REVIEW ARTICLE

Monoclonal antibodies (mAbs) could be a Future in Biomedicine

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Received: 25th March, 2024; Revised: 10th July, 2024; Accepted: 09th August, 2024; Available Online: 31st August, 2024

ABSTRACT

The discovery of mAbs has fundamentally changed the field of biomedicine by offering precise treatment options for a variety of illnesses, including autoimmune disorders and cancer. Future developments in the state of affairs and breakthroughs in mAbs in the multidisciplinary fields of biomedicine were explored. We begin by reviewing the developments in mAb technology, the production of fully human antibodies, bispecific antibodies, and antibody-drug conjugates, all of which have greatly increased the potency and specificity of their therapeutic effects. Next are the latest developments in mAb engineering, such as the use of AI in antibody discovery and optimization and the development of novel delivery systems that maximize bioavailability while minimizing side effects. The most recent developments in clinical practice and scientific research that will boost the therapeutic potential of mAbs for many applications, including rare diseases and personalized medicine, are also reviewed. In summary, the present research highlights the difficulties that the discipline faces due to large run-costs and the need for new methods. While not providing a comprehensive overview of this ever-evolving topic, the study does offer enough information to understand how mAbs in biomedicine could impact the development of novel treatment techniques in the future.

Keywords: Biomedicine, drug delivery, monoclonal antibody, stability.

International Journal of Pharmaceutical Quality Assurance (2024); DOI: 10.25258/ijpqa.15.3.54

How to cite this article: Prasad U, Ingle RG, Sonwane SM. Monoclonal antibodies (mAbs) could be a Future in Biomedicine. International Journal of Pharmaceutical Quality Assurance. 2024;15(3):1444-1448.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Monoclonal antibodies (mAbs) have become indispensable in today's medical environment. Because of their special ability to bind to target molecules with extreme affinity, mAbs have emerged as important players in the treatment of numerous diseases. These antibodies, which were developed from a single-cell clone, have made tremendous progress against cancer, autoimmune illnesses, and infectious diseases because they are specific to the proteins that cause illness. MAbs have been surprisingly effective since their first approvals in the 1980s, and several medicines are being used in clinical settings. Selected topics including the state of mAb technology today, recent achievements, and the field's promising future are covered in this overview. Gaining a deeper comprehension of this evolution can help one to see how the potential of mAbs is always being improved toward bettering patient outcomes and addressing intricate medical issues.

Historical Background

The hybridoma technology, created by Georges Köhler and César Milstein, is a novel and innovative technique that makes it possible to produce mAbs in vitro. This technique was awarded the Nobel Prize in Physiology or Medicine in 1984. By using hybridoma technology, a myeloma cell—a cancerous tissue that may replicate endlessly—is combined with a particular B cell that produces antibodies and has a set lifespan. The union produces a hybridoma cell line that possesses characteristics from both: the former's capacity to secrete a particular antibody and the latter's endless replication potential. It results in an immortal, stable cell line that can produce large quantities of a single, targeted mAb. All hybridoma technology does is ensure that pure mAbs that are extremely specific to a single antigen will be produced. Specificity is one attribute that is highly valued in this application, particularly for research and therapies. This minimizes off-target effects and enables the exact targeting of disease indicators.[1,2]

Development of mAbs in diagnosis

The application of immunological techniques in biochemical research labs has significantly advanced our knowledge of genetics, biochemistry, and human physiology. However, in actual practice, fundamental issues with controlling antigen-antibody interactions beyond the production of antibodies with consistent affinity and specificity restrict the potential advantages offered by mAb technology. The potential uses of this technology have been expanded through the utilization of contemporary technologies in the production of recombinant antigens and the creation of antibodies.[3] The 2H2.4 mAb against

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early cytomegalovirus was used in conjunction withshell vial assay with low-speed centrifugation to allow CMV infections to be detected rapidly in 16 hours postinoculation.[4]

The process of finding B cells in an animal's body that can secrete effective antibodies after immunization is another step in the discovery of mAbs; the difficult part of developing a mAb is locating the B cells secreting effective antibodies from the large population. To date, research and development in the discovery of mAbs has gone through three stages.. Using hybridoma technology, effective B cells that secrete antibodies were chosen from a pool of cells in the initial step of the process. This entails creating hybridomas, which combine immune and malignant cells. These have often made use of electroporation or PEG-based fusing methods. The combined ability of B cells to make antibodies and the unchecked cell development of cancer cells will result in these fused cells, known as hybridoma cells.[5]

Recent development on treatment

Currently available treatment methods that target HER2 can be generally classified into three groups: antibody-drug conjugates, tyrosine kinase inhibitors, and antibodies. All that aBs typically do is attach to the extracellular domain of HER2, which prevents HER2 from forming hetero-dimers and obstructs down-flow targets involved in ERBB2 signaling; this is followed by a recruitment of immune cells in the extracellular environment to carry out ADCC. ZW25, pertuzumab, and trastuzumab are a few agents that have these kinds of actions. The binding sites of pertuzumab and trastuzumab, respectively, are located on HER2 extracellular region II and IV, which can be bound by the bispecific antibody ZW25 to trigger ADCC activity. Small molecule TKIs, in contrast to antibodies, have the ability to catalyze the kinase structure inside the cells and compete with ATP to block the HER2 family's downstream signaling. These medications inhibit the process of phosphorylation of tyrosine kinase residues in the MAPK and PI3K/AKT pathways, which are essential in promoting angiogenesis, drug resistance, apoptosis, and the proliferation of tumor cells. Additionally, TKI medications' high lipid solubility and low molecular weight improve their ability to pass through the blood-brain barrier, which makes them especially promising for cancers that have spread to the brain.[6] IgA nephropathy, membranous nephropathy, ANCA-associated vasculitis, and lupus nephritis are among the diseases in the latter category. On the other hand, C3 glomerulopathy, complement-mediated atypical hemolytic uremic syndrome (HUS), and focal segmental glomerulosclerosis are caused by activation of the dominant complement pathway without the need for an antibody. Focusing on the alternate complement pathways or the terminal and lectin in these different glomerular disorders.[7]

Recent development on novel drug delivery system

mAbs have been approved for more than 100 treatments at the time of this analysis, and they make up about 20% of recent FDA1 approvals for both acute and chronic illnesses. Just 30% of these mAbs are given intravenously (IV) in a clinical environment; the balance are given as injections. In comparison to the intravenous route, the subcutaneous method is less intrusive, can be administered faster, and in certain cases, can be self-administered at home by the patient or a healthcare provider.. More mAbs as single-use injections are being made available in an attempt to lessen the financial burden of healthcare, enhance the lives of patients and the people who care for them, and lower expenses and demands on infusion facilities. Industry development teams are collaborating with formulation subject matter experts in the fields of medical sciences, drug delivery, and preclinical and clinical pharmacology to assist determine whether it is feasible to produce, distribute, and commercialize single-chain mAbs across a wide variety of therapeutic areas.[8]

Whereas a few decades ago, there were very limited or no medical treatment options for diseases, novel life-changing treatment alternatives were made available to patients. Currently, more than 117 mAbs and mAb derivatives are approved in the US for several indications. The majority of approved biologic therapies include mAbs, ADCs, antibody fragments, and Fc fusion proteins. Successive technological evolutions have extended the possibilities of application of mAbs by allowing, first of all, the production of mouse/human chimeric and humanized and fully human mAbs starting from antibodies of pure murine origin. Actually, the decrease of the xenogenic portion of mAb structure reduced the immunogenic potential of murine mAbs, enabling their wider application.[9]

Emerging Therapeutic Applications

In particular, the COVID-19 pandemic gave this boost to licensed mAbs, though in 2019 multiple phase 1 studies were underway for other infectious diseases such as malaria and yellow fever. MAbs could be used, for example, for the prophylaxis of malaria or for the treatment of, for example, rabies, dengue fever, and yellow fever. Applications of mAbs are taking off and bound to dominate this field. Whereas in 2014 only two mAbs were registered, today over ten mAbs are registered or received an EUA by the end of October 2023, and many more are in different (pre)clinical phases. An update on the mAbs currently being developed for infectious diseases that may be of interest to travelers is provided, along with a discussion of the opportunities and challenges for using mAbs in the prevention and treatment of (tropical) infectious diseases as observed in returning travelers.[10]

Table 1: Overview of licensed immunoglobulins used in the prevention and treatment of infectious diseases

Type	Trade name	indication	Year licensed	Administration route
Ansuvimab	Ebanga™	Treatment of Ebola	2020 (FDA	i.v.
Casirivimab/Imdevimab	Ronapreve®	PrEP, PEP, treatment of COVID	2020 (FDA, 2022)/2021 (EMA)	i.v.
Sotrovimab	Xevudy	Treatment of COVID	2021 (FDA, 2022)/2021 (EMA)	s.c/i.v.
Bamlanivimab/etesevimab	none	PEP, treatment of COVID	2021 (FDA, 2022)	i.v.
Regdanvimab	Regkirona™	Treatment of COVID	2021 (EMA)	i.v.
Tixagevimab/cilgavimab	Evusheld™	PrEP COVID	2021 (FDA)/2022 (EMA)	i.m.

Typical bioprocess for production of mAbs

The two main phases in the general manufacture and purification of mAbs are upstream (USP) and downstream processing, which are supplemented by steps for final product formulation, stability, fill, and finish. In turn, the downstream process entails a series of separation/purification steps for gathering the product of interest and removing various impurities related to the procedure, host cell, or product with a minimum loss in yield. The initial process involves the cell culture in bioreactors in cascades and the manufacturing of the product of interest. Although continuous culture systems occasionally use these techniques, fed-batch cultivation systems and batch separation technologies currently handle these tasks. depicts the flow diagram for a typical mAb and recombinant protein manufacturing platform.

When initiating an off-upstream process, the vial must be frozen, and the inoculum of cells from a cell bank must be developed in shake flasks or spinner flasks using the appropriate media. Subsequently, true upstream begins with cell culture in increasingly larger and/or more volumetric seed bioreactors. In order for the medium to express proteins, active cells are subsequently transferred to production bioreactors.

Finally, prior to proceeding with the additional purification procedures, a standard harvest operation is conducted by centrifugation, depth, and membrane filtering in order to remove cells and cell debris Shukla and Kandula, 2008 The fed-batch strategy is usually employed in the upstream process, where a small amount of feed nutrients are supplied to the bioreactors while the cells are still in the growth phases.[11]

Humanization and mAbs

Humanization Process

Humanized Fab Opt.h10C9Fab was produced after the mouse Fab for CTX3C was successfully humanized. This has shown to be a crucial advancement in the development of potent antibodies that are less likely to cause an immunological reaction in humans. Because it makes mAb therapies safe and effective, this process is essential to their development. High-affinity connection: If the optimized transformed Fab binds to completely CTX3C with high affinity, it has been successful in humanization. A high-affinity interaction would require an antibody to effectively target and neutralize the antigen as one of the prerequisites for a successful therapeutic application.-. 3D11: 3D11 is a mouse mAb that targets the right wing of CTX3C, another epitope. It is a candidate for consideration. It has demonstrated signs of a collection of humanized antibodies that can optimize the effectiveness of treatment against CTX3C. Combination Treatment This line of reasoning therefore suggests that combining two humanized anti-CTX3C antibodies can enhance the neutralization of ciguatoxin. Because greater surface area on the antigen is covered by this diversification of epitopes, which also improves binding and neutralization overall, mAbs may be better able to neutralize toxins.

CTXs and Analogs

This study's association with environmental toxins is only shown by the discovery of CTXs and their Pacific equivalents. The creation of potent and neutralizing Abs against these toxins is essential to combat them as ciguatoxins are only one of the marine toxins that cause ciguatera poisoning, a major health issue in endemic areas.[12]

Recently development in biosimilar drug

Recently, the utilization of Rituximab-Pvvr was reviewed with respect to indications, patient demographics, prescribing practices, and data on biosimilars to the reference product Rituximab. That demonstrates the trend from the growing market availability of biosimilars to their real-world applications. Signs and symptoms: The data suggests common use indications, including Chronic Lymphocytic Leukemia (11.2%) and Non-Hodgkin's lymphoma (77.5%). This indication supports the product's resemblance and is consistent with the information provided on the reference drug Rituximab. Switching: The data presented here indicate that, overall, 39.3% of patients with chronic lymphocytic leukemia and 42.5% of patients with non-Hodgkin's lymphoma switched to the reference product or another biosimilar for Rituximab-Pvvr. It is possible to interpret this as evidence of the healthcare community's increased acceptance and incorporation of these new biosimilars into treatment regimens, given the trend use. The age and gender distribution of the patients showed that 54.6% of them were male and 63.5% of them were 65 years of age or older. The use of this demographic information will facilitate understanding of the patient group most impacted by and receiving treatment for these conditions from Rituximab-Pvvr.

Regional Practice

This provides information on the variations in regional practice; the majority of Rituximab-Pvvr prescribers were located in the Southern United States, accounting for 59.0% of the total. This may be relevant for understanding how biosimilarity in adoption could be different geographically. Adoption in the real world: The fact that combination regimens and rituximab-PVVR are being used in accordance with approved and extrapolated indications is as fundamental as it gets, as it emphasizes the practical integration of biosimilars into current treatment protocols in an environment where mAb therapy is undergoing dynamic changes.

Challenges in Development and Regulation

High production costs

Challenges and opportunities for the future of mAb development: Improving safety, efficacy, and accessibility.

Immunogenic potential

Successive technological evolutions have extended the possibilities of application of mAbs by allowing, first of all, the production of mouse/human chimeric and humanized and fully human mAbs starting from antibodies of pure murine origin.[13]

Control of antigen-antibody interactions

Recent technologies in generating recombinant antigens and in the engineering of antibodies have been applied to extend the potential applications for this methodology. The process of selecting efficient B cells that secrete antibodies involves fusing immune cells and cancer cells through the creation of hybridomas. Traditionally, this has involved the use of PEG or electroporation fusing techniques. To increase bioavailability and reduce side effects, industry development teams collaborate with formulation subject matter experts in the fields of medical sciences, drug delivery, and preclinical and clinical pharmacology to support and steer the viability of s.c. mAb development, delivery, and commercialization across a broad range of therapeutic areas.[14]

Regulatory Challenges

New approaches patented

Future challenges and opportunities of antibody combination therapies: the need to match promise with product.

Legal status

MAbs could be used, for instance, for malaria prevention or for treatment, for instance, against rabies, dengue fever, and yellow fever.

Ensuring safety and efficiency

Unlike antibodies, the small molecule TKIs are capable of catalyzing the kinase structure inside the cells and competitively inhibiting ATP from downstream signaling of the HER2 family.

Addressing health economic burden

Industry development teams work in concert with formulation subject matter experts in preclinical and clinical pharmacology, medical sciences, and drug delivery to help guide the feasibility of development, delivery, and commercialization of s.c. mAbs over a broad range of therapeutic areas.

In step with the new emerging therapeutic applications,-mAbs could be used, for instance, for malaria prophylaxis or for treatment, for example, against rabies, dengue fever, and yellow fever.[15-19]

CONCLUSION

MAbs have revolutionized medicine by offering a targeted approach to treatment and prevention. Despite their great potential, there are developmental and regulatory challenges that make development difficult for mAbs due to the following reasons: high production cost, immunogenic potential, control of antigen-antibody interactions, selection of effective antibody-secreting B cells, enhancement of bioavailability, and reduction of side effects are some key challenges during development. Further, new approaches will be required to deal with the regulatory frameworks, ensuring safety and efficacy, addressing health economic burdens, and working out of emerging therapeutic applications. These latest technological advances have now expanded the application possibilities of mAbs by allowing production of mouse/human chimeric and humanized and fully human mAbs. Industry development teams, in concert with formulation subject matter experts, are guiding the feasibility of the development, delivery, and commercialization of subcutaneous mAbs across a wide range of therapeutic areas. While there are challenges in the area, potential benefit of mAbs attracts this area to be a point of research and development. Thus, addressing challenges in development and regulation allows mAb harnessing for improving human health and quality of life.

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