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Monoclonal Antibodies in Modern Medicine and Laboratory: A comprehensive review

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ABSTRACT

Monoclonal antibodies (mAbs) are a revolutionary advancement in therapeutic interventions, offering specificity in the treatment of various diseases, including cancers, autoimmune disorders, and infectious diseases. These agents have also changed diagnosis tests, particularly immunoassays which are based on antibodies like ELISA, Immunohistochemistry and Flowcytometry. This review article critically evaluates the development, mechanisms of action, clinical applications of monoclonal antibodies, and theirusage in diagnosis. We also explain the process of mAb production, such as hybridoma technology, as well as the emergence of novel formats such as bispecific antibodies and antibody-drug conjugates. Additionally, we analyze the current landscape of mAb therapies in clinical practice and highlight recent FDA approvals and ongoing clinical trials. Challenges such as immunogenicity, production costs, and access to therapy are also discussed. This comprehensive review aims to provide a deep understanding of monoclonal antibodies' impact on modern medicine and their potential to shape future therapeutic plans. Additionally, this review highlights monoclonal antibody projects in Iran, particularly at the Razi Vaccine and Serum Research Institute.

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1. Introduction

mAbs are an important advancement in the field of biomedical and immunology sciences and have revolutionized the model of disease treatment and prevention. The development of these molecules has yielded remarkable improvements in therapeutic interventions, particularly in oncology, autoimmune diseases, and infectious diseases. The pioneering work by Köhler and Milstein in 1975 introduced hybridoma technology, which led to the creation of highly specific antibodies to recognize and bind to specific antigens (1-3). The importance of monoclonal antibodies lies not only in their specificity but also in their versatility. These antibodies are produced to target a broad range of antigens, from surface markers on cancer cells to cytokines involved in inflammatory processes. Although traditional therapies often affect both healthy and diseased cells indiscriminately, "mAbs offer more targeted approaches that minimize off-target damage. This specificity is important in the treatment of various malignancies, such as breast cancer, lymphomas, and leukemias (3-6).

In recent years, the introduction of different classes of monoclonal antibodies like fully human antibodies, chimeric antibodies, and bispecific antibodies has changed this landscape (7, 8). Each class offers unique properties and mechanisms of action. For instance, bispecific antibodies can simultaneously engage two different antigens, which can enhance therapeutic efficacy and reduce probable resistance mechanisms (9). Additionally, engineered formats such as antibody-drug conjugates (ADCs) combine the specificity of mAbs with the cytotoxic potency of chemotherapeutic agents, which can pave the way for targeted cancer therapies (10).

The clinical success of monoclonal antibodies is not limited to oncology. In immunology, agents like Infliximab (Remicade) and Adalimumab (Humira) have revolutionized the treatment of rheumatoid arthritis and inflammatory bowel disease (11).

Despite their progress, the development and application of monoclonal antibodies face significant challenges. High production costs remain a critical barrier, which limit accessibility and affordability. Also, the potential for immunogenic reactions and the emergence of resistant variants can complicate treatment with these antibodies. Ongoing research is crucial to overcome these obstacles and improve the safety and efficacy of mAb therapies(12).

Advancements in biotechnology, bioinformatics, and high-efficiency screening techniques hold the promise of enhancing monoclonal antibody development. (8).

This review aims to provide a comprehensive overview of monoclonal antibodies, exploring their history, mechanisms of action, diverse applications in therapy and diagnostics, current challenges, and potential future directions in research and clinical practice. It also seeks to offer valuable insights into the future of monoclonal antibody therapies and their transformative role in contemporary medicine.

1.1. History

The concept of monoclonal antibodies was first developed by Georges Köhler and César Milstein in 1975. They created a method to produce a single type of antibody by fusing myeloma cells (cancerous B cells) with normal B cells that produce antibodies. This fusion produced hybridoma cells, which can produce large amounts of a specific antibody.In 1984, Köhler and Milstein were awarded the Nobel Prize in Physiology or Medicine for their development of hybridoma technology (13). The first therapeutic monoclonal antibody approved in 1986 by the U.S. Food and Drug Administration (FDA) was muromonab-CD3 (OKT3), a mouse-derived antibody for preventing kidney transplant rejection (14). However, mAbs were mostly made from mouse proteins, which could lead to immune reactions in human patients. To reduce these immune reactions, researchers developed chimeric antibodies, which are part human and part mouse (15). The first chimeric mAb approved was rituximab (Rituxan) in 1997 for treating certain types of cancer (16).

Further advances led to humanized antibodies, in which only a small part of the antibody was derived from mouse, which could minimize further immune responses. New technologies, such as phage display lead to the creation of fully human antibodies. The first fully human mAb approved by the FDA was adalimumab (Humira) in 2002 for treating rheumatoid arthritis and other autoimmune disorders (17). mAbs began to be used widely across various therapeutic areas, including oncology, autoimmune diseases, infectious diseases, and more.

2. Types of Monoclonal Antibodies

The different types of monoclonal antibodies represent advancements in biopharmaceutical technology and highlight their critical role in various medical challenges. From murine antibodies to sophisticated fully human and

bispecific antibodies, the development of mAbs continues to evolve. There are some types of monoclonal antibodies:

2. 1. Murine Monoclonal Antibodies

Murine monoclonal antibodies are produced from mouse B cells, so they are parts of mouse immunoglobulin proteins. While they were among the first types of monoclonal antibodies developed, their use in humans is limited because of their high immunogenicity.

When murine antibodies are administered to human patients, the human immune system can recognize them as foreign, which can lead to the production of anti-mouse antibodies. This response can reduce therapeutic efficacy and lead to allergic reactions. Despite these limitations, murine mAbs were valuable as research tools and served as the basis for subsequent antibody engineering (18).

2. 2. Chimeric Monoclonal Antibodies

Chimeric monoclonal antibodies are hybrid antibodies that integrate mouse variable regions with human constant regions. This modification decreases the immunogenic potential compared to murine antibodies while retaining the specificity for the target antigen. Chimeric mAbs are typically indicated in various therapeutic contexts, including some forms of cancer treatment. An example of a chimeric antibody is rituximab (Rituxan) (19).

2. 3. Humanized Monoclonal Antibodies

Humanized monoclonal antibodies primarily comprise human amino acid sequences, with only the hypervariable regions (responsible for antigen binding) derived from the mouse. This engineering significantly reduces the immunogenicity while preserving the binding affinity for the target antigen. Humanized mAbs have become increasingly prevalent in clinical applications because they provide a better safety profile and tolerability in human patients. Trastuzumab (Herceptin) is a well-known example of a humanized monoclonal antibody (20).

2. 4. Fully Human Monoclonal Antibodies

Fully human monoclonal antibodies are engineered entirely from human immunoglobulin sequences, which minimizes the risk of immune reactions when administered to patients. They are produced by using transgenic mice or phage display technology, allowing for the generation of antibodies that closely resemble natural human antibodies. Adalimumab (Humira) is an example of fully human mAbs (21).

2. 5. Bispecific Antibodies

Bispecific antibodies are engineered to bind two different antigens or epitopes simultaneously. This unique property enables bispecific mAbs to engage multiple targets and enhance therapeutic efficacy. They are particularly promising in oncology because they can redirect immune cells to tumor cells, improving the body's ability to mount an immune response against cancer. Examples include blinatumomab (Blincyto), which is used in the treatment of acute lymphoblastic leukemia by engaging both T cells and B cells (7).

2. 6. Conjugated Antibodies

Conjugated antibodies are linked to a therapeutic agent, such as a cytotoxic drug or radioactive isotope, which can lead to targeted delivery to diseased cells, especially in cancer therapy. This approach minimizes damage to healthy tissues while maximizing the therapeutic impact on cancer cells. An example of this class is trastuzumab-emtansine (Kadcyla), an antibody-drug conjugate that combines trastuzumab with a cytotoxic drug to treat HER2-positive breast cancer (22).

2. 7. Checkpoint Inhibitors

Checkpoint inhibitors are a class of monoclonal antibodies designed to block immune checkpoint proteins that tumors use in order to evade immune detection. By inhibiting these checkpoints, such as PD-1 or CTLA-4, these mAbs reinvigorate the immune system's ability to recognize and destroy cancer cells. Pembrolizumab (Keytruda) and nivolumab (Opdivo) are prominent examples of this kind of antibody (23).

2. 8. Neutralizing Antibodies

Neutralizing antibodies specifically target and neutralize pathogens, such as viruses, preventing them from entering or infecting host cells. They play essential roles in both therapeutic and preventive actions, including antiviral treatments and vaccine development. For instance, the use of neutralizing antibodies against SARS-CoV-2 highlights their importance in managing infectious diseases(24).

3. Production of Monoclonal Antibodies

The production of monoclonal antibodies (mAbs) involves a series of important and sensitive steps, starting from the immunization of host animals to the final purification of the antibody product. This process relies on the principles of hybridoma technology, pioneered by Köhler and Milstein in 1975. Their work laid the

foundation for producing antibodies with high specificity and pure homogeneity. The initial step involves immunizing a suitable mouse strain, commonly the BALB/c, with an antigen of interest. To enhance the immune response, the antigen is often attached to a carrier protein and administered with an appropriate adjuvant. Following the immunization, a robust immune response is elicited, leading to the production of a diverse type of antibody-producing B cells. After sufficient antibody production is achieved, spleen cells from the immunized mouse are harvested. These B cells are then fused with myeloma cells—cancerous B cells that lack the ability to produce antibodies but can proliferate indefinitely. The fusion is typically facilitated by polyethylene glycol (PEG), which promotes the merging of the two cell types. Following fusion, the resulting hybrid cells (hybridomas) are cultured in a selective medium that allows only the surviving hybridomas to grow. This medium is known as HAT (hypoxanthine-aminopterin-thymidine) selection, which ensures that only the fused cells survive and non-fused myeloma and spleen cells undergo apoptosis.

Surviving hybridomas are screened for their ability to produce antibodies specific to the original antigen commonly using enzyme-linked immunosorbent assay (ELISA). Clones that demonstrate desired characteristics—such as high affinity and specificity—are selected for further characterization. Selected hybridomas are expanded in culture, and limiting -dilution techniques are used to isolate single-cell clones. This ensures that each resulting culture produces antibodies from a single mother cell, which yield a homogeneous population of mAbs. The final step involves the characterizing the produced monoclonal antibodies to assess their affinity, specificity, and potential isotype. Finally, mAbs are purified using processes such as protein A affinity chromatography, which exploits the binding affinity of antibodies for protein A (a bacterial protein). This purification step is crucial for obtaining mAbs suitable for therapeutic or diagnostic applications (25-27).

4. Mechanisms of Action of Monoclonal Antibodies

Monoclonal antibodies (mAbs) exert their therapeutic effects through a variety of mechanisms, which can be broadly categorized into direct and indirect modes of action. Understanding these mechanisms is crucial for using the full potential of mAbs in clinical applications, particularly in oncology and autoimmune diseases. There are many different mechanisms of action of monoclonal antibodies, ranging from directly inhibiting tumor growth to recruiting immune cells for targeted destruction. Ongoing research continues to unveil new opportunities for their application and improving in personalized treatment.

mAbs can directly bind to specific antigens on the surface of target cells, such as cancer cells,which can result in direct inhibitory effects. This binding can block critical signaling pathways required for cell proliferation and survival. For instance, mAbs that target growth factor receptors can inhibit downstream signaling, effectively reducing tumor growth (28).One of the important immune mechanisms is ADCC. When mAbs bind to antigens on the surface of target cells, they can recruit effector immune cells, such as natural killer (NK) cells. Engagement of these effector cells with Fc receptors on the mAbs leads to the release of cytotoxic factors which results in the lysis of the target cell. This mechanism is particularly important in treating malignancies (29).

mAbs can also activate the complement system, a group of proteins that play a vital role in immune responses. By binding to their target antigens, mAbs can initiate a cascade of events that leads to the formation of the membrane attack complex (MAC) on the surface of the target cell. This results in cell lysis and death(30). CDC is another critical mechanism employed particularly in hematological cancers (31). Some mAbs facilitate internalization of the targeted antigen, which can lead to receptor down regulation. This is particularly relevant to mAbs to target growth factor receptors or immune checkpoints (32). After binding and internalization, the mAbs-tagged receptors are degraded within the cell to reduce the availability of these receptors on the cell surface. This can effectively decrease signaling pathways that drive cell growth or immune evasion(33). mAbs can directly neutralize pathogens, such as viruses and bacteria by binding to critical epitopes, which are necessary for their infectivity. For example, neutralizing antibodies against viral surface proteins can prevent the virus from entering host cells. This mechanism is not only important in treatment of infectious diseases, but also acts as a protective strategy following exposure to toxins. Some mAbs are designed to modulate immune responses rather than directly targeting cancer cells or pathogens. For instance, monoclonal antibodies targeting inhibitory checkpoint receptors, such as PD-1 or CTLA-4 ,which

can enhance T-cell activation and proliferation to reinvigorate the immune response against tumors. This checkpoint blockade strategy has become an important point of cancer immunotherapy (34).

5. Therapeutic Applications of Monoclonal Antibodies

mAbs are at the forefront of modern therapeutics, and their applications are broad;

5. 1. Cancer Therapy

The application of monoclonal antibodies in oncology is successful that leads to improved outcomes in many cancers. They can bind to specific antigens on the surface of cancer cells. For example, Trastuzumab (Herceptin) was developed for HER2-positive breast cancer. This drug binds to the HER2 receptor and inhibits downstream signaling pathways that promote cell proliferation. This has not only been effective in treating breast cancer, but has also impacted other HER2-positive tumors (6) Beyond direct action, some mAbs, like Rituximab (Rituxan) can recruit immune effector cells. Rituximab targets CD20 on B lymphocytes, resulting in antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Such mechanisms have been crucial in treating hematological malignancies like non-Hodgkin lymphoma and chronic lymphocytic leukemia (18). Combining mAbs with other therapeutic actions or drugs, like chemotherapy and checkpoint inhibitors, has shown synergistic effects. For instance, the combination of Pembrolizumab (an anti-PD-1 mAb) with conventional chemotherapy has improved outcomes in various cancers like lung and gastric cancers (26).

5. 2. Autoimmune Diseases

Monoclonal antibodies have significantly influenced the management of autoimmune disorder and provided targeted interventions that address the underlying pathology of these diseases.

Agents such as Adalimumab (Humira) and Infliximab (Remicade) target tumor necrosis factor-alpha (TNF-α), an important inflammatory mediator in conditions like rheumatoid arthritis and ankylosing spondylitis. By inhibiting TNF-α, these mAbs reduce inflammation, decrease joint damage, and improve quality of life for patients (11). Other mAbs target specific immune pathways. For example, Ustekinumab (Stelara) inhibits interleukin-12 and interleukin-23, which can be helpful in psoriasis and Crohn's disease.

The focus on regulating immune pathways results in more tailored therapy with fewer side effects compared to using immunosuppressants (35). Agents like Rituximab have also been evaluated for their potential to prevent disease flares in autoimmune patients which marks a shift towards more proactive treatment strategies aimed at maintaining remission (18).

5. 3. Infectious Diseases

Using monoclonal antibodies has expanded into the treatment of infectious diseases, particularly in the face of emerging global health threats. Monoclonal antibodies can provide rapid passive immunity. For example, Casirivimab and Imdevimab were developed as a treatment for COVID-19, directly targeting the SARS-CoV-2 spike protein. Clinical trials demonstrated these mAbs' ability to reduce viral load and improve clinical outcomes effectively (36). mAbs also can be effective in preventing infections after exposure. They can be administered to high-risk individuals, such as patients undergoing cancer treatments or those exposed to specific pathogens, to provide an essential part of protection (37).

6. Role of Monoclonal Antibodies in Diagnosis

Monoclonal antibodies (mAbs) have become crucial in medical diagnostics because of their high specificity and sensitivity for particular antigens. They are used in various diagnostic tests to enable early and accurate detectionof diseases. These antibodies can be used for detection of infectious diseases. Rapid antigen tests for COVID-19 use mAbs that specifically bind to the SARS-CoV-2 virus, detecting viral proteins and giving results in 15–30 minutes, which is essential for early diagnosis and infection control (38).

These antibodies are also widely used in immunoassays such as ELISA. For instance, the detection of Human Immunodeficiency Virus (HIV) uses mAbs to identify HIV antigens or antibodies in a patient's blood (38).Breast cancer diagnosis often involves tests for the Human Epidermal growth factor Receptor 2 (HER2).

mAbs are used in immunohistochemistry to determine HER2 overexpression in tumor samples (39). Home pregnancy tests typically use mAbs that detect the hormone human chorionic gonadotropin (hCG) in urine (40). Antinuclear antibody (ANA) tests, used to diagnose autoimmune conditions like lupus, employ mAbs to detect autoantibodies in patients' serum(41). Additionally, Flow cytometry utilizes mAbs to identify specific markers on

the surface of blood cells in the diagnosis of leukemias and lymphomas (e.g. the detection of CD19 and CD20 markers in classification of B-cell malignancies) (42). The other example of mAbs usage is QuantiFERON® to detect interferon-gamma release from T-cells in response to Tuberculosis (TB) antigens, helping the diagnosis of latent or active TB infection (43). mAbs are often included as positive controls in assays, such as those used for detecting Hepatitis B and C, ensuring that the function of assay is correct and accurate (44).

7. Monoclonal Antibody Production in Iran: The Role of Razi Vaccine and Serum Research Institute

Monoclonal antibodies have gained significant attention in Iran to enhance its biopharmaceutical abilities and address public health challenges. Razi Vaccine and Serum Research Institute (RVSRI), established in 1924, is one of the leading biopharmaceutical research centers in the country. It has played a pivotal role in the production of vaccines and therapeutic serums, including monoclonal antibodies. Initially, in 1995, a cell culture laboratory established by Dr. Rasool Madani within the institute's biotechnology sector began producing hybridoma.

RVSRI has made substantial progress in the development and production of monoclonal antibodies for various applications, particularly in diagnosing infectious diseases. In Dr Madani's laboratory, several monoclonal antibodies have been produced against agents such as measles virus, the F. protein of N.D virus, midgut epithelial cells of Hyalomma anatolicum, Peste des petits ruminants (PPR) virus, Avian Influenza Virus,the nucleoprotein of H9N2 influenza and S and N antigens of new corona virus (35, 45-49). Also, some ELISA tests were developed in this laboratory to diagnose infectious diseases in human or animal, which rely on self-produced monoclonal antibodies (46, 50).

The institute utilizes established technologies such as hybridoma methods to generate mAbs tailored for specific targets.

One notable achievement of RVSRI is the development of monoclonal antibodies against various pathogens, which are critical for diagnostic and therapeutic purposes. The institute collaborates with universities and other research organizations to advance its research capabilities, focusing on the enhancement of antibody specificity and efficacy.

Despite advancements, the production of monoclonal antibodies in Iran faces several challenges, including the need for infrastructure development, access to cutting-edge technologies, and regulatory hurdles. However, RVSRI has been actively seeking international collaborations to overcome these barriers and improve its production processes.

The future of monoclonal antibody production in Iran appears promising. With ongoing investments in biotechnology and biopharmaceutical research, RVSRI, a well-known a century-old institute, has the ability to contribute to the global scientific community, particularly in the context of emerging infectious diseases and chronic conditions.

8. Challenges and Limitations of Monoclonal Antibody Therapies

While monoclonal antibodies have tremendous therapeutic potential, several challenges and limitations complicate their applications. The production of monoclonal antibodies is a complex and costly process, often involving hybridoma technology or recombinant DNA technology. Consequently, this results in high treatment costs,often exceeding tens of thousands of dollars per year. The financial burden of mAbs can affect healthcare systems and their potentially creating disparities in health outcomes, especially in low-income settings.

Another problem is that mAbs can provoke immune responses in some patients. Immunogenicity can lead to the formation of anti-drug antibodies neutralizing the therapeutic effects of the mAb or leading to adverse effects. Furthermore, infusion reactions ranging from mild (fever, chills) to severe (anaphylaxis), can also occur and worsen and complicate treatmentprotocols (51). The success of monoclonal antibodies in treatment can be limited by patient heterogeneity. Genetic variations among individuals may affect therapeutic responses. For instance, not all patients with HER2-positive breast cancer respond to trastuzumab, highlighting the need for the identification of predictive biomarkers and also personalized approaches to maximize the efficacy of monoclonal antibodies and minimize the risk of treatment failure (52). In conclusion, monoclonal antibodies have changed therapeutic strategies from cancer treatment to autoimmune disorders, and infectious diseases.

While challenges remain, ongoing research and technological advancements promise to improve their efficacy, accessibility, and safety. Additionally, improvement in this landscape can be helpful to increase accuracy and specificity of diagnosis tests.

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Authors' Contribution

Study concept and design: R.M, M.H, F.G
Acquisition of data:F.G ,M.H, A.Gh
Analysis and interpretation of data: F.G &M.H
Drafting of the manuscript: M.H
Critical revision of the manuscript for important intellectual content: R.M
Statistical analysis: F.G
Administrative, technical, and material support:R.M

Ethics

We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

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