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Review Article

Monoclonal Antibodies: Insight Review

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ABSTRACT

Monoclonal antibodies (mAbs) are a significant achievement in biotechnology and medicine. Kohler and Milstein's Nobel Prize-winning research on murine hybridoma technology in 1975 resulted in the development of mAbs, which are designed to function as substitute antibodies that can restore, augment, or mimic the immune system's attack on cancer cells and other infections. In 1986, the FDA approved the first monoclonal antibody, Orthoclone OKT3® (muromonab-CD3), a huge step forward in antibody research and development. Monoclonal antibodies are glycoproteins produced by identical B cell clones that target a specific antigen. They are made up of heavy and light chains that form a Y shape. Variable regions, or antigen-binding sites, are highly selective to their target antigens. The constant areas mediate effector actions such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity. Monoclonal antibodies work by attaching to specific antigens on target cells' surfaces, neutralizing or destroying them. This can happen through either direct processes, such as inhibiting receptor-ligand interactions, or indirect mechanisms, such as attracting immune cells to cause cell death. Monoclonal antibodies are created by hybridoma technology or phage display. The hybridoma approach creates hybridomas, which are permanent antibody factories, by fusing B cells and myeloma cells. Phage display is a molecular approach that involves expressing antibody fragments on the surface of bacteriophages to select high-affinity antibodies.The future of monoclonal antibodies depends in improving their selectivity while decreasing immunogenicity through humanization and engineering. Biotechnology advancements will broaden their use in a variety of therapeutic areas, including infectious diseases, cardiovascular ailments, and neurological problems.

INTRODUCTION

Vertebrate is always evolving to protect itself from pathogens. An antigen is a foreign substance that is injected into vertebrates, including humans, or that they naturally reveal. In human, WBC (lymphocytes) that make up the immune system

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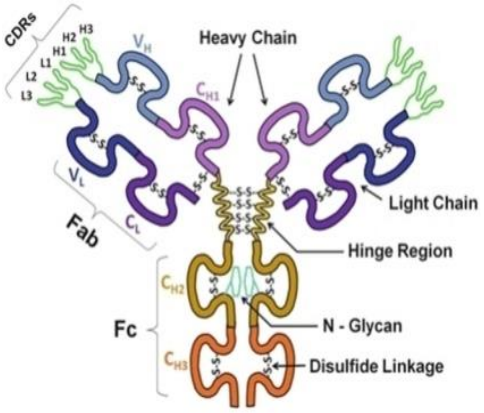
are responsible for identifying foreign materials in the body. In blood humoral factor are present which generated in order to bind to and remove antigen from the body. Antibodies are the aggregate term for humoral immunity that humoural factors offer to the host against antigen. Trained B cells generate glycoproteins known as antibodies, or immunoglobulins (Ig). Antibodies are Y-shaped proteins made up of heavy and light chains, peptides whose ends differ from one antibody to the next. Antibodies are helpful research instruments for treatment and diagnosis. Biological therapy might come in the form of immunotherapy or therapeutic monoclonal antibodies (mAbs). 1 By attaching to antigens on the surface of cancer cells, monoclonal antibodies (mAbs) are described as "laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance, or mimic the immune system's attack on cancer cells." A class of antibodies known as monoclonal antibodies (mAbs) are created by B cell clones that are identical to one another and are directed against a specific antigen. 2 The first monoclonal antibody to receive FDA approval was Orthoclone OKT3® (muromonab-CD3) in 1986. Based on the Nobel Prize-winning research on murine hybridoma technology by Kohler and Milstein, it was produced. In the history of antibody research and development, the development of hybridoma technology in 1975 to produce monoclonal antibodies is a significant turning point. license for monoclonal in 1986. Monoclonal antibodies are now utilized to treat a variety of diseases and are unique in their ability to detect mutations and structural defects in proteins. A potent instrument for medical applications, monoclonal antibodies are not just used as drugs. The development of monoclonal antibodies has turned out to be a crucial pivotal moment in the study of science. Antibodies can be used to target specific molecules or create a variety of disease models, both of which have important implications for the development of disease understanding and medication discovery. Today's monoclonal antibody growth and benefits outweigh those of earlier biotechnology types and more conventional medications. The first medication approved by the Food and Drug Administration (FDA) was rituxan, which contains roughly 30 mAb. As of June 30, 2022, there were 162 approved and marketed antibody treatments available to treat a variety of illnesses, such as hematological disorders, immune-related diseases, and cancer. The sector has prospered due to the significant demand for monoclonal antibodies in research and therapy. It has grown into the most lucrative market for biological drugs, with intense competition. 3

Structure and Functions:-

Glycoproteins known as immunoglobulin, or antibodies, are secreted by specialized B cell lymphocytes called plasma cells. There are four polypeptides that make up an antibody. Disulfides and non-covalent bonds hold two identical copies of the heavy and light chains together, resulting in a molecule that is Y-shaped. Five structured molecules can be joined to make one antibody, depending on Ig. Mammals have five different classes of Ig (IgG, IgM, IgA, IgD, and IgE), and in some cases, polymorphism has caused IgG and IgA to be split. Polypeptide light chains have a constant area that varies depending on whether they are in the K or λ light chain, as well as a variable portion that determines specificity. The primary immunoglobulin isotypes are determined by the heavy chain's variable and constant regions. The primary function of antibodies is to recognize and bind to antigen; this is accomplished by the amino terminal ends of the chain. Additionally, the carboxyl terminal end of the heavy chain performs an effector function. 4 The heavy and light chains' variable domains combine to generate the antibody's high-specificity antigen binding site, which can identify a specific antigen or epitope.

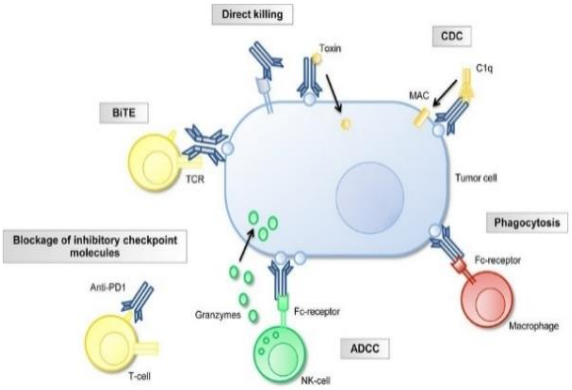
Repeated structures of 110 amino acids (AA) with beta folds known as domains light chain have 1 in constant region are found within the structure of Ig chains. The heavy chain's domain variable region is chain 1, while the constant region is chain 3 and 4.The Hinge region of the antibody is the area situated between the effectore and antigen binding regions. It facilitates binding to antigen on target cells or molecules by allowing the antigen binding arms to shift and become more flexible. Three hypervariables in the variable sections of the light and heavy chains combine to produce the antigen binding site known as CDR 1, 2, and 3.Antibody effector action is medicated by the constant area of the heavy chain (CH2 and CH3 form FC region).A certain amino acid is frequently linked to molecules in the FC region of monoclonal antibodies, which is known as glycoslylation.



2.1 **Figure:- Structure of Monoclonal Antibody** [Liu, L. *et al.* (2014) 'Freezing-induced perturbation of tertiary structure of a monoclonal antibody', *Journal of Pharmaceutical Sciences*, 103(7), pp. 1979–1986. doi:10.1002/jps.24013.]

2.1 Mechanism of Action :

Antibodies have the ability to attract more immune cells and chemicals, such complement, which facilitate the destruction of target cells.The heavy-chain second and third constant sections are part of the antibody's Fc (fragment crystallizable) component, which mediates this recruitment. Through complement- or antibody-dependent cellular cytotoxicity (ADCC) or CDC, Fc receptors can control the death of cells.6



2.2 Figure:- Mechanism of action of monoclonal antibodies [Increased risk of hematologic malignancies in primary immunodeficiency disorders: opportunities for immunotherapy - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Mechanisms-of-action-in-monoclonal-antibody-immunotherapy-Induction-of-direct-tumor-cell_fig1_323441802 [accessed 1 Aug 2024]

2.2 Function:-

i) Targeted Therapy: Certain antigens on the surface of infections or cancer cells can be targeted by monoclonal antibodies. They can either directly stop the growth of cancer cells by adhering to these antigens or identify them so that the immune system can destroy them.7

ii) Diagnostic Tools: To find particular chemicals or cells, a variety of diagnostic assays employ monoclonal antibodies. For instance, they can be used to find aberrant cells in disorders like leukemia or to find indicators of infectious diseases.8

iii) Immunotherapy: To strengthen the body's defenses against illnesses like cancer, monoclonal antibodies can be utilized in immunotherapy. Some monoclonal antibodies, for example, function by obstructing immunological checkpoints, which enhances the immune system's capacity to identify and combat cancer cells.9

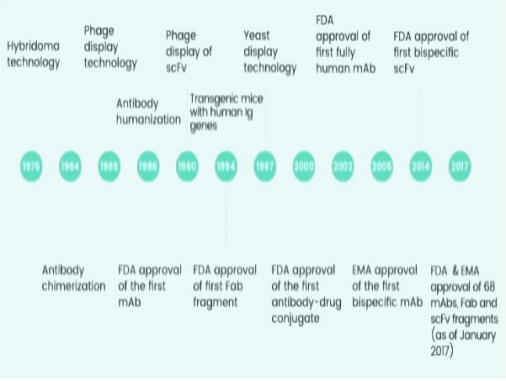
iv)Autoimmune Disease Treatment: Overactive immune system components in autoimmune illnesses can be targeted using monoclonal antibodies. They can aid in lowering tissue damage and inflammation by inhibiting particular molecules involved in the immune response.10

v) Neutralization of Toxins: Monoclonal antibodies can be designed to bind to and neutralize toxins, such as the venom from snake bites, in situations where the body has been exposed to toxins.11

vi) Drug Delivery: In order to minimize harm to healthy cells, monoclonal antibodies can be utilized as vehicles to deliver medications, poisons, or radioactive materials directly to particular cells or tissues.12

3. Development in monoclonal antibody :-13

High hopes for the manufacture of antibodies for therapy were raised when Kohler and Milstein developed mouse hybridoma technique in 1975. The first trustworthy source of monoclonal antibodies was mouse hybridomas, which were created for a variety of in vivo medicinal uses. However, the dismal results of the clinical trials have been caused by the fact that the monoclonal antibodies (mAbs) . were derived from mice, which is why they made people sick. To solve this issue, it was essential to comprehend the structure and function of antibodies. Disulfide bonds bind two heavy chains to two light chains and, in a flexible hinge area, bind the two heavy chains to one another. Chimeric antibodies with human constant domains fused to mouse variable domain sections were created in order to lessen the possibility of human anti-mouse antibody (HAMA) responses (Boulianne et al. 1984).



3.1 **Figure:- Development in Monoclonal Antibody**.[Wang, T. *et al.* (2022) 'How neutron scattering techniques benefit investigating structures and dynamics of monoclonal antibody', *Biochimica et Biophysica Acta (BBA) - General Subjects*, 1866(11), p. 130206. doi:10.1016/j.bbagen.2022.130206.]

4. Production of monoclonal antibody: -

Hybridoma technology

Phage display

4.1) Hybridoma technology:-

In 1975, Milstein and Kohler published a description of the first method for producing stable antibodies.Using this method, a stable hybrid cell called a hybridoma is created that can produce a single type of antibody directed against a particular epitope found in an antigen. 14

i) Immunization: -

The test antigen is injected into laboratory animals, usually mice or rabbits, and after a few weeks, the processes for B cell maturation and differentiation that have been previously described take place, leading to the production of plasma and memory B cells. Once a sizable amount of serum antibodies are found and the required vaccination is obtained, the animal is killed. 15

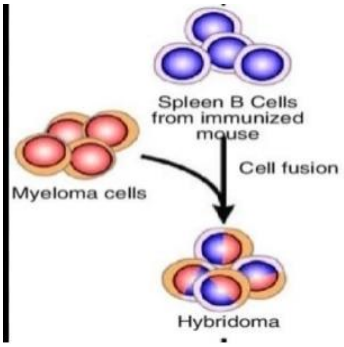
4.1Figure:- Immunization of mouce with antigen [Hassan, A.O. *et al.* (2020) 'A single-dose intranasal Chad vaccine protects upper and lower respiratory tracts against SARS-COV-2', *Cell*, 183(1). doi:10.1016/j.cell.2020.08.026.]

ii) Cell isolation:-

B cell extracted from lymph nodes or the spleen of an animal. The inoculated animal's spleen or bone marrow is used to extract antibody-producing cells, also known as plasma cells, once a significant immune response has been produced, usually over the course of a few weeks. 16

iii) Fusion with Myeloma Cells:-

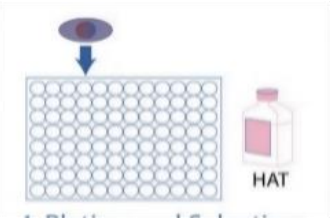
To form hybridoma cells, the extracted antibody-producing cells are merged with immortal malignant plasma cells called myeloma cells, which can divide endlessly. These hybridoma cells are able to make antibodies forever and without interruption.17



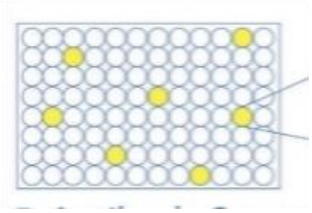
4.2 Figure:- Fusion of Myeloma [Genetic Engineering of Antibody Molecules - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Hybridoma-production-for-the-generation-of-mouse-monoclonal-antibodies-Mice-immunized_fig3_319143211 [accessed 1 Aug 2024]

iv) Screening & selection:- 18

The goal of this stage is to locate and pick hybridomas that generate antibodies with the right level of specificity. If you don't use merciless selection, a lot of undesirable hybridomas will compete with you for your time and cost you extra money on culture plates and medium.



4.3 Figure:- Plating and selection with HAT medium [Carbonetti, S. *et al.* (2017) 'A method for the isolation and characterization of functional murine monoclonal antibodies by single B cell cloning', *Journal of Immunological Methods*, 448, pp. 66–73. doi:10.1016/j.jim.2017.05.010.]]



4.4 Figure:- Screening of Monoclonal Antibody [Carbonetti, S. *et al.* (2017) 'A method for the isolation and characterization of functional murine

monoclonal antibodies by single B cell cloning', *Journal of Immunological Methods*, 448, pp. 66–73. doi:10.1016/j.jim.2017.05.010.]

v) Antibody production :-

To guarantee monoclonality, the chosen hybridoma cells are cloned (i.e., all cells make identical antibodies). Then, these cells are grown in culture to generate enormous amounts of monoclonal antibodies.19

vi) Purification:-

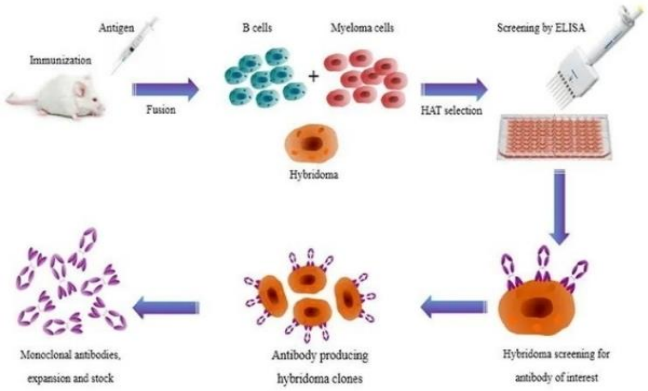
From the culture medium, the monoclonal antibodies are separated. Affinity chromatography is a common technique used in this, where antibodies are separated according to their affinity for the antigen. 20

vii) Characterization :-

To verify the specificity, potency, and other qualities necessary for their intended use, the purified monoclonal antibodies go through a rigorous characterisation process.

viii) Formulation: -

The monoclonal antibodies are then prepared into the required dosage form (such as an injection-ready liquid) and may go through additional testing to guarantee stability and quality.21



4.5 Figure :- Production of Monoclonal Antibody with Hybridoma technology [Antibody Engineering for Pursuing a Healthier Future - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Illustration-showing-the-production-route-of-hybridoma-technology-Monoclonal-antibodies_fig2_315849444 [accessed 1 Aug 2024]]

4.2) Phage display technique :- 22

One technique for producing monoclonal antibodies instead of using conventional hybridoma technology is phage display. The technique was created in 1985 by George P. Smith, who showed that by inserting a DNA fragment into the phage's coat protein gene, a peptide of interest could be seen on the surface of filamentous phages. Parmley and Smith then describe a selection and affinity enrichment procedure that is referred to as "panning or biopanning." according to their distinct binding affinities, in order to isolate peptide-phage fusion. Lastly, McCafferty and Winter employed phage display technology for the first time to produce antigen-specific mAbs through the development of combinatorial antibody libraries on filamentous phages.

5. Characteristics of monoclonal antibodies :

Identical immune cells that are all clones of a single parent cell produce monoclonal antibodies (mAbs). The following are some essential traits of monoclonal antibodies:23

Specificity: The high specificity of monoclonal antibodies. Because of their similar structures, they are made to bind to a single epitope—a precise area—on an antigen, or foreign material.24

Uniformity: The structure and functionality of every monoclonal antibody generated from a single clone are the same. This guarantees

uniformity in their binding efficiency and affinity. 25

Monospecificity: A monoclonal antibody can detect a single antigen or a small set of closely similar antigens. Targeted medicines and diagnostics make use of this characteristic.26

Production: Using cell culture methods, monoclonal antibodies are made in enormous quantities. Their creation is sometimes facilitated by hybridoma technology, which combines a myeloma cell with a certain B cell that produces antibodies. 27

Applications: They are used in medicine for a variety of purposes, such as research (such as protein purification, detection techniques), therapy (such as cancer treatment, autoimmune illnesses), and diagnostics (such as pregnancy tests, disease markers). 28

Humanization: To lower immunogenicity and boost therapeutic efficacy in humans, monoclonal antibodies are frequently "humanized" in their applications. This entails adjusting the antibody's non-human components while maintaining its ability to bind antigens specifically.29

Versatility: Monoclonal antibodies are utilized in a wide range of disciplines outside of medicine, such as research, biotechnology, and environmental science, because of their specificity and strong affinity for a target.

All things considered, monoclonal antibodies' specificity, predictability, and customizability make them an effective tool for use in both clinical and research settings.30

6. Application:-

6.1 Pharmacokinetics:-

The intricate structure and enormous size of monoclonal antibodies (mAbs) cause them to have a different pharmacokinetic profile than small drugs because of their low gastrointestinal stability, big size polarity, and restricted membrane permeability. Because of their poor oral absorption, monoclonal antibodies are often not given orally[.31]

Absorption:- [32]

The injection site processes into the lymphatic system through the interstitial space, then drains into the system circulation.Intravenous (IV) infusion is used to administer the majority of mAbs that are currently being developed for clinical use or that have been licensed. Subcutaneous injection and intramascular injection are examples of extravascular routes that have been selected as alternatives.Intravenous injection of monoclonal antibodies is done. Rapid full bioavailability of mAbs SC/IM Convective transfer of antibodies through lymphatic channels is dependent on systemic absorption. Through the convective passage of interstitial fluid into the porous lymphatic channels, the mAb penetrate the lymphatic system. Lower bioavailability is provided by the IM/SC modes of administration.A few examples of factors that may affect the absorption rate are the injection site, formulation, and volume.

Distribution:-

The process by which these molecules are moved throughout the body after entering the bloodstream is referred to as the dispersion of monoclonal antibodies.After being administered, monoclonal antibodies (mAbs) diffuse across the interstitial space, extravasate into the tissue, bind to tissue constituents, and then are cleared.Since mAbs have a low volume of distribution in steady state, systemic circulation is the primary site of their presence.The mAbs may concentrate in a tissue where the target antigen is highly expressed, raising the tissue's dry level and possibly increasing its efficacy.Large molecules like mAbs can only pass through tissue with restricted permeability, such as the blood-brain barrier.The distribution of the mAb can also be influenced by its own characteristics, such as size, charge, and hydrophobicity. Higher molecular weight mAbs,

for instance, could be mAbs with a higher hydrophobicity may be more likely to accumulate in fatty tissues, but they are also more likely to accumulate in blood vessels.[33]

Elimination:-[34]

Depending on variables including their target, size, and level of glycosylation, elimination half-life can change. The reticuloendothelial system and the liver both use proteolysis as a means of metabolism. More non-human antibodies will cause degradation more quickly. The half life is longer the lower the nonhuman component. Chimeric, humanized, and murine attaching itself to an antigen The distribution of mAbs is influenced by their binding, which also indicates alternative methods of removal. High affinity foreign-antigen binding needs to be considered virtually irreversible.

- Rituximab (Rituxan):-

Target: CD20 antigen on B cells

Use: For the management of autoimmune illnesses such as rheumatoid arthritis, chronic lymphocytic leukemia, and specific forms of non-Hodgkin lymphomas. Rituximab binds to the CD20 protein on the surface of B lymphocytes, causing the immune system to attack and kill the cells.

- Trastuzumab (Herceptin):

Target: HER2 receptor

Use: For the treatment of gastric and breast cancers that are HER2-positive. Trastuzumab inhibits the development of cancer cells by binding to their HER2 receptors, designating them for immune system destruction.

- Pembrolizumab (Keytruda):

Target: PD-1 receptor Use: For the treatment of several cancers, suchas head and neck cancer, lung cancer, and melanoma. By inhibiting the PD-1 receptor, pembrolizumab improves the immune system's capacity to combat cancerous cells.

- Adalimumab (Humira):

Target: TNF-alpha (tumor necrosis factor-alpha) Use: For the management of autoimmune conditions such Crohn's disease, psoriatic arthritis, and rheumatoid arthritis. Adalimumab reduces inflammation and stops the course of disease by binding to TNF-alpha, a cytokine involved in systemic inflammation.

- Palivizumab (Synagis):

Target: Respiratory syncytial virus (RSV) F protein Use: Protecting newborns at high risk against deadly RSV infections. By binding to the RSV virus's F protein, palivizumab stops the virus from penetrating and infecting cells.

6.2 Pharmacodynamics:-[35]

The investigation of how these molecules interact with other molecules in the body as well as their target antigen to create their therapeutic impact.The purpose of monoclonal antibodies is to attach themselves selectively to a target molecule, which could be a soluble factor like cytokines or a cell's receptor or antigen.The likelihood of mAbs causing off-target effects is reduced because to their extremely high affinity and selectivity for their molecular target.mAbs work by attaching themselves to particular targets in the extracellular space or on the surface of cells the study of the interactions these molecules have with their target antigen and other molecules in the body to produce their therapeutic effects.Monoclonal antibodies are designed to bind specifically to a target molecule, which may be an antigen or receptor on a cell, or it may be a soluble component such as cytokines.Because of their remarkably high affinity and selectivity for their molecular target, monoclonal antibodies are less likely to have off-target effects.mAbs function by binding to specific targets on the surface of cells or in the extracellular milieu. Target mAbs function by binding to specific targets on the surface of cells or in the extracellular milieu. Blocking: They can stop a target molecule from interacting with its natural ligand by blocking binding sites or receptors.

Modulation: They have the ability to change the target molecule's activity, either by increasing or decreasing it. Antibody-dependent cellular cytotoxicity, or ADCP, is one example of how some mAbs might flag cells for immune system death. The immunological response can be influenced by monoclonal antibodies. The half-life of the monoclonal antibody in the body, which influences dosage regimens and the length of time an agent is active, is another element of pharmacodynamics. Proteolytic degradation and renal filtration are two examples of clearance mechanisms that affect how long an antibody is active. This makes them extremely helpful as instruments for determining a target's function in the pathophysiology of a disease, particularly in experimental models. Like conventional medications, mAbs frequently show effects that are dose-dependent, although Greater therapeutic responses might result from higher doses, but there is also a greater chance of side effects. When it comes to maximizing the therapeutic use of monoclonal antibodies and forecasting their outcomes in different clinical contexts, their pharmacodynamics are essential. Since monoclonal antibodies (mAbs) are highly selective and can target specific molecules with high precision, they find extensive use in both medicine and research. Here are a few applications:-

Diagnostic Application :-

A) Biochemical analys

B) Diagnostic Imging

Threpeutic Application :-

A) Direct use of mAbs as threpeutic agent

Biotechnology:-

A) Protein Purification

B) Targated Drug Delivery

6.3 Diagnostic Application :-[36]

i) Biochemical analysis :-

Frequently employed in laboratory enzyme-linked immunosorbent tests (ELISA) and radioimmunoassay (RIA).The hormones (growth hormone, progesterone, insulin, triiodothyronine, thyroxine, thyroid stimulating hormone, and human chorionic gonadotropin) As well as a number of other tissue and cell products (blood group antigens, blood clotting factors, interferons, interleukins, tumor markers) that are in circulation are measured by these assays. For instance, pregnancy by measuring human chorionic gonadotropin levels in the urine. Analysis of triiodothyronine and thyroxine in relation to hormonal diseases. Prostate specific antigen is used to measure prostate cancer while plasma carcinoembryonic antigen is used to estimate colorectal cancer.

ii) Diagnostic imaging :-

Immunoscintigraphic, a disease diagnostic imaging technique, uses radiolabeled monoclonal antibodies. Iodine-131 is a popular radioisotope used for labeling MAb. technetium-99. The MAb labeled with radioactivity are given intravenously into patients. Radioactivity imaging can be used to identify the specific locations (tumors) where these MAbs localize. Recently, a more sensitive three-dimensional image of the radiolabeled-MAb-localized areas has been obtained by using single photon emission computed tomography (SPECT) cameras. Myocardial infarction, DVT, atherosclerosis etc.

iii) Therapeutic Application :-[37]

Direct use of monoclonal antibodies as therapeutic agents. MAbs improve phagocytosis and facilitate effective opsonisation of harmful organisms. Immunosuppressive medicines such as cyclosporine and prednisone are commonly used to combat organ transplant rejection. In recent years, MAbs specific to T cell surface antigens have been employed for this purpose.

6.4 Biotechnology: - [38]

i) Protein Purification:-

Any protein can be used to create monoclonal antibodies. Furthermore, it is convenient to

employ the generated MAb for the purification of the protein it was raised against. MAbs can be manufactured into a column by connecting them to chromatographic matrix (cyanogen bromide-activated Sepharose). This approach of immobilizing MAbs is highly helpful for the immunoaffinity method of purifying proteins. There are a few benefits to purifying proteins with MAbs. The high level of purification, highly effective elution from the chromatographic column, and specificity of the MAb to bind to the intended protein are examples of these.

ii) Targeted drug delivery:-

This exact therapeutic strategy, which uses monoclonal antibodies (mAbs) to target

diseased cells while limiting impacts on healthy tissues, is intended to deliver medications directly to those cells. In addition to lowering adverse effects, this tactic increases the drug's effectiveness.

iii) Utilizing monoclonal antibodies for treatment:- [39] A kind of targeted therapy used in medicine to treat a variety of ailments, such as cancer and infectious disorders, is called monoclonal antibodies (mAbs). This is a summary of their application in treatment:

iv) Diseases caused by viruses, such as COVID-19:- [40]

COVID-19: Monoclonal antibodies such as imdevimab, casirivimab, and bamlanivimab have been utilized as preventative measures in high-risk persons or to treat mild to moderate instances of COVID-19. By binding to particular proteins on the SARS-CoV-2 virus, these antibodies neutralize the infection and aid in the immune system's removal.

v) Cancer treatment:-

Target therapy :-

Monoclonal antibodies that are specifically designed to target proteins, or antigens, on cancer cells, are known as targeted therapies. The growth, survival, and dissemination of cancer cells may all be directly hampered by this targeting. Rituximab, for instance, targets CD20-positive B cells in lymphomas and leukemia, while trastuzumab targets HER2-positive breast cancer cells. [41]

6.5. Autoimmune disorders:

Monoclonal antibodies are utilized to target particular immune system components that support the disease process in order to decrease the immune response in autoimmune disorders. Some examples are rheumatoid arthritis and inflammatory bowel disease, where adalimumab and infliximab are utilized. [42]

6.6. Transplantation:

By inhibiting the immune system's reaction to the donated organ, monoclonal antibodies such as alemtuzumab and basiliximab can stop organ rejection in recipients of transplants. [43]

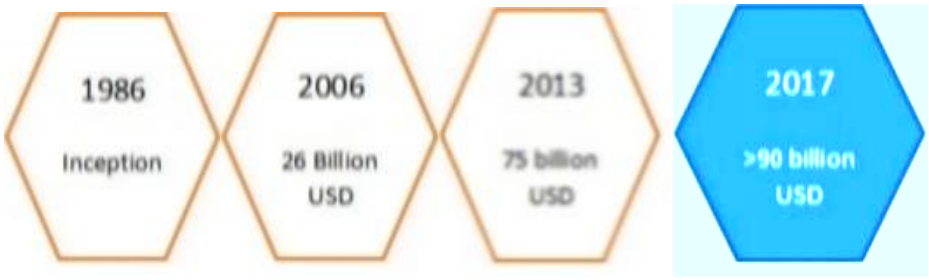
6.7. Other Uses:

The application of monoclonal antibodies in the management of various ailments, including neurological illnesses and cardiovascular ailments, is being investigated. [44]

7. Directions for the future of monoclonal antibodies:

Humanized or totally human antibodies that most closely mimic naturally occurring antibodies will be the main emphasis, but not the exclusive focus, of mAb therapies in the future. This finding underscores that, over the course of the next ten years, the great majority of new products derived from all forms of antibody technology will remain what we currently refer to as "conventional" fully intact antibodies. It does not lessen the fact that variations on antibody technology have already led to a number of new therapeutic products, and they are likely to do so in the future. [45]

Diagram :



7.1 Figure : Growth of Monoclonal Antibody Market

In the near future, the prevalence of the monoclonal market will rise due to the rapidly expanding number of approved products on the market. Currently, the FDA has approved about 75 monoclonal antibodies for use in treating a wide range of illnesses and conditions in people, such as cancer, transplantation, infectious diseases, chronic inflammatory diseases, and cardiovascular diseases. In order to treat chronic pain, Glenmark is requesting approval from the MHRA, U.K. to begin Phase 1 clinical trials for one of its mAb candidates, GBR 900 mAb, which targets TrKA, the receptor of nerve growth factor.

India is a promising market for mAbs because of its large patient base, expanding economy, skilled labor pool, and affordable R&D expenses. Monoclonal antibodies (mAbs) have the potential to revolutionize numerous important fields in the future. [46]

i) Personalise medicine :-

treating patients according to their unique genetic profiles and the features of their diseases. Our capacity to pinpoint precise targets for monoclonal antibodies is improving with the advent of sequencing technologies and analytics.[47]

ii) New Therapeutic Areas:-

Beyond oncology and autoimmune illnesses, we are expanding into infectious diseases, cardiovascular disease, neurology, and other areas. For example, mAbs have showed potential in treating Alzheimer's and COVID-19.[48]

iii) Engineering and Design:-

Antibody engineering advancements enhance specificity, efficacy, and reduce immunogenicity. This includes the development of bispecific and multispecific antibodies capable of targeting numerous antigens or pathways at the same time.[49]

iv) Delivery and Formulation:-

Improving delivery strategies to increase bioavailability and decrease dose frequency, such as subcutaneous and intravenous formulations.[50]

v) Combination Therapies:-

Using mAbs in conjunction with other medicines, such as small molecules, other biologics, or traditional treatments, to increase efficacy and prevent resistance.[51]

vi) Cost and Access:-

Addressing cost-effectiveness and accessibility issues in order to increase worldwide patient access to these therapies.[52]

vii) Biosimilars and Market Dynamics:-

Increasing biosimilar competition and managing market dynamics to balance innovation, affordability, and sustainability.[53]

viii) Technological Integration:-

Using improvements in AI, machine learning, and high-throughput screening to speed up mAb discovery, development, and optimization.[54]

8. Global Health Implication of Monoclonal Antibodies :-[55]

In immune therapies, an active or passive anti-tumoral immune response has been induced using vaccines, viruses, cytotherapy, and antibodies. Wilhelm Busch in Germany reported in 1866 that a patient's sarcoma had shrunk after contracting erysipelas, the first indication that the immune

system may fight cancer. In 1891, orthopedic surgeon Coley used a direct bloodstream injection of streptococcus and its toxins to induce remission in a few patients suffering from incurable sarcomas. Since then, immunological therapies have developed and are now grounded in a deeper comprehension of immunology as well as the pharmaceutical industry's financial interest, resulting in the development of tumor vaccines, T-cell- and natural killer-cell-based medications and therapies, repurposing monoclonal antibodies (mAbs) and their modified versions, and a stratospheric spike in scientific output and stock prices. mAbs can be useful in the diagnosis and treatment of diseases in children. mAbs are frequently employed in in vitro diagnostics to detect normal cells, providing information on their origin, level of activity or weariness, and the existence of druggable surface antigens and malignant cells. Integrating licensed monoclonal antibodies (mAbs) from adults into the current pediatric standard of treatment has proven to be challenging, especially when it comes to childhood cancer. While there is a growing body of knowledge on mechanisms of action (MOA), target discovery, and therapeutic potentials for pediatric malignancies, most monoclonal antibodies (mAbs) either never make it to phase 1 trials or are shelved following the initial regulatory assessment. We must combine profit and service by working with academic institutions and pharmaceutical companies that specialize in treating orphan illnesses in order to guarantee that everyone has access to high-quality, affordable, and sustainable healthcare. This paper aims to review the many mAbs now being used and investigated for pediatric cancer, with a particular emphasis on solid tumors and anti-GD2 mAbs for neuroblastoma, as well as the obstacles that have prevented their widespread usage up until now.

Monoclonal antibodies (mAbs) have been used to treat COVID-19, and this has had a significant impact on world health by influencing public health policies and providing novel therapeutic options. The global health response to COVID-19 has benefited immensely from monoclonal antibodies, which offer efficient choices for both prevention and treatment.

CONCLUSION: -

In conclusion, monoclonal antibodies are a ground-breaking development in biomedical science that provide very effective and focused treatment options for a range of illnesses, including autoimmune disorders and cancer. Their advancement has completely changed the way that diseases are treated by enabling precision medicine that minimizes side effects while precisely targeting the chemicals that cause disease. The intricate and inventive nature of this technology is shown by the laborious process of producing mAbs, which starts with the selection of the antigen and continues through antibody manufacturing and optimization. The remarkable influence of monoclonal antibodies (mAbs) on patient outcomes, as evidenced by their clinical success, has resulted in increases in survival rates and quality of life for persons with illnesses that were previously untreatable or problematic. Furthermore, continuing research is broadening the use of monoclonal antibodies by developing new treatments that target a wider spectrum of illnesses and have unique mechanisms of action.

There are still difficulties, though, such as those with affordability, accessibility, and resistance development. To ensure that monoclonal antibodies can help a larger patient population and reach their full potential, it will be imperative to address these issues. Monoclonal antibodies are expected to become increasingly more effective and versatile in the future due to research and technical developments, which could result in even more novel treatments. Interdisciplinary cooperation and ongoing research funding will be essential as the field develops to get over current

obstacles and realize the full promise of this revolutionary technology.

REFERENCES

1. García Merino, A. (2011) 'Monoclonal antibodies. basic features', Neurología (English Edition), 26(5), pp. 301–306. doi:10.1016/s2173-5808(11)70063-3.
2. Bayer, V. (2019) 'An overview of monoclonal antibodies', Seminars in Oncology Nursing, 35(5), p. 150927. doi:10.1016/j.soncn.2019.08.006.
3. Fleming, S., Lucas, F. and Schofield, M. (2001) 'A therapeutic area review of oncology products and players', Expert Opinion on Emerging Drugs, 6(2), pp. 317–329. doi:10.1517/14728214.6.2.317.
4. Parija, S.C. (2023). Structure and Function of Immune System. In: Textbook of Microbiology and Immunology. Springer, Singapore. https://doi.org/10.1007/978-981-19-3315-8_11
5. Cymer, F. et al. (2018) 'Therapeutic monoclonal antibody N-glycosylation – structure, function and therapeutic potential', Biologicals, 52, pp. 1–11. doi:10.1016/j.biologicals.2017.11.001.
6. Weiner, G.J. Monoclonal antibody mechanisms of action in cancer. Immunol Res 39, 271–278 (2007). https://doi.org/10.1007/s12026-007-0073-4
7. Nielsen, D.L., Andersson, M. and Kamby, C. (2009) 'HER2-targeted therapy in breast cancer. monoclonal antibodies and tyrosine kinase inhibitors', Cancer Treatment Reviews, 35(2), pp. 121–136. doi:10.1016/j.ctrv.2008.09.003.
8. Coetzer, A. et al. (2014) 'Comparison of biotinylated monoclonal and polyclonal antibodies in an evaluation of a direct rapid immunohistochemical test for the routine diagnosis of rabies in Southern Africa', PLoS Neglected Tropical Diseases, 8(9). doi:10.1371/journal.pntd.0003189.
9. Christiansen, J. and Rajasekaran, A.K. (2004) 'Biological impediments to monoclonal antibody–based cancer immunotherapy', Molecular Cancer Therapeutics, 3(11), pp. 1493–1501. doi:10.1158/1535-7163.1493.3.11.
10. Hafeez, U., Gan, H.K. and Scott, A.M. (2018) 'Monoclonal antibodies as immunomodulatory therapy against cancer and autoimmune diseases', Current Opinion in Pharmacology, 41, pp. 114–121. doi:10.1016/j.coph.2018.05.010.
11. Volk, W.A. et al. (1984) 'Neutralization of tetanus toxin by distinct monoclonal antibodies binding to multiple epitopes on the toxin molecule', Infection and Immunity, 45(3), pp. 604–609. doi:10.1128/iai.45.3.604-609.1984.
12. Quinteros, D.A. et al. (2017) 'Therapeutic use of monoclonal antibodies: General aspects and challenges for drug delivery', Nanostructures for Drug Delivery, pp. 807–833. doi:10.1016/b978-0-323-46143-6.00025-7.
13. Liu, H.F. et al. (2010) 'Recovery and purification process development for monoclonal antibody production', mAbs, 2(5), pp. 480–499. doi:10.4161/mabs.2.5.12645.
14. Parray, H.A. et al. (2020) 'Hybridoma technology a versatile method for isolation of monoclonal antibodies, its applicability across species, limitations, advancement and future perspectives', International Immunopharmacology, 85, p. 106639. doi:10.1016/j.intimp.2020.106639.
15. Liu, S., Wang, S. and Lu, S. (2016) 'DNA immunization as a technology platform for monoclonal antibody induction', Emerging Microbes & Infections, 5(1), pp. 1–12. doi:10.1038/emi.2016.27.

16. Huang, J., Doria-Rose, N., Longo, N. et al. Isolation of human monoclonal antibodies from peripheral blood B cells. Nat Protoc 8, 1907–1915 (2013). https://doi.org/10.1038/nprot.2013.117
17. Karpas, A., Dremucheva, A. and Czepulkowski, B.H. (2001) 'A human myeloma cell line suitable for the generation of human monoclonal antibodies', Proceedings of the National Academy of Sciences, 98(4), pp. 1799–1804. doi:10.1073/pnas.98.4.1799.
18. Hoogenboom, H. Selecting and screening recombinant antibody libraries. Nat Biotechnol 23, 1105–1116 (2005). https://doi.org/10.1038/nbt1126
19. Li, F. et al. (2010) 'Cell Culture Processes for monoclonal antibody production', mAbs, 2(5), pp. 466–479. doi:10.4161/mabs.2.5.12720.
20. Chahar, D.S., Ravindran, S. and Pisal, S.S. (2020) 'Monoclonal antibody purification and its progression to commercial scale', Biologicals, 63, pp. 1–13. doi:10.1016/j.biologicals.2019.09.007.
21. Alt, N. et al. (2016) 'Determination of critical quality attributes for monoclonal antibodies using quality by design principles', Biologicals, 44(5), pp. 291–305. doi:10.1016/j.biologicals.2016.06.005.
22. Schmitz, U. et al. (2000) 'Phage display: A molecular tool for the generation of antibodies— a review', Placenta, 21. doi:10.1053/plac.1999.0511.
23. BOSCH, A.M.G. et al. (1982) 'Characteristics of monoclonal antibodies against human chorionic gonadotrophin', Protides of the Biological Fluids, pp. 837–842. doi:10.1016/b978-0-08-027988-6.50195-6.
24. Starr, C.G. and Tessier, P.M. (2019) 'Selecting and engineering monoclonal antibodies with drug-like specificity', Current Opinion in Biotechnology, 60, pp. 119–127. doi:10.1016/j.copbio.2019.01.008.
25. Vázquez-Rey, M. and Lang, D.A. (2011) 'Aggregates in monoclonal antibody manufacturing processes', Biotechnology and Bioengineering, 108(7), pp. 1494–1508. doi:10.1002/bit.23155.
26. Lipman, N.S. et al. (2005) 'Monoclonal versus polyclonal antibodies: Distinguishing characteristics, applications, and information resources', ILAR Journal, 46(3), pp. 258–268. doi:10.1093/ilar.46.3.258.
27. Boyd, J.E., James, K. and McClelland, D.B.L. (1984a) 'Human monoclonal antibodies — production and potential', Trends in Biotechnology, 2(3), pp. 70–77. doi:10.1016/0167-7799(84)90013-1.
28. Qin, Z. et al. (2023) 'DNA-based materials inspired by natural extracellular DNA', Advanced Functional Materials, 33(31). doi:10.1002/adfm.202211669.
29. Vaughan, T., Osbourn, J. & Tempest, P. Human antibodies by design. Nat Biotechnol 16, 535–539 (1998). https://doi.org/10.1038/nbt0698-5353
30. Parray, H.A. et al. (2020a) 'Hybridoma technology a versatile method for isolation of monoclonal antibodies, its applicability across species, limitations, advancement and future perspectives', International Immunopharmacology, 85, p. 106639. doi:10.1016/j.intimp.2020.106639
31. Lin, J. (2009) 'Pharmacokinetics of biotech drugs: Peptides, proteins and monoclonal antibodies', Current Drug Metabolism, 10(7), pp. 661–691. doi:10.2174/138920009789895499.
32. Datta-Mannan, A. et al. (2020) 'Influence of physiochemical properties on the subcutaneous absorption and bioavailability of monoclonal antibodies', mAbs, 12(1). doi:10.1080/19420862.2020.1770028.
33. ARENDS, J.W. et al. (1983) 'Distribution of monoclonal antibody-defined

monosialoganglioside in normal and cancerous human tissues: An immunoperoxidase study', Hybridoma, 2(2), pp. 219–229. doi:10.1089/hyb.1983.2.219.

34. Tabrizi, M.A., Tseng, C.-M.L. and Roskos, L.K. (2006) 'Elimination mechanisms of therapeutic monoclonal antibodies', Drug Discovery Today, 11(1–2), pp. 81–88. doi:10.1016/s1359-6446(05)03638-x.
35. Kamath, A.V. (2016) 'Translational pharmacokinetics and pharmacodynamics of monoclonal antibodies', Drug Discovery Today: Technologies, 21–22, pp. 75–83. doi:10.1016/j.ddtec.2016.09.004.
36. Fesseha, H. (2020) 'Monoclonal antibody and its diagnostic application- review', Biomedical Journal of Scientific & Technical Research, 30(4). doi:10.26717/bjstr.2020.30.004997.
37. Berger, M., Shankar, V. and Vafai, A. (2002) 'Therapeutic applications of monoclonal antibodies', The American Journal of the Medical Sciences, 324(1), pp. 14–30. doi:10.1097/00000441-200207000-00004.
38. Lin, J. (2009a) 'Pharmacokinetics of biotech drugs: Peptides, proteins and monoclonal antibodies', Current Drug Metabolism, 10(7), pp. 661–691. doi:10.2174/138920009789895499.
39. Ritz, J. and Schlossman, S. (1982) 'Utilization of monoclonal antibodies in the treatment of leukemia and lymphoma', Blood, 59(1), pp. 1–11. doi:10.1182/blood.v59.1.1.1.
40. Lloyd, E.C., Gandhi, T.N. and Petty, L.A. (2021) 'Monoclonal antibodies for COVID-19', JAMA, 325(10), p. 1015. doi:10.1001/jama.2021.1225.
41. Bayer, V. (2019) 'An overview of monoclonal antibodies', Seminars in Oncology Nursing, 35(5), p. 150927. doi:10.1016/j.soncn.2019.08.006.
42. García Merino, A. (2011) 'Monoclonal antibodies. basic features', Neurología (English Edition), 26(5), pp. 301–306. doi:10.1016/s2173-5808(11)70063-3.
43. Golay, J. and Introna, M. (2012a) 'Mechanism of action of therapeutic monoclonal antibodies: Promises and pitfalls of in vitro and in vivo assays', Archives of Biochemistry and Biophysics, 526(2), pp. 146–153. doi:10.1016/j.abb.2012.02.011.
44. Golay, J. and Introna, M. (2012b) 'Mechanism of action of therapeutic monoclonal antibodies: Promises and pitfalls of in vitro and in vivo assays', Archives of Biochemistry and Biophysics, 526(2), pp. 146–153. doi:10.1016/j.abb.2012.02.011.
45. Lomonte, B. et al. (2009) 'Neutralization of bothrops asper venom by antibodies, natural products and synthetic drugs: Contributions to understanding snakebite envenomings and their treatment', Toxicon, 54(7), pp. 1012–1028. doi:10.1016/j.toxicon.2009.03.015.
46. Nielsen, D.L., Andersson, M. and Kamby, C. (2009) 'HER2-targeted therapy in breast cancer. monoclonal antibodies and tyrosine kinase inhibitors', Cancer Treatment Reviews, 35(2), pp. 121–136. doi:10.1016/j.ctrv.2008.09.003.
47. Gambardella, V. et al. (2020a) 'Personalized medicine: Recent progress in cancer therapy', Cancers, 12(4), p. 1009. doi:10.3390/cancers12041009.
48. Sharma, P. et al. (2023) 'Therapeutic antibodies in medicine', Molecules, 28(18), p. 6438. doi:10.3390/molecules28186438.
49. Chiu, M.L. et al. (2019) 'Antibody structure and function: The basis for Engineering Therapeutics', Antibodies, 8(4), p. 55. doi:10.3390/antib8040055.
50. Viola, M. et al. (2018) 'Subcutaneous delivery of monoclonal antibodies: How do we get there?', Journal of Controlled Release, 286, pp. 301–314. doi:10.1016/j.jconrel.2018.08.001.

51. Lirbouret, C. et al. (2021) 'Improving biologics' effectiveness in clinical oncology: From the combination of two monoclonal antibodies to oligoclonal antibody mixtures', Cancers, 13(18), p. 4620. doi:10.3390/cancers13184620.
52. Wahlster, P. et al. (2015) 'Barriers to access and use of high cost medicines: A Review', Health Policy and Technology, 4(3), pp. 191–214. doi:10.1016/j.hlpt.2015.04.009.
53. Vandenplas, Y. et al. (2021) 'Off-patent biological and biosimilar medicines in Belgium: A market landscape analysis', Frontiers in Pharmacology, 12. doi:10.3389/fphar.2021.644187.
54. Singh, R., Chandley, P. and Rohatgi, S. (2023) 'Recent advances in the development of monoclonal antibodies and next-generation antibodies', ImmunoHorizons, 7(12), pp. 886–897. doi:10.4049/immunohorizons.2300102.
55. Larrosa, C., Mora, J. and Cheung, N.-K. (2023) 'Global impact of monoclonal antibodies (mAbs) in children: A focus on anti-GD2', Cancers, 15(14), p. 3729. doi:10.3390/cancers15143729

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