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AN OVERVIEW ON MONOCLONAL ANTIBODIES AND THEIR APPLICATIONS.

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ABSTRACT

BACKGROUND: Monoclonal antibodies (MAbs) have undergone a remarkable metamorphosis during the past three decades, evolving from scientific instruments to potent human treatments. The first therapeutic MAb licensed by the FDA to prevent kidney transplant rejection was muromonab CD3, a murine MAb. Rituximab was the first chimeric monoclonal antibody to be licensed for the treatment of low-grade B cell lymphoma in the late 1990s, following a reduction in additional applications and approvals since its 1986 approval. The pace of approval and the number of monoclonal antibodies on the market for the treatment of different diseases has significantly expanded since licensing authorities approved chimeric, humanized, and finally fully human monoclonal antibodies. About 60 therapeutic MAbs have been licensed by the FDA as of March 2017, the FDA had licensed about 60 therapeutic Mabs.

OBJECTIVE :MAbs are authorized to treat conditions affecting the cardiovascular, respiratory, hematological, renal, immunological, and oncological systems. In addition to treating cancer and multiple sclerosis, where hundreds of patients are treated, MAbs are approved to treat orphan diseases or indications like paroxysmal nocturnal hemoglobinuria. Millions of people are treated for conditions like rheumatoid arthritis, asthma, and breast cancer. The kinds, molecular targets, mechanisms of action, and therapeutic indications of FDA-approved MAb drugs that are presently on the market are briefly covered in this study.

CONCLUSION :Since the development of completely human MAbs, the effectiveness and safety of treating a variety of infections, autoimmune disorders, respiratory, cardiovascular, and hematological conditions have increased. The availability of biosimilars will make MAbs more affordable and widely used for treating a range of illnesses.

INTRODUCTION :

The immune system protects the body from a wide range of infectious microorganisms that can lead to a number of diseases. The two primary elements are the humoral (antibody-mediated) and cellular (cell-mediated) immune responses. The humoral immune system, which produces specific antibodies in response to external antigens, includes lymphocytes. The ability of an antibody to provide long-term resistance to a particular antigen and its specificity are its two most important characteristics. Because of their special qualities, scientists employ them to shield people from diseases.[1] One kind of defense mechanism that can identify and eliminate invasive organisms like bacteria and viruses is the antibody. Each of them may be able to identify a specific antigen that is specific to its target since they each possessed antigen-binding sites and a paratope (like a lock) at the higher ends of the "Y" shaped antibody molecules. These two structures can exactly bind together because this paratope is specific for a particular epitope on a single antigen, much like a key. Because of this method, an antibody may tag a microorganism or an infected cell, making it possible for other immune system components to target it and immediately kill it.[2]Antibodies bind to soluble poisons, preventing them from acting, and pathogen antigens on the surface, preventing them from infecting human cells or marking them for elimination. By triggering complement, antibody-dependent cellular cytotoxicity (ADCC), or antibody-dependent cellular phagocytosis (ADCP), immune cells eliminate microorganisms. A crystallizable component (Fc) that propels biological activity and an antigen-binding fragment (Fab) that confers target specificity make up antibodies. The specificity, duration, and outcome of the antibody-dependent response are affected by changes in the Fab and Fc sections.[3]When Kohler and Milstein created monoclonal antibodies (MAbs) in 1975, they transformed immunology. The first MAb was fully licensed in 1986.[4] Since then, numerous MAbs have been created for use in immunotherapy and diagnostic processes. Much effort has been put into creating chimeric and humanized antibodies for usage in humans since it was found that the therapeutic use of heterologous MAbs produced immunogenic responses in humans. The development of MAbs in transgenic animals and plants has been a significant achievement.[5]

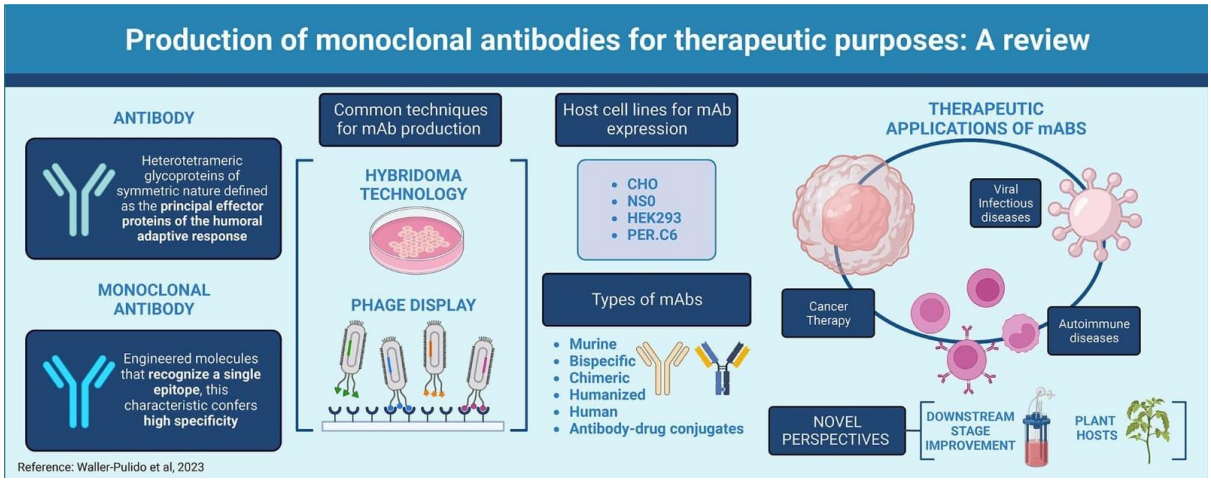

Figure 1 Therapeutic Purposes Of Monoclonal Antibodies.

In recent years, MAbs—glycoproteins that may bind an antigen to a specific epitope—have become more popular in therapy, with numerous compounds winning regulatory approval.[6]The study and creation of MAbs is a novel strategy to target specific mutations and anomalies in protein structure and expression in a range of diseases and circumstances. Thanks to significant advancements in genetic sequencing and the application of basic medical sciences research to clinical practice, humanized MAbs are currently the group of biotechnology-derived medicines with the greatest rate of growth in clinical trials. [7]

ADVANTAGES OF MONOCLONAL ANTIBODIES DISADVANTAGES :

High specificity:

- By targeting particular antigens or cells, monoclonal antibodies (mAbs) can minimize off-target effects.[8]
- Targeted therapy: by delivering medications straight to particular cells or tissues, mAbs might boost effectiveness and lessen negative effects. [9]

Efficacy:

- Better results from treatment: mAbs have demonstrated notable clinical advantages in a number of illnesses, such as cancer, autoimmune conditions, and infectious diseases.[10]
- Improved disease outcomes can result from mAbs' ability to boost immune responses.[11]

Safety:

- Decreased toxicity: By reducing toxicity and adverse effects, mAbs can enhance patient safety.[12]
- Fewer side effects: When compared to conventional treatments, mAbs are less likely to result in side effects.[13]

Convenience:

- Administration ease: Patients can get treatment more conveniently because mAbs can be given by injection or infusion.[14]
- Reduced dosage: Because some mAbs have longer half-lives, patients can take them less frequently, which improves patient compliance.[15]

Versatility:

- Multiple formats: full-length antibodies, antibody fragments, and bispecific antibodies are among the different formats in which mAbs can be created.[16]
- Combination therapies: To increase effectiveness, mAbs can be used in conjunction with other therapies including immunotherapy or chemotherapy.[17]

Economic Benefits

- Cost-effective: By enhancing treatment results, decreasing hospital stays, and lowering the need for subsequent treatments, mAbs can lower healthcare expenses.[18]
- Enhanced patient productivity: When mAbs are used effectively, patients' quality of life can be improved, allowing them to resume their jobs and continue to be productive.[19]

DISADVANTAGES OF MONOCLONAL ANTIBODIES DISADVANTAGES :

Immunogenicity

- Immune responses: Monoclonal antibodies (mAbs) can induce immune responses, leading to reduced efficacy or increased toxicity. [8]
- Antibody-dependent enhancement: mAbs can enhance disease severity by facilitating viral entry or immune complex formation.[20]

Toxicity

- Infusion reactions: mAbs can cause infusion reactions, including anaphylaxis, fever, and chills.[21]
- Cytokine release syndrome: mAbs can trigger cytokine release syndrome, a potentially life-threatening condition. [22]

Resistance

- Antigenic modulation: mAbs can induce antigenic modulation, leading to reduced target expression and treatment resistance.[12]
- Genetic mutations: mAbs can select for genetic mutations, resulting in treatment resistance.[11]

Cost and Accessibility

- High development costs: mAbs are expensive to develop, which can limit accessibility.[19]
- High treatment costs: mAbs are often costly, making them inaccessible to some patients.[23]

Manufacturing Challenges

- Complex manufacturing processes: mAbs require complex manufacturing processes, which can lead to batch-to-batch variability.[14]
- Scalability issues: mAbs can be challenging to scale up for large-scale production. [24]

APPLICATIONS :

1. **Therapeutic Applications**

Cancer treatment :

Numerous cancer types are treated with monoclonal antibodies (mAbs), which have transformed cancer therapy. These are a few ways that mAbs are used in cancer treatment.[25]

Treatment results have been enhanced by mAbs that target EGFR (cetuximab), VEGF (bevacizumab), and HER2 (trastuzumab).

Targeted Therapy :

One kind of targeted medication therapy that targets and binds to proteins on cancer cells is monoclonal antibodies. mAbs can impede the growth and survival of cancer cells by specifically targeting these proteins.[26]

Asthma :

mAbs have demonstrated potential in the management of asthma. To lessen airway inflammation and enhance asthma management, they can target particular molecules that are implicated in the inflammatory response, such as interleukins or immunoglobulin E (IgE).[27]

COVID-19 :

One promising treatment strategy for COVID-19 is the use of monoclonal antibodies. A number of monoclonal antibodies have been approved for the treatment of COVID-19, either in full or for emergency use. They have the ability to neutralize the SARS-CoV-2 virus, lower the viral load, and maybe stop the progression of severe disease.[26]

Viral Infections

The potential of monoclonal antibodies to fight off different viral infections has been studied. They can boost immune responses, directly destroy infections, and offer preventative advantages. Ebola, respiratory syncytial virus (RSV), cytomegalovirus (CMV), and other viruses have all been the subject of mAb research.[28]

mAbs in renal and hepatic impairment

In general, mAbs' large molecular weight (150 kDa) hinders their excretion by the kidneys (Ryman and Meibohm, 2017). Renal excretion only occurs for mAb fragments with molecular weights ≤ 60 kDa. A medication used to treat age-related macular degeneration (Ranibizuma) with a molecular weight of 48 kDa is said to be eliminated by the kidneys. Patients with renal impairment, however, have a reduction in its clearance. Conditions that impair glomerular filtration can change. [29]

2. **DIAGNOSTIC APPLICATIONS :**

MEDICAL IMAGING

Certain tumor antigens are imaged using radiolabeled monoclonal antibodies (mAbs), such as arcitumomab.[30]

Immunoassays and ELISA

mAbs identify certain proteins in conditions like hepatitis, HIV, and allergies.[31]

3. **RESEARCH APPLICATIONS :**

Flow Cytometry: cell populations are examined using mAbs coupled to fluorophores.[32]

Western Blotting: In complicated mixtures, mAbs can identify particular proteins.[32]

Chromatin Immunoprecipitation (ChIP): mAbs are useful for researching interactions between proteins and DNA.[32]

4. **INDUSTRIAL APPLICATIONS :**

Production of Biopharmaceuticals: mAbs guarantee quality control in the manufacturing of medications and vaccines.[33]

Food Industry: Used to find pollutants or diseases such as Listeria.[33]

5. **TRANSPLANT APPLICATIONS :**

Organ Rejection: By preventing immunological reactions, monoclonal antibodies such as basiliximab lessen organ rejection.[34]

Table 1 : Examples Of Monoclonal Antibodies Used For Autoimmune Diseases.

MONOCLONAL ANTIBODY	TYPE	TARGET MOLECULE	AUTOIMMUNE DISEASE
Adalimumab (Humira)	Human	TNFα	**RA, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis, juvenile idiopathic arthritis**
Belimumab (Benlysta)	Human	BAFF	**SLE**
Certolizumab pegol (Cimzia)	Humanized	TNFα	**RA, Crohn's disease.**
Epratuzumab	Humanized	CD22	**SLE**

Infliximab (Remicade)	Chimeric	TNFα	**Crohn's disease, psoriasis, ankylosing spondylitis, psoriatic arthritis, RA, ulcerative colitis.**
Natalizumab (Tysabri)	Humanized	a4 integrin	**Multiple sclerosis, Crohn's disease.**
Rituximab (Rituxan)	Chimeric	CD20	**RA**
Tocilizumab (Actemra)	**Humanized**	**IL-6R**	**RA. Castelman's disease.**

Table 2 : Examples Of Monoclonal Antibodies Used For cancer treatment.

Drug Name	Cancer treated
Alemtuzumab (Campath)	Chronic lymphocytic leukemia
Cetuximab (Erbitux)	Head/neck and colorectal cancer
Daratumumab (Darzalex)	Multiple myeloma
Denosumab (Xgeva)	Cancer metastasis to bone
Durvalumab (Imfinzi)	Urothelial carcinoma, non-small cell lung cancer
Ipilimumab (Yervoy)	Melanoma
Nivolumab (Opdivo)	Non-small cell lung cancer, melanoma, renal cell carcinoma, Hodgkin lymphoma, Head/neck cancer, urothelial
Olaratumab (Lartruvo)	Sarcoma
Panitumumab (Vectibix)	Colorectal cancer
Rituximab (Rituxan)	Non-Hodgkin lymphoma, chronic lymphocytic leukemia
Trastuzumab (Herceptin)	Breast cancer, gastric cancer
Pembrolizumab (Keytruda)	Lung cancer (small cell and non-small cell), melanoma, head and neck squamous cell cancer, Hodgkin lymphoma, primary mediastinal non-Hodgkin lymphoma, urothelial cancer, renal cell carcinoma, microsatellite instability- high cancer, gastric cancer, cervical cancer, hepatocellular carcinoma, Merkel cell cancer, esophageal cancer

RESULTS :

The study and creation of MAbs is a novel strategy to target specific mutations and anomalies in protein structure and expression in a range of diseases and circumstances. Thanks to significant advancements in genetic sequencing and the application of basic medical sciences research to clinical practice, humanized MAbs are currently the group of biotechnology-derived medicines with the greatest rate of growth in clinical trials.

CONCLUSION :

Because of their versatility and specificity, monoclonal antibodies (mAbs) are a key component of contemporary biomedical innovation, providing game-changing solutions in the fields of therapy, diagnosis, and research. Their uses have changed over the years, progressing from simple lab instruments to crucial components in precision medicine.Monoclonal antibodies are essential to contemporary medicine, and their uses are only growing and changing. They promote innovation in therapeutic interventions and diagnostics in addition to addressing important healthcare issues. To ensure a wider impact on global health, future research should concentrate on lowering immunogenicity, increasing cost effectiveness, and combining monoclonal antibodies with cutting-edge technologies like gene editing and artificial intelligence.

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