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A Comprehensive Review of Therapeutic Applications of Monoclonal Antibodies and Their Future Prospects

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ABSTRACT

In 1975, Georges Kohler of West Germany and Cesar Milstein of Argentina discovered how to produce monoclonal antibodies (MAbs) utilizing hybridoma technology. Since the US Food and Drug Administration (US FDA) approved the first monoclonal antibody in 1986, more than three decades have passed, and a significant advancement in antibody engineering has been made. Marketing approval has been given to over 100 mAbs so far. Although MAb therapies are mostly used to treat cancer and immunological/infectious illnesses, they are also being used to treat other types of diseases like arthritis and other conditions brought on by organ transplantation and have many uses in applied biology, biotechnology, and biochemistry. MAbs have more uses today than ever before, according to research being conducted in labs all over the world. It is anticipated that the therapeutic pipeline will continue to include the several monoclonal antibodies that are now in research due to their distinct characteristics. Therapeutic monoclonal antibodies have drawn a lot more attention in recent years. The development of a new generation of therapeutic drugs is made possible by the advent of molecular targeting medicine. Their extremely specific target of antigens can result in very successful medical treatment. This review examines cutting-edge technology relevant to the future prospects of MAbs and highlights the therapeutic applications of MAbs.

Keywords: monoclonal antibodies, US Food and Drug Administration, immunological/infectious illnesses, molecular targeting medicine, therapeutic applications.

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INTRODUCTION

Vertebrates' immune systems are constantly changing to fend off various invasive infections and serve as a line of defense against a variety of infectious pathogens that cause various diseases. The immune responses revolve around a few innate mechanisms, as well as adaptive procedures like the creation of antibody (Ab) molecules that can bind to every molecular structure of microbial pathogens like viruses, bacteria, fungi, nematodes, and other parasites, and keep up with the variety of mutations in an organism. A molecule or component of a molecule that the immune system may identify as a foreign substance is referred to as an antigen [1]. The humoral (antibody-mediated) and cellular (cell-mediated) immune responses are two important parts. B-lymphocytes, which are part of the humoral immune system, can identify the type of invading antigens from outside the body and make particular antibodies to fight them [2]. An antibody's specificity to the antigen and its guarantee of ongoing resistance to that specific type of antigen are its two most crucial properties [3]. Scientists utilize them to protect people from diseases because of their special characteristics. Antibodies may recognize and bind with specific antigens in a specific and strong manner, making them essential research tools in diagnosis and therapy. Polyclonal antibody mixtures are made up of several antibodies that have been produced in the blood of immunized animals from various cell types. Many distinct B-cell clones can be stimulated to proliferate and differentiate since most antigens include multiple epitopes. As a result, a heterogeneous pool of serum antibodies can be produced that are specific for a given antigen's epitope or epitopes [4].

Monoclonal antibodies:

As antibodies are regarded as "biopharmaceuticals" by the Food and Drug Administration (FDA), the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) of the FDA are responsible for regulating MAb applications [5]. The FDA defined data that should be included in applications for licenses for investigational new drugs or biologics, and it prepared a "Points to Consider" document to advise manufacturers of aspects to take into account in the creation and testing of MAbs intended for human use. It serves to "indicate the agency's current thinking on MAb products for human use" in the "Points to Consider" document [6].

Additionally, methods for producing antibodies in vitro were devised, leading to the creation of monoclonal antibodies for both therapeutic and diagnostic purposes [7]. Monoclonal antibodies (MAb(s)), in contrast, are a collection of homogenous antibody molecules with affinity for a particular antigen. These antibodies are frequently created via a hybridoma, which involves fusing a B-cell with a single lineage of cells that contain a specific antibody gene. In the end, a colony of

identical cells (or clones) that release the same antibodies is created. MAbs have an advantage over polyclonal antibodies because of their great repeatability employing culture techniques and specificity. There is a high demand for MAbs in the business since they are utilized more frequently in fields including research, diagnosis, therapeutics for diseases like cancer and immune disorders, and pharmacy. The crucial qualities that give MAbs therapeutic application include their homogeneity and specificity of binding, as well as their capacity to be generated in endless amounts [8]. Another distinctive benefit of hybridoma synthesis is the ability to produce targeted antibodies from a variety of antigens. Additionally, it makes it possible to isolate a single cell clone by screening a desired antibody from a mixture of an antibody population and a purified antigen. The processes for producing antibodies vary, but the general concepts are the same as those shown in Figure 1 [9].

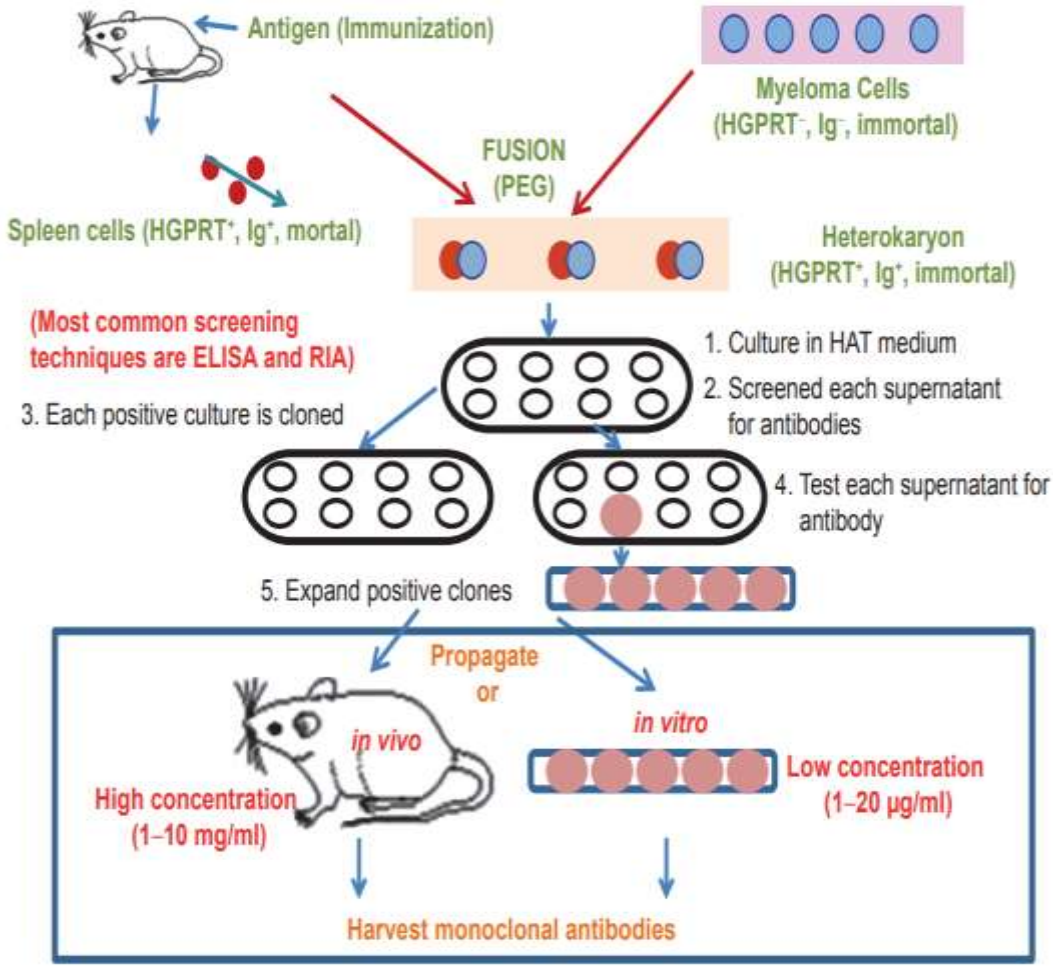

Figure 1: Production of monoclonal antibody by hybridoma technology.

THERAPEUTIC MONOCLONAL ANTIBODIES:

Similar to the global pharmaceutical business, the biopharmaceutical market has been growing annually and is predicted to double in size by 2018 to reach over 230 billion dollars. In 2024, it is

anticipated to reach more than 380 billion dollars [10]. The main components of the biopharmaceutical market in the past have been recombinant proteins, followed by therapeutic antibodies. Antibody-based drug sales, however, assumed the top spot in 2017, with projected sales of 172.8 billion dollars in 2022, or roughly 20% of the worldwide pharmaceutical industry [11].

It is noteworthy that since the late 1990s, the variety of therapeutic monoclonal antibodies has grown noticeably, with the total number approved by the US FDA reaching 64 in 2018 [12]. There were 11 therapeutic monoclonal antibodies approved in total in 2017. The properties of the antibodies have undergone some intriguing alterations that have attracted notice. The overall amount of human and humanized antibodies has significantly grown. The market for therapeutic antibodies is constantly growing due to factors such as a rise in approvals, efforts to find new target diseases for the therapeutic antibodies that have already received approval, and advancements in formulation and dosage forms [13].

The development of next-generation products is currently focused on antibody-drug conjugates [14], bispecific antibodies [15-17], low molecular weight antibodies [18–20], and sugar chain-modified antibodies [21, 22]. Some antibody-drug conjugates and bispecific antibodies are already available on the market; examples of the latter include inotuzumab ozogamicin [23], gemtuzumab ozogamicin [24], and brentuximab vedotin [25].

THERAPEUTIC APPLICATIONS OF MONOCLONAL ANTIBODIES:

With a current estimated value of $115.2 billion in 2018 [26] and an encouraging pipeline, the MAb industry is anticipated to expand at an accelerating rate. Oncology, immunology, and hematology continue to be the three medical specialties where MAbs are most frequently employed. Most mAbs have several disease indications, at least one of which is connected to cancer. As a result, oncological disorders are the condition for which MAb therapies are most readily available [27].

Immune-mediated diseases:

Several MAbs have been introduced in the past three decades for the treatment of various illnesses. Monoclonal antibodies have transformed the way that autoimmunity-related diseases are treated. The activation of auto-reactive CD4+ lymphocytes in peripheral lymph nodes, where naive T cells interact with antigen-presenting cells (APCs) and B cells, is a hallmark of autoimmune disorders. The disease-targeted organ parenchyma is invaded by multiplying and migrating activated T cells. Here, the recognition of endogenous ligands triggers the synthesis of cytokines and pro-inflammatory molecules, which cause cell damage and the development of the illness [28].

Monoclonal antibodies can target several immune system elements to reduce the disproportionate immune responses that characterize autoimmune disorders [29]. Inhibiting the interaction between T cells and antigen-presenting cells, blocking the recruitment of T and B cells, blocking the differentiation or activation of T cells, and blocking pro-inflammatory cytokines are some of the mechanisms used by MAbs to treat autoimmune disorders [28]. The latter is the strategy that is most frequently used, particularly when TNF-targeting MAbs are used. TNF is a cytokine that plays a crucial role in autoimmunity and causes inflammation and vasodilation. Since more than ten years ago, these antibodies have been used to treat rheumatoid arthritis. They are also effective against psoriatic arthritis, Crohn's disease, ulcerative colitis, psoriasis, inflammatory bowel ailment, and ankylosing spondylitis [30].

MAbs have the potential to be utilized to induce tolerance to transplanted organs or tissues or to inhibit the immune system following transplant. Daclizumab, a humanized anti-IL-2a antibody, has recently been shown to be an efficient addition to dual immunosuppression therapy in renal transplant patients and may lessen transplant recipients' rates of CMV infection as well as the risk of acute rejection following a kidney transplant [31, 32]. In general, the ability of MAbs to promote tolerance to self-antigens and transplanted tissues may offer significant therapeutic potential [33]. Rituximab, an anti-CD20 MAb, may be used to treat posttransplant lymphoproliferative disorder, and anti-LFA-1 MAb (odulimomab), which may prevent ischemia-reperfusion injury after kidney transplants, is being studied as a treatment for other posttransplant complications [34].

Since the FDA put a clinical hold on safety-related trials, magrolimab, a first-in-class anti-CD47 antibody, has not been proven to be safe and effective. Similar phagocytosis checkpoints, such as Stanniocalcin 1, have also been discovered, although clinical trials are still needed to assess the effectiveness of antibody therapies against these targets [35]. A significant amount of efficacy has been demonstrated by antibodies against innate and adaptive immunological checkpoints. To increase effectiveness and widen use, delivery techniques that can combat systemic toxicity are needed [36]. Infliximab (Remicade), a chimeric IgG1k antibody, works by attaching to soluble and transmembrane tumor necrosis factor (TNF), blocking it from attaching to its receptors on activated macrophages. Patients with moderately to severely active Crohn's disease may find remission from the anti-TNF antibody. In addition, the FDA has approved the use of infliximab in combination with methotrexate for the treatment of rheumatoid arthritis [37].

In 2018, adalimumab (Humira) had the highest global sales. Adalimumab is also used to treat psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis

suppurativa, uveitis, and juvenile idiopathic arthritis. It has been demonstrated that Adalimumab lessens the signs and symptoms of moderate to severe rheumatoid arthritis in adults [38]. It can be used either on its own or in conjunction with medications that treat rheumatic diseases [39].

Oncology:

For the treatment of numerous neoplasias, including both hematologic malignancies and solid tumors, several monoclonal antibodies have been created. The first strategy involves using MAbs to specifically target tumor antigens and eradicate cancer cells. Growth factor receptors that are overexpressed in tumor cells, such as those in the EGFR and HER2 families of receptors, are the primary targets for therapeutic MAbs for anticancer applications [40]. These receptors are blocked by MAbs, which also prevent ligand binding and signaling. This can slow tumor development, trigger apoptosis, and make tumors more susceptible to chemotherapy. The blocking of the HER2 receptor by trastuzumab (Herceptin) and other mAbs used to treat HER2-positive breast cancer is an illustration of this therapeutic strategy. 30% of invasive breast tumors have an overexpression of HER2. Trastuzumab prevents receptor dimerization and internalization, which causes the receptor to be destroyed by the endocytic process and activates the immune system [41].

Hematopoietic differentiation antigens (CD20, CD30, CD33, and CD52), which are glycoproteins present on the surface of normal and malignant cells, are additional targets besides growth factors [40]. For instance, the MAb rituximab (Rituxan), which is used to treat lymphoproliferative diseases, targets CD20, a pan-B-cell marker [42]. This causes interactions between the Fc region of the MAb and the Fc receptor expressed on immune cells. Immune cells that are activated in an FcR-dependent manner release inflammatory mediators that either directly destroy opsonized target cells or trigger phagocytosis [43].

For instance, bevacizumab (Avastin) inhibits angiogenesis by preventing the binding of vascular endothelial growth factors to the receptor in the vascular endothelium, which is overexpressed in several malignancies [41]. Targeting immune cells is a different strategy for MAb-based treatments that are anti-cancers. These MAbs, also known as immunological-checkpoint inhibitors, improve anticancer immune responses. Programmed cell death protein 1 (PD1)/PD1 ligand 1 (PDL1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) are the major targets of immune checkpoint inhibitors [44]. Regulatory T cells that have infiltrated tumor lesions can express CTLA-4, which mediates immunosuppression by impairing T-cell activities. Blocking CTLA4 allows T cells to once again destroy cancerous cells [45]. 2011 saw the approval of the anti-CTLA4 mAb ipilumab (Yervoy) for metastatic melanoma [46].

The receptor and ligand combination PD1/PDL1 controls T cell-mediated immune responses adversely and can be utilized by malignancies to evade antigen-specific T cell immunologic responses. Examples of mAbs that target this immune checkpoint pathway include nivolumab (Opdivo), a PD1 inhibitor, and atezolizumab (Tencentriq), a PDL1 inhibitor, both of which have been approved for the treatment of various malignancies [47]. Immune checkpoints play a crucial role in preserving self-tolerance and regulating physiologic immune responses in peripheral tissues. As a result, cancer immunotherapy has recently shown a lot of interest in the chemicals that underlie checkpoints [48]. Anti-PD-1 MAbs nivolumab and pembrolizumab were the second and third-best-selling MAb medications in 2018, respectively. Compared to docetaxel, the conventional second-line treatment, NSCLC patients treated with nivolumab and pembrolizumab (both approved by the US FDA in 2014) had improved overall survival [49].

CD40 is a different immunological checkpoint that is presently being researched for the treatment of cancer. Immune checkpoints CTLA4 and PD1 are inhibitory, but CD40 is stimulatory. This receptor belongs to the TNF receptor family, which B cells and APCs express [41] When this receptor on APCs is activated, tumor-specific cytotoxic T lymphocytes are mobilized to destroy tumor cells. The mAbs being developed to target this receptor in this instance (such as dacetuzumab from Seattle Genetics) are agonists, even though their clinical efficacy hasn't been great so far [50].

Immunoconjugates may now be given to cells thanks to developments in radiolabelling, which have shown promise in clinical trials [51-53] Targeted cells receive radioactive isotopes by radiolabelled MAb treatment. In addition to harming the attached cell, emitting radioisotopes like yttrium-90 and iodine-131 might also harm nearby tumor cells that antibodies might not be able to reach within tumors. Radioisotope use is hampered by ignorance of the proper dose, biodistribution, and antigen shedding. Radiolabelled MAbs can be used to detect cancer in addition to being utilized in radiotherapy [54, 55]. In a procedure known as immunoscintigraphy, radioactive isotopes associated with MAbs may aid in locating malignancies. For instance, an MAb coupled to indium-111 called OncoScint may be utilized to identify an antigen called TAG-72 that is present in colorectal adenocarcinomas [56]. An MAb tagged with Yttrium 90 or Indium 111 and used to treat non-Hodgkin's lymphoma is Ibritumab tiuxetan (Zevalin). Other mAbs focus on the tumor microenvironment, with outcomes including angiogenesis inhibition [41, 57].

A fully human IgG1 mAb called ganitumab (AMG 479) binds to the type I insulin-like growth factor receptor's extracellular domain, blocking the binding of IGF-1 and IGF-2 ligands. This

prevents downstream signaling, such as the PI3K/Akt pathway, which in turn prevents tumor cell proliferation and triggers apoptosis [58, 59].

For the treatment of patients with a variety of malignancies, 45 monoclonal antibodies (mAbs) have been authorized; however, none have been authorized for pancreatic cancer. The effects of preclinical research and clinical trials using mAbs in pancreatic cancer, as well as the factors influencing the poor response to antibody therapy (such as tumor heterogeneity and desmoplastic stroma), were covered by Gustavo et al. They concluded that the development of different antibody-based therapeutic agents and companion diagnostic tests for the selection of patients who are more likely to benefit from such therapy are all made possible by MAb technology, which is a great tool for studying the complex biology of pancreatic cancer [60]. In a phase 1b/2 research including patients with metastatic pancreatic cancer, cixutumumab (IMC-A12), a completely human IgG1/mAb against IGF-IR [61], was investigated in combination with erlotinib and gemcitabine [62]. Additionally, a phase 1/2 research assessed the effects of dalotuzumab (MK-0646), an IgG1 humanized mAb specific to IGF-1R, in conjunction with gemcitabine [63].

In addition to mAbs that target growth factor receptors, mAbs that target other Tumor-associated antigens have also received a lot of attention. One of the best targets is CD20, which B cell lymphoma expresses. The first anti-CD20 mAb to receive FDA approval was rituximab, which was followed by obinutuzumab and ofatumumab. Rituximab is one of the first-line treatments for B-cell non-Hodgkin lymphomas that express the CD20 antigen [64]

By Ravetch et al., the mechanism of anti-CD20 mediated tumor clearance has been thoroughly investigated. They proved that anti-tumor T cell responses are only produced when CD11c+ antigen-presenting cells express the Fc receptor (FcR), which is necessary for ADCC-mediated tumor clearance [65]. Numerous cancer forms have also been reported to exhibit aberrant overexpression, particularly those of the digestive system [66]. A phase 3 clinical trial with chemotherapy and the anti-CLDN monoclonal antibody medication zolbetuximab (IMAB362) has been conducted [67].

Infectious diseases:

Number of MAbs that have been approved for use in treating or preventing infectious illnesses. The infusion of hyperimmune sera from donors who had received immunizations in animals or humans was the first successful treatment for infectious diseases. Although antibiotic therapy has largely superseded this strategy, it is still effective in treating infectious disorders like those brought on by the cytomegalovirus, and hepatitis A and B viruses, among others. MAbs provide advantages over immune sera-derived preparations for the treatment of infections, including low

lot-to-lot variability, a low risk of pathogen transmission, and no immunological side effects related to the use of heterologous sera.

In contrast to their development for oncology and immune/inflammatory illnesses, MAbs for infectious diseases have taken longer to develop. Palivizumab (Synagis), intended to prevent severe respiratory disease caused by the respiratory syncytial virus in high-risk individuals, was the first MAb to be licensed for an infectious disease. This MAb prevents the multiplication of the virus and lowers the incidence of serious illness in preterm newborns [68].

Ibalizumab (Trogarzo), which was licensed in 2018 for the treatment of HIV-1 infection that is multidrug-resistant, is another illustration [69]. This MAb functions as a post-attachment inhibitor by binding to CD4 receptors and preventing viral entry into the host CD4+ T cells. It was the first novel HIV treatment drug licensed in more than ten years [70]. MAbs may be used in the creation of immunological complex vaccines as both a preventive and a therapeutic immunization strategy. Antigen-MAb immune complex-based vaccinations have been used to prevent infectious bursa disease in poultry by simulating the functions of the immune complex. Following this success, this strategy is now being used to combat herpes simplex virus, HIV-1, hepatitis B and C, and Ebola, among other human infectious diseases [71-73].

In patients at risk for Cytomegalovirus infection, many doctors combine antiviral medications and immunoglobulins. Additionally, MAbs may reduce the quantity of antiviral medications needed for therapy. In animal models, MAbs against murine CMV polypeptides have proven to be protective [74]. Serious lower respiratory tract sickness brought on by the respiratory syncytial virus (RSV) necessitates extensive supportive care, the provision of humidified oxygen, and breathing support. The FDA has given the go-ahead for the use of a humanized MAb to treat RSV, which primarily affects newborns and young children younger than 24 months of age. The antibody therapy, known as palivizumab, demonstrated a 55% decrease in RSV infection in hospitalized patients [75]. MAbs have additionally been applied to the treatment of HSV infections [76]. The Medical Research Institute of the US Army has discovered protective antibodies that target epitopes on the membrane-anchored glycoprotein of the Ebola virus [77].

In the US, 12 novel mAbs in total were authorized in 2018. The fact that most of these medicines were approved for uses other than treating cancer may be an indication of the greater approval success rate for antibodies used to treat other diseases. Ibalizumab is used to treat HIV infection, and three antibodies, erenumab, galcanezumab, and fremaezumab, were licensed for the treatment of migraines. The three medications listed above are mAbs that inhibit the calcitonin gene-related peptide (CGRP) receptor's function in migraine genesis [78].

Only four monoclonal antibodies (mAbs) have currently received US FDA approval for the treatment of infectious diseases: raxibacumab and obiltoxaximab for the treatment of inhalational anthrax [79], palivizumab for the prevention of respiratory syncytial virus in high-risk infants [80], and ibalizumab for the treatment of HIV patients [81]. Ibalizumab is a CD4 domain 2-directed post-attachment HIV-1 inhibitor that is an IgG4 mAb that has been humanized. Ibalizumab has been approved by the US FDA for use in adult HIV-positive patients who have had prior treatment but are no longer responsive to such treatments.

Other indications:

Although many MAbs have been created for antiplatelet treatment, only one, abciximab, has so far received approval. The integrin IIb3 is the target of this antibody, which was created from the murine human chimera c7E3 Fab and prevents integrin binding to fibrinogen and von Willebrand factor, two blood glycoproteins essential for hemostasis [82].

The prevention and management of migraines is another application for MAbs. A target for migraine prevention medication is the calcitonin gene-related peptide (CGRP). This peptide modulates pain perception, and central sensitization, and operates on the CGRP receptor. Since CGRP is increased in migraine sufferers, MAbs that target this peptide have demonstrated efficacy in these individuals [83]. Erenumab (Aimovig), fremanezumab (Ajovy), and galcanezumab (Emgality) are examples of this strategy [84].

Bronchial hyperresponsiveness, a risk factor for asthma, may be brought on by high levels of IgE. IgE-mediated immune responses have a significant role in the development of allergic asthma. Recombinant humanized anti-IgE antibody (rhuMAB-E25), which forms complexes with free IgE and blocks its interaction with mast cells and basophils, was administered twice weekly to subjects in a recent study who had moderate to severe allergic asthma. This treatment reduced asthma symptom scores and serum IgE levels compared to the placebo group. Anti-IgE therapy allowed patients to use fewer corticosteroids overall. Even if the study needs to be evaluated carefully, it represents a positive development in the search for more successful asthma treatments [85].

FUTURE PROSPECTS:

In recent years, the field of therapeutic antibodies has expanded quickly, dominating the therapeutics market. However, the therapeutic antibody market still has a lot of room for expansion. Antibodies have historically been used to treat autoimmune disorders, infectious infections, and cancer. Antibodies may be a useful therapeutic option if the molecular mechanisms of a particular disease can be precisely understood and the unique proteins or molecules implicated in pathogenesis can be identified**.** It is simple to see how complex formats were created in response

to difficulties presented by therapeutic indications by looking at currently approved mAbs. Antibody-drug conjugates, glycoengineered mAbs, immunomodulators, bispecific mAbs, and CAR-T cells are examples of these mAb engineering solutions [86].

The stringent specificity, low toxicity, immune-modulatory activity, and high affinity for target antigens of monoclonal antibodies have led the way for further engineered protein-based biotechnology products, including Fc fusion proteins, bispecific mAbs, ADC, and alternative scaffolds. Bispecific antibodies, which can distinguish between two different antigens, have already been created and employed as therapeutic agents for hemophilia, leukemia, and carcinomas [87–89]. Identification of target molecule combinations suitable for the production of high-potency antibodies is essential for the development of innovative therapeutic bispecific antibodies. The enzyme-mediated activation of radical source (EMARS) technique described by Kotani et al. is a method for analyzing hetero-protein complexes (bi-molecular complexes) formed on cell membranes under physiological conditions [90] and is also useful for locating cancer cell-specific bi-molecular complexes for creating therapeutic bispecific antibodies against cancer cells. This may assist in alleviating the existing challenge of finding candidate antigens in the investigation of innovative therapeutic methods because the possible combinations of molecules are practically endless.

Monoclonal antibodies with stereo-specificity may act as catalysts. Recent thorough research on catalytic antibodies has advanced to the point where useful applications are now possible. Due to their capacity to both identify and destroy antigens, catalytic antibodies have potential advantages over monoclonal antibody treatments [91-95]

It is widely acknowledged that when mice are used as vaccination animals, immunological tolerance makes it challenging to develop monoclonal antibodies against mouse antigens. This makes the mouse, a great candidate model animal for many diseases, less useful for the investigation of crucial disease-related antigens. However, from the perspective of stereospecific recognition, it is feasible to cross-react with antigens from other species by identifying shared conformational structures. Monoclonal antibodies that are specific for linear epitopes have never been documented to cause this.

CONCLUSION:

One of the fastest-expanding medication classes in history is mAbs. The development of large-scale manufacturing techniques for monoclonal antibodies (mAbs) utilized in diagnostic and therapeutic applications has been prompted by the rising demand for these substances. The market for mAbs has expanded dramatically in recent years. With so many mAbs now in research and

pharmaceutical companies continuing to show interest, the mAb market is also anticipated to expand over the next years. Production enhancements are made possible via ongoing optimization of the underlying systems. In the last few years, there has been considerable growth in the number of monoclonal antibodies (mAbs) that have already received regulatory approval for therapeutic uses and usage in clinical trials. Numerous enhancements and alterations to monoclonal antibodies have been created in response to the drawbacks and limits of mAbs. The treatment of infectious disorders brought on by bacterial, viral, fungal, and parasitic species is one of the therapeutic uses for mAbs made possible by these alterations. These medications could be created for a variety of conditions, such as cancer, autoimmune diseases, and infectious diseases.

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