Indian Journal of Pharmacy and Pharmacology 2024;11(1):23–28

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Pharmacy and Pharmacology

Journal homepage: https://www.ijpp.org.in/

Review Article

The impact of monoclonal antibodies in preventing antimicrobial resistance (AMR)

Raja Chakraverty[1]*, Jyotirmoy Bondyopadhyay[2], Tatini Debnath[3]

[1]*Dept. of Critical Care Medicine, Institute of Postgraduate Medical Education and Research, Kolkata, West Bengal, India*
[2]*Hooghly B.C Roy Institute, Kolkata, West Bengal, India*
[3]*Dept. of Pharmaceutical, Technology, Maulana Abul Kalam Azad University of Technology, Kolkata, West Bengal, India*

ARTICLE INFO

Article history:
Received 12-04-2024
Accepted 02-05-2024
Available online 07-05-2024

Keywords:
Monoclonal antibodies
AMR
Antibiotic therapy
Development process
Precision targeting

ABSTRACT

Monoclonal antibodies (mAbs) have transformed modern medicine through precision targeting and therapeutic efficacy. This summary summarises the development, applications, and comparative characteristics of mAbs in the context of antiviral medicines and antibiotic treatment durations. Monoclonal antibodies are designed to target specific antigens with great affinity and specificity, making them important for diagnostics and treatments. Anti-virulence mAbs, a type of mAb, target pathogen virulence factors rather than pathogens themselves, providing a promising technique for combating infectious diseases while limiting resistance development. When comparing the duration of antibiotic medication versus mAb treatment, mAbs frequently provide a shorter and more tailored therapeutic regimen. This can lead to better patient outcomes, less resistance, and a lower risk of side effects associated with long-term antibiotic usage. Antigen selection, hybridoma creation, antibody synthesis, purification, and characterization are all steps in the mAb development process, with advances like recombinant DNA technology improving efficiency and scalability.

1. Introduction

Since their initial discovery, antibiotics have been considered a fundamental component of contemporary medicine. The development of effective antibiotics has greatly benefited the treatment of trauma, routine invasive surgery, and immunosuppressed populations, such as organ transplant recipients and cancer chemotherapy patients, extending life expectancy and improving the quality of life for countless numbers of people worldwide. Antibiotics are now considered essential to medicine, and their affordability, effectiveness, and accessibility are often taken for granted. A time when most bacterial diseases that are considered mild today were virtually incurable cannot be recalled by most people.[1–4]

Resistance was developed by the pathogens that antibiotics were intended to treat shortly after they became widely available. This was not seen as a major issue because, until the 1960s, antibiotic development essentially kept up with the rate of resistance. But, after several decades of using and abusing empirical broad-spectrum antibiotics without success, as well as failing to create novel antibiotics with different modes of action, resistance has grown into an epidemic that poses a threat to the return of the pre-antibiotic era.

In the early 1890s, serum therapy, the first clinical use of antibodies for the treatment of infectious disorders, was introduced by Emil von Behring and Shibasaburo Kitasato. The development of antimicrobial chemotherapy was sparked by the discovery of sulfonamides in 1937, and

* *Corresponding author*.
E-mail address: rchakraborty20@yahoo.com (R. Chakraverty).

https://doi.org/10.18231/j.ijpp.2024.005

serum therapy was dropped in favor of antimicrobials due to their substantial benefits, which included lower toxicity and cost, increased efficacy, and broad-spectrum activity. Regrettably, a decline has been observed in the rate at which new antibiotics are approved while medication resistance has increased. From an average of five new antibacterial medications approved per year in the 1980s to less than one in the 2000s, the number has declined.[4–6]

New attention has been attracted to the development of antibacterial antibody therapeutics as a result of the discovery of hybridoma technology in 1975 and current developments in monoclonal antibody (mAb) engineering, which enable the synthesis of an infinite number of human mAbs. Although the use of monoclonal antibodies (mAbs) to treat bacterial infections has been slow to grow, they are routinely utilized to treat immunological deficiencies, malignancies, multiple sclerosis, rheumatoid arthritis, and psoriasis. As of right now, only three mAbs for use in the management of bacterial infections have been approved by the FDA. Muromonab-CD3 was the first monoclonal antibody licensed for therapeutic use by the US Food and Drug Administration (FDA). It was used to treat organ transplant-associated rejections after receiving approval in 1985. From then on, 100 mAbs as of 2021 have been approved by the FDA.[7]

Approximately 40 Hu-mAbs for various illnesses and therapies were licensed by the US Food and Drug Administration (FDA) from 2002 to 2016. In 2002, the first entirely human antibody (HUMIRA®/adalimumab) was approved. None of these were for bacterial infections; the majority were linked to autoimmune disorders and malignancy. Anthim® (obiltoxaximab), the first Hu-mAb for antibacterial treatment, was approved by the FDA in 2016. This injection is used to treat inhalational anthrax in conjunction with the recommended antibiotics, most commonly ciprofloxacin. Additionally, by the Animal Rule for Biothreat Organisms, Anthim® has been approved to prevent inhalational anthrax when no other therapy is available or suitable.[4–7]

Anthim®'s effectiveness was assessed using New Zealand white rabbits by the Animal Rule. Anthrax infection can be induced by spores from Bacillus anthracis when inhaled, and because they can survive in extreme conditions, they can also act as a source of infection for others. The usefulness of Anthim® was further supported by an additional intriguing trial that was conducted after licensure and revealed that the medication could also prevent these illnesses. Zinplava (bezlotoxumab), the second antibody for bacterial infections, was authorized by the FDA later that year in October 2016 for adult Clostridium difficile infections. It's critical to rea0lize that this medicine was authorized to lessen infection recurrence, which is common with C. difficile infections; it does not prevent or treat initial or primary infections. Through this review of the literature, more about the amount of research being done on monoclonal antibodies and how to combat various bacteria, particularly gram-negative bacteria, by using fewer antibiotics is hoped to be learned. Ultimately, insight into the potential applications of these antibodies in the future is hoped to be gained.[4–7]

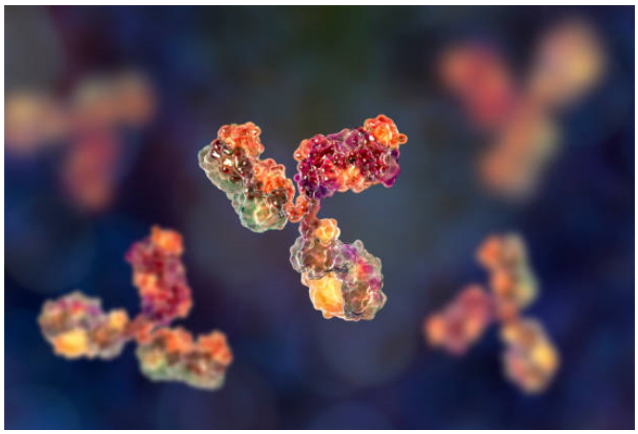

Figure 1: Monoclonalantibody[5,6]

2. Monoclonal Antibodies and Resistance

Research has focused on identifying more relevant biomarkers by implementing more uniform sub-population studies over time to create more precisely targeted treatment candidates. Therefore, monoclonal antibodies (mAbs) directed against a single target have the potential to revolutionize the way sepsis is treated. With just three FDA-approved medications to date, the use of mAbs in the treatment of bacterial infections is still relatively new, with viral and cancerous infections garnering the most attention. Two main ways that monoclonal antibodies can be helpful are by directly suppressing the production of inflammatory mediators through mAbs targeting inflammatory signaling and by targeting the pathogen and its constituent parts.[5]

The necessity for new strategies to improve the functional qualities of mAbs that had already been found and to find incredibly potent human mAbs as treatments was made clear by the limitations of the first technologies. An unprecedented level of control over antibody molecules was allowed by the development of structural-based methods and molecular biology techniques in the late 1990s and early 2000s, opening the door for the engineering of fragment crystallizable (Fc) and fragment antigen-binding (Fab) regions. Through fab engineering, the affinity of the antibody for its corresponding antigen could be increased. To accomplish this, two primary strategies—the display- and structure-based methods—were devised. Libraries of variations were hence created by using an error-prone PCR to create random mutations in the antibody Fab region, as employed in the display-based approach.[8–10]

Alterations were arbitrarily introduced throughout the entire variable region, as was demonstrated by Maynard and associates in 2002, who used this method to produce a series of toxin-neutralizing antibodies against Bacillus anthracis. Selective alterations of the antibody's complementary determining regions (CDRs) were documented by Yang and associates, utilizing this technique to boost the binding affinity of a powerful human anti-HIV-1 monoclonal antibody. The analysis of intricate antibody-antigen structures and the alteration of particular contact sites within the antibody variable region serve as the foundation for the structure-based approach to Fab engineering and affinity augmentation. The application of the structure-based approach to mAbs against viral diseases such as dengue virus, HIV, and influenza has become commonplace. While Fab changes were intended to increase the mAb's capacity to bind its cognate antigen, Fc engineering was sought to improve the pharmacokinetics and effector functions of the antibody. That the serum half-life of therapeutic mAbs must be prolonged beyond the 23 days of natural IgGs is a critical component of these antibodies.[8–12]

2.1. Are antibacterial MAbs affect the levels of SCFAs or bile acids?

The effect of Antibacterial MAbs on the levels of SCFAs or bile acids was covered in the research paper by Omari Jones-Nelson et al. The growth of certain bacteria that belong to the Bacteroidetes phylum (Porphyromonadaceae and Alistipes spp.) and the Firmicutes phylum (Lachnospiraceae and Lactobacillus) might be caused by some SCFAs, such as acetate, propionate, or butyrate, as they talked about. When compared to the controls, fecal samples from mice treated with vancomycin, linezolid, or levofloxacin showed decreased relative abundances of acetate, propionate, and butyrate on day 7. It was evidenced by the fact that the SCFA levels in the MEDI4893*-treated samples did not differ from those in the saline control and that the fecal microbiota was not affected by pathogen-specific MAbs. Both health and sickness have been linked to bile acids, according to recent research. A decreased conversion of taurochenodeoxycholic acid (TCDCA) into the secondary BAs lithocholic acid (LA) or taurine-conjugated lithocholic acid (TLCA) and taurocholic acid (TCA) into deoxycholic acid (DCA) or taurodeoxycholic acid (TDCA) was shown in samples treated with antibiotics when compared to the controls. Conversely, the transformation of primary BAs into secondary BAs in the samples treated with MAb continued to resemble those in the control group.[13–15]

3. Developmental Process of Antibacterial Monoclonal Antibodies

Monoclonal antibodies (MAbs) are uniform antibodies made from a single B-cell clone that can identify a single epitope in an antigen, as was talked about by Hsiao-Chun Chen et al. in their paper. Employing mAbs as a therapy option was quite expensive, even though there were a lot of antibiotics on the market in the past. Therefore, the development of antibacterial mAbs has proceeded comparatively more slowly than in the fields of autoimmune disorders and malignancies. Due to the development of biotechnology and precision medicine, there is currently a rising need for mAbs in anti-infective therapeutic applications. Many benefits over the use of antibiotics are offered by the use of monoclonal antibodies (mAbs) as bacterial infection treatment techniques.[16,17]

(1) High specificity is characterized by effectively targeting multidrug-resistant bacteria; (2) A safety profile is achieved by protecting normal intestinal flora; (3) The ability to be combined with conventional antibiotics (antibody-drug conjugates) is seen, potentially lowering the dose and presenting with selective pressure; (4) The safety and affinity of monoclonal antibodies (mAbs) that may be genetically engineered, such as fully human antibodies and single-chain fragment variable (scFv) antibodies, are observed; (5) A long half-life is guaranteed, ensuring bioavailability for several weeks to months after administration, potentially offering advantages in terms of dosing, compliance, and adherence; (6) Therapeutic advantages are provided for immunocompromised patients and those for whom vaccination is not recommended; (9) Drug resistance is less likely to occur because specific virulence factors rather than crucial survival proteins are targeted; (7) Production is carried out with minimal chemical usage compared to antibiotics, promoting environmental friendliness; (8) Easy degradation under various conditions, including temperature changes, pH shifts, or oxidation, is ensured, preventing accumulation in the environment like antibiotics. Moreover, mAbs have been investigated as possible supplements to antibiotic therapy in several clinical trials.[16–19]

By directly delivering antibiotics to the illness site, the excess toxicity and unintended consequences of antibiotic overuse can be reduced by monoclonal antibodies (MAbs). This method not only allows for the reduction of the adverse effects associated with antibiotics but also enables the possibility of lowering antibiotic dosages. The lowering of antibiotic dosages may lessen the selection pressure imposed by antibiotics, which would reduce the chance of multidrug resistance emerging. The ultimate goal of replacing or reducing the use of antibiotics is supported by these efforts, which have the potential to improve treatment outcomes. Based on the type of development source, mAbs can currently be generically classified as mouse-derived, human-mouse chimera, humanized, and human mAbs.[16–19]

The mouse-derived monoclonal antibody, known as the hybridoma, is created by the union of mouse myeloma cells with B lymphocytes from immunized mice. This

is widely utilized in antibody research and represents the first generation of mAb production techniques. The human-mouse chimeric mAb is characterized by genetic recombination between the constant region (Fc) of the human antibody and the variable region (Fv) of the mouse antibody and is injected into myeloma cells, preserving around 30% of the murine antibody characteristics. To achieve about 90% humanization, humanized antibodies are created by substituting the relevant places in the variable sections of murine mAbs with the sequences of the complementarity-determining regions (CDRs) in the mutant areas of murine mAbs. This kind of antibody maintains affinity in humans while possessing the specificity of mouse mAbs. The ideal alternative for mAb therapy is seen in fully human mAbs. By eliminating human variability across species, this class of monoclonal antibodies minimizes the likelihood of a human anti-chimeric antibody (HACA) response.[16–20]

The primary methods used in the creation of fully human mAbs include transgenic mouse technology, ribosome display technology, and phage antibody library expression. In any case, the immune system of the individual is triggered to view mAbs as foreign antigens, which results in the creation of antibodies that can counteract their effects or cause a pathogenic immune response. Murine fragments, being a natural component of all chimeric mAbs, will always result in HACA responses. Although fully human or humanized mAbs may still cause an anti-drug antibody response, which could impact mAb potency and pharmacokinetics (PKs).[16–20]

4. Anti-virulence mAbs Using Functional Information

Functional information on the necessity of a protein containing the putative mAb epitope or its role in virulence serves as a logical strategy for using anti-virulence mAbs. A significant chance of epitope masking or switching exists if certain critical/virulence-associated epitopes are not targeted, which might quickly evade the monoclonal therapy. Species-specific virulence factors from specialized research publications are gathered by expert sites like Victors, VFDB, and PATRIC. High-throughput methods such as signature-tagged mutagenesis, which allow for laboratory and animal-model screens, enable the explicit identification of putative genes crucial for disease. Such pertinent data serves as a good starting point when selecting and prioritizing antigens to precisely and knowledge-based block virulence characteristics with mAbs. Unlike deadly antibiotics, neutralization by mAbs is akin to preventing virulence rather than affecting the pathogen's viability and follows the anti-virulence medication paradigm since most virulence components are not necessary for basic viability. Currently approved monoclonal antibodies (mAbs) that inhibit the function of exotoxins represent virulence-blocking therapeutics.[21]

5. Duration of Antibiotic Therapy vs. Monoclonal Antibodies

A more recent therapeutic option for a variety of disorders, including infectious diseases, is represented by monoclonal antibodies (mAbs), yet antibiotics have long been utilized as the primary treatment for bacterial infections. Understanding the ideal duration of antibiotic therapy in comparison with monoclonal antibodies is vital for enhancing patient outcomes and mitigating the emergence of antibiotic resistance. The length of antibiotic therapy has traditionally been decided based on the type and severity of the illness, patient-specific characteristics, and professional recommendations.[21–23]

For common illnesses such as simple skin infections or UTIs, short doses of antibiotics, lasting three to seven days, have often been found beneficial. To ensure total pathogen eradication and avoid recurrence, longer periods are required for more serious infections, such as sepsis or pneumonia. Monoclonal antibodies are known as proteins designed to target specific antigens or receptors involved in disease processes. Bacteria are directly killed or their growth is inhibited by antibodies, whereas toxins are neutralized, immune responses are modified, or chemicals on the surface of pathogens are targeted by monoclonal antibodies (mAbs). The duration of antibiotic therapy and monoclonal antibody treatment is affected by the type of illness, the features of the pathogen, the patient, and the therapeutic objectives. Treatment regimens must be customized based on these factors to effectively manage infectious diseases, promote antibiotic stewardship, and reduce the possibility of resistance. Further investigation and clinical studies are deemed necessary to clarify the best ways to employ monoclonal antibodies and the duration for their use in infectious disease situations.[21–23]

6. Discussion

The therapeutics sector has been completely transformed by monoclonal antibodies (mAbs) by providing specialized and focused treatment options for a wide range of medical conditions. The search for novel therapeutic targets represents one of the most pivotal developments in the field of monoclonal antibodies. A wide range of diseases, including cancer, autoimmune disorders, and infectious diseases, has seen the successful production of mAbs targeting novel antigens, receptors, and signaling pathways in ongoing research. Opportunities for enhancing personalized medicine techniques and treating diseases that were previously difficult to manage are being created by this diversification. By developments in antibody engineering and design methodologies, the efficacy, specificity, and safety profiles of monoclonal antibodies are being enhanced. This includes the development of bispecific and multi-specific antibodies

capable of targeting multiple antigens or immune cells simultaneously, to improve therapeutic outcomes and circumvent resistance mechanisms. The therapeutic potential of mAbs is further increased by advancements in glycoengineering, conjugation technologies, and antibody fragment design.[24,25]

7. Conclusion

Future monoclonal antibody research will also look into the potential synergistic benefits of combination therapies. Researchers hope to reduce adverse effects while increasing therapeutic advantages by combining mAbs with other biologics, tiny molecules, or conventional medicines. Immunomodulation, which is critical for modulating immune responses in diseases such as autoimmune disorders, inflammatory conditions, and cancer immunotherapy, is significantly dependent on mAbs. Future improvements may concentrate on improving immune modulation tactics to provide the best therapeutic outcomes with the least amount of risk. Monoclonal antibodies (mAbs) are being studied in a variety of developing domains, including neurological diseases, infectious diseases (such as viral infections like COVID-19), regenerative medicine, and aging disorders. Monoclonal antibodies have promising uses in advancing precision medicine approaches and meeting unmet medical requirements in a variety of healthcare settings, such as targeting specific pathogenic pathways, modifying immune responses, and encouraging tissue regeneration. Monoclonal antibodies will continue to drive future innovation, therapeutic applications, and insights into immunology and disease pathways. As academics and biopharmaceutical companies continue to engage in mAb development, advances that benefit patients throughout the world by enhancing the efficacy, safety, and accessibility of these revolutionary biologics should be expected.

8. Source of Funding

None.

9. Conflict of Interest

None.

References

1. Digiandomenico A, Sellman BR. Antibacterial monoclonal antibodies: the next generation? *Curr Opin Microbiol*. 2015;27:78–85. Available from: https://www.sciencedirect.com/science/article/pii/S1369527415001058.
2. Lin SW, Balthasar J. Pharmacokinetic and Pharmacodynamic Considerations for the Use of Monoclonal Antibodies in the Treatment of Bacterial Infections. *Antibodies*. 2018;7(1):1–5.
3. Vacca F, Sala C, Rappuoli R. Monoclonal Antibodies for Bacterial Pathogens: Mechanisms of Action and Engineering Approaches for Enhanced Effector Functions. *Biomedicines*. 2022;10(9):2126.
4. Zurawski DV, Mclendon MK. Monoclonal Antibodies as an Antibacterial Approach Against Bacterial Pathogens. *Antibiotics*. 2020;9(4):155.
5. Baker SJ, Payne DJ, Rappuoli R, Gregorio D. Technologies to address antimicrobial resistance. *Proceedings Nat Acad Sci*. 2018;115:12887–95.
6. Szijártó V, Guachalla LM, Hartl K, Varga C, Badarau A, Mirkina I, et al. Endotoxin neutralization by an O-antigen specific monoclonal antibody: A potential novel therapeutic approach against Klebsiella pneumoniae ST258. *Virulence*. 2017;8(7):1203–18.
7. Horspool AM, Kilic S, Malkowski AC, Breslow SL, Mateu-Borras M, Hudson MS, et al. Development of an anti-Pseudomonas aeruginosa therapeutic monoclonal antibody WVDC-5244. *Front Cell Infect Microb*. 2023;13:1117844.
8. Kharga K, Kumar L, Patel S. Recent Advances in Monoclonal Antibody-Based Approaches in the Management of Bacterial Sepsis. *Biomedicines*. 2023;11(3):765.
9. Troisi M, Marini E, Abbiento V, Stazzoni S, Andreano E, Rappuoli R. A new dawn for monoclonal antibodies against antimicrobial resistant bacteria. . *Front Microbiol*. 2022;13:1080059. doi:10.3389/fmicb.2022.1080059.
10. Stazzoni S, Troisi M, Abbiento V, Sala C, Andreano E, Rappuoli R, et al. High-throughput bactericidal assays for monoclonal antibody screening against antimicrobial-resistant Neisseria gonorrhoeae. *Front Microbiol*. 2023;14:1243427. doi:10.3389/fmicb.2023.1243427.
11. Hua L, Hilliard JJ, Shi Y, Tkaczyk C, Cheng LI, Yu X. Assessment of an Anti-Alpha-Toxin Monoclonal Antibody for Prevention and Treatment of Staphylococcus aureus-Induced Pneumonia. *Antimic Agent Chemother*. 2013;58(2):1108–25.
12. Varshney AK, Wang X, Macintyre J, Zollner RS, Kelleher K, Kovalenko OV. Humanized Staphylococcal Enterotoxin B (SEB)-Specific Monoclonal Antibodies Protect From SEB Intoxication and Staphylococcus aureus Infections Alone or as Adjunctive Therapy With Vancomycin. . *J Infect Dis*. 2014;210:973–81.
13. Nelson OJ, Tovchigrechko A, Glover MS, Fernandes F, Rangaswamy U, Liu H. Antibacterial Monoclonal Antibodies Do Not Disrupt the Intestinal Microbiome or Its Function. *Antimicrob Agents Chemother*. 2020;64(5):e02347–19.
14. Wang Q, Chang C, Pennini M, Pelletier M, Rajan S, Zha J. Target-Agnostic Identification of Functional Monoclonal Antibodies AgainstKlebsiella pneumoniaeMultimeric MrkA Fimbrial Subunit. *J Infect Dis*. 2016;213(11):1800–8.
15. Li J, Yang Y, Fan Z, Huang Z, Chen J, Liu Q. Salmonella typhimurium targeting with monoclonal antibodies prevents infection in mice. *PLoS Neglected Trop Dis*. 2023;17(12):e0011579.
16. Chen HC, Pan YL, Chen Y, Yang TH, Hsu ET, Huang YT, et al. Monoclonal Antibodies as a Therapeutic Strategy against Multidrug-Resistant Bacterial Infections in a Post-COVID-19 Era. *Life*. 2024;14(2):246.
17. Kurbatfinski N, Goodman SD, Bakaletz LO. A Humanized Monoclonal Antibody Potentiates Killing by Antibiotics of Diverse Biofilm-Forming Respiratory Tract Pathogens. *Antimicrob Agent Chemother*. 2022;66(3):e0187721.
18. Lee HJ, Cho SS, Simkhada JR, Yoo JC. Monoclonal antibody production and immunochemical detection of polyether antibiotics. . *Arch Pharmacal Res (Seoul Print)*. 2009;32:437–78.
19. Su Y, Shatil SM, Shree N, Andrabi SM, Wang C. It Takes Two to Tangle: Microneedle Patches Co-delivering Monoclonal Antibodies and Engineered Antimicrobial Peptides Effectively Eradicate Wound Biofilms. . *Macromol Biosci*. 2024;13:e2300519.
20. Mcconnell MJ. Where are we with monoclonal antibodies for multidrug-resistant infections? *Drug Discov Today*. 2019;24:1132–40.
21. Martín-Galiano AJ, Mcconnell MJ. Using Omics Technologies and Systems Biology to Identify Epitope Targets for the Development of Monoclonal Antibodies Against Antibiotic-Resistant Bacteria. *Front Immunol*. 2019;10:2841.
22. Smith K, Garman L, Wrammert J, Zheng NY, Capra JD, Ahmed R, et al. Rapid generation of fully human monoclonal antibodies specific to a vaccinating antigen. *Nature*. 2009;4(3):372–84.

23. Verma V. Leveraging monoclonal antibodies as therapeutics to address antimicrobial resistance in bacteria. *J Appl Biol Biotechnol*. 2022;11(3):53–60.
24. Oleksiewicz MB, Nagy G, Nagy E. Anti-bacterial monoclonal antibodies: Back to the future? . *Arch Biochem Biophysics*. 2012;526:124–55.
25. Berg SD, Bonarius HPJ, Kessel KV, Elsinga GS, Kooi N, Westra H, et al. A human monoclonal antibody targeting the conserved staphylococcal antigen IsaA protects mice against Staphylococcus aureus bacteremia. *Int J Med Microb*. 2015;305(1):55–64.

Author biography

Raja Chakraverty, Research Scientist https://orcid.org/0000-0002-7193-3604

Jyotirmoy Bondyopadhyay, Assistant Professor

Tatini Debnath, Doctoral Research Scholar

Cite this article: Chakraverty R, Bondyopadhyay J, Debnath T. The impact of monoclonal antibodies in preventing antimicrobial resistance (AMR). *Indian J Pharm Pharmacol* 2024;11(1):23-28.