1 drug-to-antibody ratio (Lehar et al. 2015; Staben et al. 2016; Zhou et al. 2016). In vitro studies demonstrated that DSTA4637S is capable of killing vancomycin-resistant bacteria. When DSTA4637S-opsonized MRSA was internalized into host cells, the linker was efficiently cleaved to release the active payload to kill *S. aureus*. In a mouse bacteremia model, DSTA4637S exhibited superior efficacy than vancomycin (Lehar et al. 2015). In healthy volunteers, DSTA4637S was well-tolerated and safe. The phase I study of DSTA4637S in patients with *S. aureus* bacteremia receiving standard-of-care antibiotics has already completed.

MEDI4893 (Suvratoxumab)

S. aureus α-hemolysin (HLA; α-toxin, AT) is a crucial virulence factor that can bind to the receptor metalloproteinases (ADAM10) on the cell surface. The interaction could result in protein conformational changes and polymerization, leading to the formation of pores, followed by the destruction of the membrane, cell lysis, and tissue damage. In addition, AT could mediate subcellular lysis, disrupt the tight junction between endothelial and epithelial cells, and contribute to bacterial immune evasion (Cohen et al. 2016; Hua et al. 2014; Powers et al. 2012). MEDI4893 binds to discontinuous epitopes of AT to inhibit AT binding to its receptor and block its oligomerization (Oganesyan et al. 2014). The antibody protected both normal and immunocompromised mice from *S. aureus* pneumonia, significantly increased survival rate, reduced bacteria load in the lungs, and mitigated lung tissue pathological damage. In addition, co-administration of MEDI4893 with vancomycin or linezolid had synergistic effects and extended the antibiotic treatment window (Hua et al. 2015). A double-blind phase II study of MEDI4893 showed a trend toward a decreased incidence of *S. aureus* pneumonia and a favorable safety profile in ICU patients colonized with *S. aureus* and receiving mechanical ventilation (Francois et al. 2019). In this phase II pilot study, the most recent findings indicate that MEDI4893 did not significantly reduce the incidence of *S. aureus* pneumonia at 30 days compared to placebo (François et al. 2021).

AR301 (Tosatoxumab, Salvecin, KBSA301)

AR301 is also an AT inhibitor. The phase I/II clinical trial of AR301 demonstrated its favorable safety and tolerability. AR301 could improve the microbiological outcomes and shorten the duration of mechanical ventilation in patients. In treating ventilator-associated bacterial pneumonia (VABP), the combination of AR301 and antibiotics displayed a significant synergistic effect. Phase III clinical study of AR301 is in the recruitment process.

ASN100

Bi-component leukocidins are also among the most important of *S. aureus* virulence factors. Five types of bi-component leukocidins, including γ-hemolysins AB and CB (HlgAB, HlgCB), leukocidins ED (LukED), leukocidins SF (LukSF), and leukocidins GH (LukGH, also known as LukAB), had been identified in *S. aureus*. The S-component of these toxins first binds to the cell membrane, inducing the recruitment and aggregation of the F-component to form an octamer (composed of 4 S-component and 4 F-component). Then, the conformation of each toxin subunit changes and assembles to form a β-barrel structure, followed by the perforation of the cell membrane perforation. The β-barrel pore-forming toxin is capable of destroying cell adhesion junctions of epithelial barriers, altering intracellular signal transduction processes, regulating host immune response, and killing eukaryotic and non-immune cells (Reyes-Robles and Torres 2017). ASN-100, developed by Arsanis Inc., is an antibody cocktail containing two mAbs: ASN-1 and ASN-2. ASN-1 cross-reacts with AT and four bi-component leukocidins (HlgAB, HlgCB, LukED, and LukSF), whereas ASN-2 binds to LukGH (Badarau et al. 2016; Rouha et al. 2015). In vitro studies showed that ASN-1 simultaneously inhibited multiple virulence pathways of *S. aureus*, thus preventing the lysis of human phagocytes, epithelial cells, and erythrocytes (Rouha et al. 2015). ASN-1 provided substantial protection in models of pneumonia and sepsis (Rouha et al. 2015). ASN-2 binds with a high affinity to the LukGH dimer complex to prevent its binding to host cells (Badarau et al. 2016). *S. aureus* strains express all five types of leukemicides; therefore, the antibody cocktail ASN100 is theoretically an effective method. Unexpectedly, the phase II clinical trial was abruptly terminated in June 2018 since it failed to meet its primary endpoint.

F598

Poly-N-acetyl-glucosamine (PNAG) is broadly expressed in a variety of bacteria, fungi, and parasites. PNAG is related to biofilm development, bacterial intercellular adhesion, and antibody-independent OPK resistance (Cerca et al. 2007). Due to the insufficiency of the serum complement cofactor system, the natural antibody to PNAG does not induce a robust opsonization or immune response against the bacteria (Skurnik et al. 2010, 2012). Studies have shown that the deacetylated PNAG (dPNAG) is more preferentially retained on the cell surface. Therefore, antibodies targeting dPNAG have superior

effects in in vitro opsonization and in vivo protection. (Cerca et al. 2007; Kelly-Quintos et al. 2006). F598, a human IgG1 mAb, binds both PNAG and dPNAG. F598 exhibited opsonic activities and protective effects in mice infected with different multidrug-resistant bacteria (Roux et al. 2012). According to the manufacturer Alopexx Inc., Phase I and pilot phase 2 trials of F598 have been completed. The antibody was found to be safe, well tolerated and a single infusion can provide 2–3 months of sustained levels in serum.

514G3

Staphylococcal protein A (SpA) anchoring to the cell wall of *S. aureus* is a pivotal pathogenicity factor. SpA can bind to the Fcγ of immunoglobulin (including IgG from a variety of mammalian species and certain IgM and IgA) to shield *S. aureus* from the OPK. SpA consists of the X domain and the immunoglobulin binding domain (Kane et al. 2018). The X domain is involved in cell wall attachment. The N-terminal five immunoglobulin binding domains (E, D, A, B, C) can bind with high affinity to the Fcγ regions of human IgG1, IgG2, and IgG4. The binding of SpA to Fcγ can inhibit polymorphonuclear leukocytes phagocytosis and bacterial killing (Kane et al. 2018; Varshney et al. 2018). 514G3 can induce the opsonophagocytic activity to kill bacteria and block the immune escape of *S. aureus* by binding to the specific epitope of SpA. Animal experiments demonstrated that 514G3 has protective activity against lethal bacteremia and is synergistic with vancomycin (Rello et al. 2019; Varshney et al. 2018). A total of 52 patients were recruited in the phase I/II clinical trial. Due the insufficient sample size, it was not possible to draw statistically meaningful conclusions, but it conclusively showed that 514G3 lowered the occurrence of serious adverse events and shortened the average duration of hospitalization.

Pseudomonas aeruginosa

KB001 and KB001-A

T3SS, one of the essential virulence factors of *P. aeruginosa*, can inject toxins directly into host cells. Additionally, T3SS contributes to the cytotoxicity of *P. aeruginosa* to epithelial cells, neutrophils, and macrophages (Jain et al. 2018). T3SS plays a key role in the pathogenicity of *P. aeruginosa*, as it is associated with certain antibiotic resistance characteristics and has a direct impact on clinical presentation and patient outcomes (Horna and Ruiz 2021). PcrV is a protein located at the top of T3SS and crucial for the transportation of exotoxins into host cells. Studies showed that small molecule binders of PcrV could protect macrophages in a *P. aeruginosa* cell-based infection assay (Sundin et al. 2021). PcrV constitutes a valuable therapeutic target to treat *P. aeruginosa* infections. KB001 is the Fab fragment of an anti-PcrV monoclonal antibody against T3SS. In a model of acute and chronic infectious lung damage caused by *P. aeruginosa*, KB001 reduced the concentration of sputum inflammatory markers IL-8 (Jain et al. 2018). KB001-A is a polyethylene glycosylated version of KB001 (Milla et al. 2014). The phase II clinical trials of KB001 and KB001-A were completed in 2014 and 2015, respectively. The primary objective of the trail of KB001-A was to confirm its anti-inflammatory effect in cystic fibrosis (CF) individuals with chronic *P. aeruginosa* airway infection. However, no statistically significant differences were observed when compared to the placebo.

MEDI3902 (Gremubamab)

Psl, an extracellular polysaccharide expressed by non-mucinous *P. aeruginosa*, contributes to the initial colonization of bacteria. Psl can reduce the production of neutrophil ROS and weaken the killing activity of phagocytes, thus providing a survival advantage for bacteria in vivo (Mishra et al. 2012). MEDI3902 is a bispecific antibody against PcrV and Psl. MEDI3902 mediated protective activity in murine and rabbit models of pneumonia. It reduced the bacterial load, prevented the generation of proinflammatory factors in lung tissue, and mitigated pathological damage (DiGiandomenico et al. 2014; Le et al. 2018). MEDI3902 is currently in phase II development, looking to assess the effectiveness and safety outcomes in mechanically ventilated patients to prevent nosocomial pneumonia caused by *P. aeruginosa*.

Anti-bacterial monoclonal antibodies in preclinical research

With an in-depth understanding of target antigens and their pathogenic roles, anti-bacterial monoclonal antibodies against antibiotic-resistant pathogens have enormous potential. Numerous antimicrobial mAbs are being explored in preclinical research, which will be discussed according to different types of bacteria in the following article.

Staphylococcus aureus

Kim et al. isolated mAbs against nontoxigenic staphylococcal protein A (SpA_{KKAA}), and found that they can block the binding of SpA_{KKAA} immunoglobulin binding domains (IgBDs) to IgGs (Kim et al. 2012). In a mouse

model, the mAb stimulated specific immune responses and promoted MRSA phagocytosis (Kim et al. 2012). Kim's team then proposed another anti-SpA mAb, 3F6, which can protect newborn mice from *S. aureus* septicemia and improve immunity against subsequent staphylococcal infections (Thammavongsa et al. 2015). Chen et al. reported that 3F6-hIgG1 could bind and neutralize SpA to trigger C1q recruitment and OPK for *Staphylococci* (Chen et al. 2020). They subsequently introduced amino acid mutations to the Fcγ domain of 3F6-hIgG1. The alteration could allow 3F6-hIgG1 to escape the binding and interference of SpA and Staphylococcal binder of immunoglobulin (Sbi), hence restoring its complement activation and enhancing its anti-staphylococcal activity. Moreover, the engineering had no effect on the interactions of 3F6-hIgG1 with antigens and hFcγRs. In addition, the same engineering strategy has also been applied to Tefibazumab (anti-ClfA) (Chen et al. 2022). Shokri et al. constructed an anti-SpA antibody-gold nanorods (GNRs) conjugate that could selectively kill MRSA using photothermal therapy. In vitro studies confirmed its targeting effect, and in vivo experiments on mouse models revealed that the GNRs have a protective effect when combined with near-infrared laser energy (Shokri et al. 2015).

Staphylococcus aureus surface protein A (SasA) is a microbial surface component that recognizes adhesive matrix molecules (MSCRAMMs). It could mediate *S. aureus* directly binding to platelets and cause infective endocarditis. Yang et al. presented a protective mAb 2H7 against the conserved domain of SasA. 2H7 improved the survival rate of mice by promoting opsonic phagocytosis and accelerating bacterial clearance in sepsis and abdominal infection models. Prophylactic administration of 2H7 significantly reduced the intraperitoneal abscess formation in mice suffering from the abdominal infection, and therapeutic administration showed an excellent protective effect in septic mice (Yang et al. 2016).

Neutralizing antibodies against AT can alleviate *S. aureus* skin infection by restoring effective host immunity and preventing skin necrosis. In nondiabetic mice, anti-AT mAb boosted the infiltration of monocytes and macrophages and decreased neutrophils. In diabetic mice, it reduced neutrophil extracellular traps (NETs). Treatment with anti-AT mAb successfully reduced wound size and bacterial burden and accelerated epithelial remodeling and wound healing (Ortines et al. 2018).

Staphylococcal enterotoxin (SE) is a large group of pyrogen toxin superantigen (PTSAgs) with comparable structures and distinct serologies. These superantigens can stimulate immune responses and the release of inflammatory cytokines. Staphylococcal enterotoxin B (SEB) and its associated superantigen toxins are powerful immune system activators. Upon binding to the major histocompatibility complex class II molecule (MHC II) and the T cell receptors (TCRs), these toxins activate T lymphocytes and monocytes or macrophages, resulting in large-scale polyclonal T cell infiltration and "cytokine storm" (Hnasko et al. 2019). In 2017, Karau et al. reported a human-mouse chimeric antibody with a high affinity for SEB, which lowered the systemic inflammatory responses caused by SEB and significantly reduced mortality in a mouse model of deadly pneumonia (Karau et al. 2017).

Aguilar et al. proposed a group of monoclonal antibodies against staphylococcal enterotoxin K (SEK) in 2017: mAb-4G3 (IgG2b), mAb-5G2 (IgG1), and mAb-9H2 (IgG1). These three mAbs could inhibit SEK-induced mitosis by suppressing immune cell proliferation and cytokine release, preventing SEK-induced lethality, and improving the survival rate of infected mice. Moreover, mAb-4G3 and mAb-5G2 non-competitively bind to two distinct epitopes on SEK. The combination of the two mAbs dramatically increased the survival rate of mice in a SEK-induced toxic shock model, and the further combination with vancomycin showed a synergistic effect (Aguilar et al. 2017).

Toxic Shock Syndrome Toxin-1 (TSST-1) is another type of PTSAgs. TSST-1 can activate peripheral blood T lymphocytes, stimulate cell proliferation and proinflammatory cytokines release, and induce toxic shock syndrome (TSS). A human scFv (Hu-scFv) suppresses the expression and secretion of inflammatory cytokines and inhibit the activation and proliferation of T cells caused by TSST1-mediated mitotic activity (Rukkawattanakul et al. 2017).

SraP is a serine-rich repeat protein (SRRP) of *S. aureus*. Through the L-lectin module, SraP binds to sialylated receptors to promote bacterial adhesion and invasion. The anti-$SraP_{L\text{-}Lectin}$ mAb significantly inhibited *S. aureus* invading and adhering to host cell and reduced the bacterial burden in the infected mice's blood (Zhou et al. 2021).

Zeng et al. developed a recombinant *S. aureus* vaccine (rFSAV, NCT03966040) that contains five antigens: Hla, SEB, SpA, IsdB-N2, and MntC (Zeng et al. 2020). They collected antiserum from volunteers immunized with rFSAV and generated 4 robust antibodies. A mAb cocktail containing the 4 antibodies could prevent MRSA252 infection by reducing bacterial burden and pathogenicity (Zeng et al. 2021). In addition, subsequent studies have demonstrated that combining the mAb cocktail with antibiotics improved survival rates in the mouse model (Hoelzgen et al. 2021).

Le et al. covalently immobilized the *S. aureus* specific antibody onto the surface of polymeric nanoparticles encapsulating antibiotics. The targeting nanocarriers enhanced the biodistribution and in vitro bactericidal activity of antibiotics and improved the therapeutic efficacy of an infection model in mice (Le et al. 2021). Other antibody-conjugated nanoparticles against *S. aureus* have also been reported, such

as light-absorbing silver nanoparticles (Ag-NPs) (Al-Sharqi et al. 2020) and nanocapsules containing antibacterial essential oil (EO NCs) (Ivanova et al. 2020), both functionalized with anti-protein A antibodies.

Pseudomonas aeruginosa

In 2014, Warrener et al. produced and characterized a group of mAbs against PcrV protein, among which V2L2MD provided an excellent level of prevention and protection in several mouse infection models. Compared with antibody KB001-A and its parent IgG Mab166, V2L2MD showed much greater protective effects in vivo (Warrener et al. 2014).

Excessive production of the extracellular polysaccharides alginate leads to the transformation of *P. aeruginosa* to mucinous colonies. The majority of the isolates recovered from CF patients' respiratory tracts are mucinous strains. In 2004, Pier et al. reported an alginate-specific fully human monoclonal antibody F429, which could bind to the intact carboxylate on the C6 carbon of mannose acid and protect against mucinous and non-mucinous strains of acute pneumonia (Pier et al. 2004). In a mouse model of conjunctivitis, Zaidi et al. reported in 2018 that an IgG1 mAb against alginate could reduce inflammatory cells infiltration, pathological corneal damage, and bacterial load level (Zaidi et al. 2018). In our lab, we constructed a scFv-Fc format antibody MFb targeting alginate and demonstrated that it could inhibit biofilm formation, reduce the bacterial adhesion and invasion to HeLa cells, and enhance the phagocytotic capacity of macrophages for *P. aeruginosa* (Gao et al. 2020).

In 2017, Ray et al. confirmed that the three anti-Psl mAbs could inhibit early biofilm formation and promote bacteria clearance from prefabricated biofilms in the presence of host cells. The mAbs bound to different Psl epitopes in mature biofilms, facilitating neutrophils to contact and eliminate bacteria (Ray et al. 2017). Anti-Psl mAbs were expected to treat established or persistent *P. aeruginosa* infections.

Patel et al. reported the DNA-delivered monoclonal antibodies (DMAbs) against *P. aeruginosa* infection (Patel et al. 2017). The DMAb consists of an anti-PcrV IgG (DMAb-αPcrV) and a clinical candidate MEDI3902 (DMAb-BiSPA). By transfecting DNA plasmids into skeletal muscle cells, DMAb could be transiently expressed and act quickly. Therefore, it can circumvent the limitations of conventional monoclonal antibody delivery and directly enter the systemic circulation. Results showed that DMAb exhibited comparable efficacy to conventional mAbs produced by biological processes in preventing *P. aeruginosa* colonization.

Gabrielle Richard et al. detected two monoclonal antibodies S20 and MF23 in 2020. These two mAbs binding to O6-OSA the O-specific antigen (OSA) of type O6 *P. aeruginosa* can disrupt the flagella and outer membrane, eventually inhibiting *P. aeruginosa* growth (Altai et al. 2016).

Kajihara et al. developed an AAC by combining antibiotic G2637 with the engineered mAb 26F8, which binds to lipopolysaccharide O antigen on the surface of *P. aeruginosa.* The linker could be cleaved by lysosomal cathepsin, and the drug-to-antibody ratio was approximately 6. The anti-*P. aeruginosa* AAC effectively eliminated viable *P. aeruginosa* within phagocytes by delivering a high intracellular concentration of free antibiotics (Kajihara et al. 2021).

Klebsiella pneumoniae

Klebsiella pneumoniae (*K. pneumoniae*) is a commensal bacterium of the colon, but it can cause infections in the presence of substantial comorbidities and risk factors (Satlin et al. 2017). The majority of the carbapenem-resistant *K. pneumoniae* strains belong to sequence type 258 (ST258) lineage, a globally distributed antibiotic-resistant pathogen responsible for severe invasive infections.

Capsular polysaccharides (CPS, K antigen) anchored on the adventitia through lipid A tail is one of the main virulence factors of *Klebsiella* and essential for its immune evasion. ST258 primarily expresses CPS1 and CPS2 (Adamo and Margarit 2018). In 2018, Kobayashi et al. reported a rabbit antibody specific to ST258-CPS2. Both rabbit immune serum and purified ST258-CPS2-specific IgG were able to enhance the killing effect of serum and phagocytosis of neutrophils in vitro. Studies also demonstrated that ST258-CPS2 is a viable target for immunoprophylaxis and immunotherapy (Kobayashi et al. 2018).

Most hypervirulent *Klebsiella pneumoniae* (hvKp) strains express K1-serotype capsular polysaccharides (K1-CPS). In 2017, Diago-Navarro et al. used K1-CPS coupled with immunogenic anthrax PA protein to generate K1-CPS–specific monoclonal antibodies 4C5 (IgG1) and 19A10 (IgG3). In vitro studies showed that the mAbs promoted FcR-mediated phagocytosis and the release of NETs. In the hvKp-colonized mice model, the mAbs dramatically inhibited the spread of hvKp from the intestine to mesenteric lymph nodes and other organs. It showed protective activity in sepsis and pulmonary infection models (Diago-Navarro et al. 2017). Later, they proposed two IgG3 antibodies against CPS2: 17H12 and 8F12, and demonstrated their broad opsonophagocytic killing efficacy in a murine intratracheal infection model. 17H12 and 8F12 recognized different glycopeptides and showed activities against various ST258 strains. The two mAbs prevented biofilm formation in part, promoted complement and MAC deposition, and enhanced neutrophils phagocytosis. Moreover, the mAbs could introduce ROS and neutrophils to kill bacteria

effectively, increase the extracellular lethality of NETs, and reduce bacteria diffusion (Diago-Navarro et al. 2018).

Furthermore, researchers compared the ability of the murine IgG1 (mIgG1) and IgG3 (mIgG3) to CR-Kp ST258 infections and found that mIgG3 possessed a superior binding effect and agglutination ability. It demonstrated higher complement-mediated serum bactericidal activity and neutrophil-mediated killing effect of mIgG3. In contrast, the mIgG1 improved macrophage-mediated phagocytosis marginally (Motley et al. 2020).

Szijarto et al. reported a humanized mAb A1102 against the LPS-O antigen in 2017. In vitro studies illustrated that the primary protective mechanism of A1102 might be Fc-independent toxin neutralization. Additionally, it possessed complement-dependent bactericidal activity and opsonic phagocytosis activity. A1102 could neutralize ST258-derived LPS to prevent LPS-induced TLR-4 activation and provide significant protective effects in mouse and rabbit models (Szijártó et al. 2017). Pennini et al. generated a group of mAbs against the LPS-O antigen in 2017. Among them, mAb-KPN70 had a high affinity to O1 and O2-LPS, possibly by recognizing D-Galactan I, a common component of O1 and O2 polysaccharides. KPE33 and KPN42 were another two mAbs highly specific to O1 and O2-LPS, respectively, which enabled the dose-dependent killing of O1 and O2 strains. These mAbs showed protective effects in mouse models of acute pneumonia, septicemia, and heat damage (Pennini et al. 2017). Tim et al. reported in 2018 a human mAb with cross-specificity targeting the LPS-O antigen. The antibody could recognize LPS of diverse gut microbes, possibly through recognizing glycan epitopes on the surface of microorganisms. The cross-specific antibody showed a protective effect against *K. pneumonia* strains expressing O3a or O3b O-antigens by neutralizing endotoxin and boosting macrophages phagocytosis to O3, O3a, and O3b strains (Tim et al. 2018).

MrkA, a significant protein in the type III pili complex, is involved in the formation of biofilm and the establishment of infections. MrkA is a potential target for antibody drugs development for its highly conserved sequence across various strains and its universal accessibility. Wang et al. demonstrated that anti-MrkA mAb KP3 might play an immune-protective role through various mechanisms, including blocking bacterial attachment to lung cell lines and biofilm formation, reducing bacterial colonization in host tissue, and promoting bacterial clearance. The anti-MrkA mAb showed great non-serotype OPK activity, reduced the colony load, and improved the survival rate of mice infected with *K. pneumoniae* (Wang et al. 2016a). In 2017, Wang et al. produced four anti-MrkA antibodies against different epitopes through hybridoma and phage display platforms, whereas the binding epitopes were all constrained to a narrow region. The activities of these antibodies in vitro and in vivo were comparable to KP3. However, they did not observe any further synergism when different antibodies were used in combination (Wang et al. 2017).

Others

Monoclonal antibodies could kill pathogens directly by a phenomenon known as complement-independent bactericidal activity. A mAb targeting outer surface protein OspB of *Borrelia burgdorferi* (*B. burgdorferi*) showed bactericidal activity in the absence of complements. It led to the osmotic dissolution of pathogens by destroying the outer membrane and causing membrane blebbing (LaRocca et al. 2008). However, this direct bactericidal activity was not shared. LaRocca et al. showed that *Escherichia coli* (*E. coli*) expressing recombinant OspB is resistant to complement-independent lysis (LaRocca et al. 2009). Therefore, the direct killing activity of mAbs is not a universal phenomenon, as it only occurs in exceptional situations and varies between strains.

MAB1 against BamA, a member of the outer membrane proteins (OMP) in gram-negative bacteria, is another mAb with directly bactericidal activity. BamA is a critical component of the assembly mechanism of β-barrel structures involved in the insertion and secretion of membrane proteins in bacteria and organelles (Chaturvedi and Mahalakshmi 2017; Doyle and Bernstein 2019). Storek et al. developed a 'targeted boost-and-sort' strategy, which can improve the efficiency of screening monoclonal antibodies by more than 600 folds. Using this strategy, they effectively screened monoclonal antibodies against BamA to alter OMP function and suppress bacterial growth (Vij et al. 2018). Without complement or other immune factors, the direct binding of MAB1 to BamA inhibited the folding activity of β-barrel structure. MAB1 demonstrated bactericidal activity against *E. coli* strains with truncated LPS by inducing periplasmic stresses and destroying the outer membrane integrity (Storek et al. 2019; Vij et al. 2018).

Using the hybridoma technique, Yang et al. developed five mAbs against Omp25: 2B10, 4A12, 4F10, 6C12, and 8F3. They found that mAbs against Omp25 contributed significantly to the detection of *Brucella* in clinical samples, and mAb 6C12 could potentially be utilized to the therapeutic efficacy of monitor brucellosis (Yang et al. 2020).

The cell wall of gram-negative bacteria is composed of polypeptidoglycan. Phospho-MurNac-pentapeptide transferase (MraY) is an enzyme that is essential for peptidoglycan synthesis. MraY is also the target of a number of naturally occurring nucleoside inhibitors (Bugg et al. 2016). In 2017, Cao et al. proposed an anti-MraY mAb M-H11. Experiments in vitro and in vivo showed that M-H11 could significantly inhibit the growth of *E. coli* BL21 (DE3) plysS in a dose-dependent manner (Cao et al. 2017).

Hyr1p is a mycelial-regulated cell surface protein that enhances toxicity by resisting phagocytosis. It shares substantial similarities with *Acinetobacter baumannii* (*A. baumannii*) antigens in three-dimensional structure and epitopes (Uppuluri et al. 2018). Youssef et al. developed a group of monoclonal antibodies H1, H2, H3, and H4, against the peptide 5 of the rHyr1p-N sequence. The results showed that these four antibodies could effectively bind to three typical antibiotic-resistant gram-negative bacteria strains: *A. baumannii* (HUMC-1, XDR clinical isolate), *K. pneumoniae RM* (KPC-RM, carbapenem-resistant clinical isolate), and *K. pneumoniae QR* (carbapenem-sensitive multidrug-resistant strain KP-QR). Among them, mAb H3 and H4 had the best binding activity with all the three bacteria. In vitro studies showed that mAbs targeting HyR1 peptide 5 could bind to *A. baumannii* and *K. pneumoniae* multidrug-resistant strains and lower their toxicity to host cells. In vivo studies demonstrated that mAb H3 and H4 reduced the bacterial burden in the lungs and increased the survival rate of mice with HUMC-1 or *K. pneumoniae* (Youssef et al. 2020).

Yang et al. generated nearly 100 human mAbs against OspA of *B. burgdorferi* by immunizing transgenic mice with human immunoglobulin genes. Four of the mAbs (221–7, 857–2, 319–44, and 212–55) displayed potent Borreliacidal activity and were effective against multiple *Borrelia* genospecies (Wang et al. 2016b). Later, they optimized the mAb 2217 by amino acids substitutions in the Fc domain. The half-life of the 2217LS mutation was significantly extended. Their work suggests that the 2217LS could be an effective preexposure prophylaxis for Lyme disease (Schiller et al. 2021).

Conclusion

Nowadays, infectious diseases caused by antibiotic-resistant bacteria have become a significant problem due to the lack of effective antibiotics and vaccines, and monoclonal antibodies represent the return of passive immunotherapy.

There are currently three licensed anti-bacterial monoclonal antibody drugs, with a number of candidates in preclinical or clinical stages. Nonetheless, some candidates have failed in clinical trials due to unsatisfactory efficacy. There are many considerations regarding the deviation between the promising preclinical results and the disappointing clinical results. First, we lack suitable in vitro research models and in vivo animal models that mimic clinical conditions, so the results of internal and external studies of clinical antecedents cannot be transferred to human trials (Motley et al. 2019). Second, the virulence factors of bacteria are extraordinarily complicated, and the pathogenic mechanisms of most pathogens can alter during invasion, colonization, and infection. Furthermore, the mAb usually targets only a specific antigen, which is insufficient to clear the bacteria. In addition, it's challenging to identify an effective target. For example, LPS is a key virulence component and a potential target of *P. aeruginosa*, but the bacteria would convert to mucinous phenotype during the infection process to hide LPS, which would prevent antibodies from recognizing it.

Despite various challenges, scientists have been attempting to push the antimicrobial mAbs research and development forward. To identify new possible antibody targets, we must extend our understanding of bacteria's virulence factors and pathogenic mechanisms. Despite the redundancy and complexity of the virulence factors and pathogenic pathways, the antibody cocktail and bispecific or even multispecific antibodies appear to be possible solutions. Natali et al. reported that the combination of antibodies against diverse antigens can activate complement synergistically, even though the expression level of each antigen was below the threshold to trigger the bactericidal activity (Natali et al. 2020).

Numerous studies have demonstrated that antimicrobial antibodies and antibiotics can work together to effectively treat infections. AAC and antibody-conjugated nanoparticles may be promising strategies for combining antibodies and antibiotics (Deng et al. 2019; Mariathasan and Tan 2017; Wang-Lin et al. 2018; Zhou et al. 2019). DSTA4637S, the first clinically tried AAC, had already completed the phase Ib study.

In addition to the therapeutic applications, antibody-based biologicals could be used to improve the diagnosis of infections. In a study, de Vor et al. demonstrated that several previously discovered mAbs against surface antigens of *S. aureus* can detect *S. aureus* biofilms in vitro and in vivo. Moreover, the mAbs detection may provide an additional approach for diagnosing implant- or catheter-related infections (de Vor et al. 2022). And these mAb products can potentially be used to prevent infections as prophylactics (Zurawski and McLendon 2020).

Overall, with the in-depth study of the pathogenic mechanisms of bacteria and the continued development of antibody drugs, we believe the antibodies would play an increasingly important role in the treatment of antibiotic-resistant bacterial infections, either alone or in combination with other therapeutics.

Author contribution All authors contributed to the study's conception and design. Hui Wang collected the literatures and drafted the manuscript. Daijie Chen and Huili Lu revised the manuscript.

Declarations

Ethics approval and consent to participate This article does not contain any new studies with human participants or animals performed by any authors.

Conflict of interest The authors declare no competing interests.

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