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An Overview Of Monoclonal Antibodies And Their Therapeutic Applications

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ABSTRACT

The use of monoclonal antibodies (MAbs) to treat a wide range of illnesses is at the forefront of medicine as it advances towards a new era of tailored therapy. Since the first MAb was approved for clinical use in 1975, the MAbs business has grown at an accelerating rate and is now worth billions. In 2018, the worldwide therapeutic MAbs market was worth roughly US$115.2 billion, with revenues anticipated to reach $300 billion by 2025. Over 100 MA bsare currently being developed, and their distinct characteristics assure that they will continue to be part of the treatment stream. MA bs might be used to treat a variety of illnesses, including viral infections, septicemia, poisoning, drug addiction, cancer, autoimmune diseases, asthma, and more. As a result of new medicines being authorized for treating a variety of human diseases, the market for therapeutic antibody therapies has exploded. Since its beginning, antibody-based treatment has progressed continually.Major turning moments in oncology include the revolution in cancer immunotherapy and the recent use of antibodies as first-line therapy. Thus, the last three years alone account for two-thirds of the decade's most significant immunotherapy transactions. Therapeutic MAbs are the most common biological medicines in research, clinical trials, and on the market today. MAbs and fusion proteins are undeniably important in the pharmaceutical business and market. This review provides an overview of the topic of history and regulation of MAbs.

Keywords: Antibody; FDA; Therapeutic MAbs; Antibody therapy;

INTRODUCTION

The immune system serves as a line of defence against a variety of infectious pathogens that cause a variety of illnesses. The humoral (antibody-mediated) and cellular (cell-mediated) immune responses are the two main components. Blymphocytes are part of the humoral immune system, which detects foreign antigens and generates particular antibodies against them. The two most essential properties of an antibody are its specificity and its ability to offer long-term resistance to a certain antigen. Scientists utilize them to protect humans from illnesses because of their unique characteristics [1].Antibodies are a type of protective mechanism that can recognize and kill invading things such as viruses and bacteria. Because they had antigen-binding sites, a paratope (similar to a lock) positioned at the higher ends of the "Y" shaped antibody molecules, each of them may detect a

particular antigen unique to its target. This paratope is specific for one epitope (similar to a key) on a single antigen, allowing these two structures to bind together precisely. As a result of this technique, an antibody might tag a microbe or an infected cell, allowing it to be targeted by other components of the immune system as well as neutralize its target directly [2]. Antibodies attach to soluble toxins, inhibiting their activity, as well as pathogen antigens on the surface, neutralizing their ability to infect human cells or tagging them for destruction. Immune cells kill pathogens by activating complement, antibody-dependent cellular cytotoxicity (ADCC), or antibody-dependent cellular phagocytosis (ADCP). Antibodies are made up of an antigen-binding fragment (Fab) that imparts target specificity and a crystallizable component (Fc) that drives biological activity. Alteration in the Fab and Fc sections have an impact on the antibody-dependent response's specificity, persistence, and result [3].

Kohler and Milstein revolutionized immunology when they developed MAbs in 1975, with the first MAb being completely licensed in 1986 [4]. Many MAbs have been produced since then for application in diagnostic procedures and immunotherapy. Since it was discovered that the therapeutic use of heterologous MAbs generated immunogenic responses in people, a lot of work has gone into developing chimeric and humanized antibodies for use in humans. The creation of MAbs in transgenic plants and animals has been a major accomplishment [5]. MAbs are glycoproteins capable of binding an antigen to a particular epitope, and they've been gaining traction in therapy in recent years, with many compounds receiving regulatory approval [6].

MAbs research and development is a unique approach to target particular mutations and abnormalities in protein structure and expression in a variety of illnesses and situations. Humanised MAbs are presently the fastest-growing group of biotechnology-derived compounds in clinical trials, thanks to substantial advances in genetic sequencing and the translation of basic medical sciences research into clinical practice.The worldwide antibody industry is estimated to be worth $20 billion each year. [Fig.1]. The FDA has authorized around 30 MAbs for human use to treat a variety of illnesses and disorders, including transplantation, inflammatory diseases, infectious diseases, cardiovascular diseases, and cancer [7]. Table 1 shows the discovery of serum treatment (1890~) and the creation of MAbs (1975~) are the two key eras in the advancement of therapeutic antibodies [8].

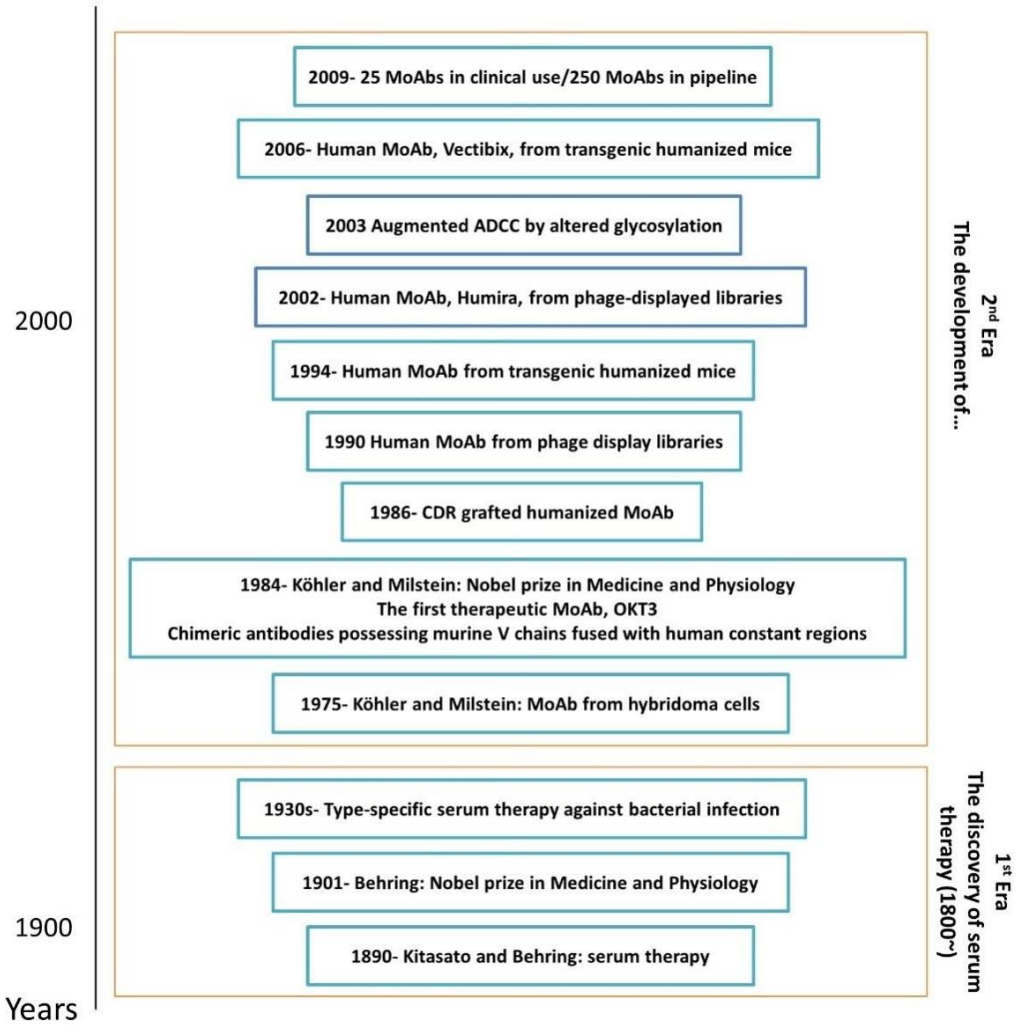

Figure 1: The development of therapeutic MAbs.

TYPES

The Food and Drug Administration (FDA), the European Medicines Agency (EMA), and other federal agencies have authorized antibodies of various sorts (murine, chimeric, humanized, and human) [Fig.2] for the treatment of a variety of illnesses. Since the licensing of OKT3, the usage of MAbs has steadily increased in all sectors of medicine [9]. Figure 2 shows the basic four types of MAbs.

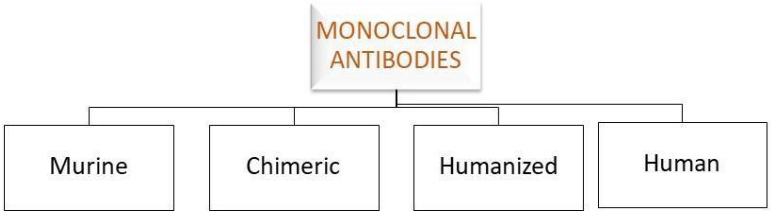

Figure 2: Types of Therapeutic Monoclonal antibodies.

I. Murine

Murine antibodies are the first MAbs to be created, as they are made completely of mouse protein. They were identified as allogeneic proteins according to the source of their synthesis, resulting in polyclonal human anti-mouse antibody responses 2-3 weeks after their initial infusion [10].

II. Chimeric

Murine antibodies have severe limits in therapeutic usage, necessitating the creation of novel medicines incorporating human components. The Fc region of the antibody molecule, which determines the antibody's activities, was chemically replaced with a human constant section at first [11].

III. Humanized

Humanized MAbs, which are 90% human and 10% mouse protein, was developed as a result of advances in molecular biology technologies. In comparison to chimeric MAbs, humanized MAbs are considerably less immunogenic [12].

IV. Human

The use of phage display and transgenic mice allowed for the creation of 100 percent human MAbs [13].

BRIEF HISTORY

MAbs were developed as mouse proteins and were thus immunogenic in humans, making them unsuitable for long-term treatment. More human-like MAbs with low immunogenicity were created utilizing molecular biology and protein engineering to overcome this restriction. MAbs and traps come in a variety of forms that are used in clinical studies. Initially, most murine Fc sequences were swapped with human Fc sequences, a process known as 'chimerisation.' The Fab sections of murine antigens are grafted onto the backbone of human immunoglobulin (IgG). The mouse hyper-variable peptide-binding loops are grafted onto the human IgG backbone during 'humanization.' Newer technologies enable the production of completely human antibodies [14,15].

A whole new era in biotechnology has begun with their initial manufacture and licensing of MAbs. The overall approach is known as 'hybridoma technology' proven to be a wide variety of MAbs capable of binding to protein, carbohydrate, nucleic acid, and hapten antigens, as well as having catalytic properties. As a result, there are far too many practical applications for MAbs in research and health care, resulting in legal disputes [16].Trastuzumab was the first monoclonal antibody to be found effective in the treatment of solid malignancies. The humanized human epidermal growth factor receptor 2 (HER2) triggered the production of these MAbs. Trastuzumab was developed via rigorous science, which also paved the way for cancer medication development and therapy based on a patient's specific biomarkers [17].

THERAPEUTIC MAbs REGULATION BY FDA

Antibodies are considered "biopharmaceuticals" by the FDA, and MAbs applications are governed by the agency's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER). The FDA has produced a "Points to Consider" paper that advises producers on issues to consider while developing and testing MAbs for human use, as well as information that should be included in Investigational New Drug (IND) or biologics licensing applications. "Indicate the agency's current thinking on MAbs products for human use," according to the "Points to Consider" paper. Because viruses and cellular DNA from antibody-producing cells with malignant morphologies may be incorporated into host cells following transformation, the agency's recommendations aim to

protect human health. Several measures, such as ensuring the purity of immunoconjugates and proving the capacity of any purification scheme to eliminate adventitious agents, are included among the Factors to Contemplate to avoid contamination of the finished product by potential pathogens. Producers must also follow wildlife protection guidelines and describe efforts to prevent cultured cells contamination [5].Therapeutic MAbs are becoming increasingly important since they have been the primary therapy technique for a variety of illnesses during the last three decades. Major technical advancements have enabled the research into the advancement of MAbs treatments quicker and more effectively throughout this time. According to the US FDA, 48 additional MAbs have been authorized since 2008, adding to a cumulative international market of 61 MAbs in therapeutic use by the end of 2017. The list of therapeutic antibodies licensed by the FDA from 2000 to 2010 is in Table 1. From 2018 to 2019, the US FDA approved a total of 18 novel antibodies, according to information gathered from numerous sources, including the news announcements, database of therapeutic antibodies, corporate pipelines, and antibody society [13].The FDA authorized 12 novels MAbs in 2018, accounting for 20% of all approved medicines. By 2024, 50% of these are anticipated to become blockbusters, with yearly revenues of at minimum $1 billion [18].

Table 1: FDA-approved therapeutic antibodies from 2000 to 2010 [19].

Brand name	Antibody	Target	Year	Indication
Campath	Alemtuzumab	CD52	2001	Chronic lymphatic leukemia, T-celllymphoma
Zevalin	Ibritumomab tiuxetan	CD20	2002	Non-Hodgkin's lymphoma
Bexxar	Adalimumab	TNF-α	2002	autoimmune disorders like rheumatoidarthritis, psoriatic arthritis, MorbusChron
Bexxar	Tositumomab	CD20	2003	Non-Hodgkin's lymphoma
Xolair	Omalizumab	IgE	2003	Severe (allergic) asthma
Avastin	Bevacizumab	VEGF	2004	Metastatic colorectal cancer, non-smallcell lung cancer, metastatic breast cancer
Tysabri	Natalizumab	α4 subunit of a4β1	2004	Multiple Sclerosis, Chron's disease
Erbitux	Cetuximab	EGFR	2004	Colorectal cancer, head and neck cancer
Vectibix	Panitumumab	EGFR	2006	Metastatic colorectal carcinoma
Lucentis	Ranibizumab	VEGF-A	2006	Wet macular degeneration
Soliris	Eculizumab	CD59	2007	Paroxysmal nocturnal hemoglobinuria

Cimzia	Certolizumab pegol	TNF-α	2008	Crohn's disease, rheumatoid arthritis
Simponi	Golimumab	TNF-α	2009	Rheumatoid and psoriatic arthritis, active an kylosing spondylitis

In 2018, adalimumab (Humira) was the best-selling medication on the globe. Adalimumab is a biological disease modifier that is given subcutaneously for the treatment of rheumatoid arthritis and other TNF-mediated chronic debilitating illnesses. It was first introduced in the United States by Abbvie in 2002, after receiving FDA clearance. Adalimumab has been found to help people with mild to severe rheumatoid arthritis, as well as ankylosing spondylitis, Crohn's disease, hidradenitis suppurativa, juvenile idiopathic arthritis, psoriasis,psoriatic arthritis, ulcerative colitis, and uveitis [20]. Table 2, lists the top-selling MAbs of 2018.

Table 2: Top 5 best-selling monoclonal antibody drugs in 2018 [13].

Company	Drug	Indication	Revenue (USD)
AbbVie	Adalimumab (Humira)	Rheumatoid arthritis Psoriatic arthritis Ankylosing spondylitis Juvenile Idiopathic Arthritis Psoriasis Crohn's disease Ulcerative colitis Hidradenitis suppurativa Uveitis	$19.9 bn
Bristol-Myers Squibb	Nivolumab (Opdivo)	Melanoma Non-small cell lung cancer Renal cell carcinoma Head and neck squamous cell	$7.6 bn
Merck & Co	Pembrolizumab (Keytruda)	Melanoma Head and neck cancer Non-small cell lung cancer Lymphoma Cervical cancer Microsatellite instability cancer	$7.2 bn
Roche	Trastuzumab (Herceptin)	Breast cancer Gastric cancer	$7.0 bn
Roche	Bevacizumab (Avastin)	Colorectal cancer Non-small cell lung cancer Breast ERB2 negative cancer Renal cell carcinoma Glioblastoma	$6.8 bn

TARGETING SARS-COV-2 WITH THERAPEUTIC MAbs

In December 2019, Covid-19 was detected for the first time in Wuhan, China, and was later declared a pandemic by the World Health Organization [21]. It is mostly a respiratory illness that also affects other organ systems such as the cardiovascular system, kidneys, and neurological system [22].

Therapeutic MAbs for COVID-19 therapy has been created at a breakneck speed that has never been seen before in any illness. Since the discovery of MAbs, the licenses were acquired in a record time of just 10 months, involving 3 to 4 months of clinical-grade MAbs manufacturing [23]. Celltrion, AstraZeneca, and Regeneron are among the pharmaceutical firms that support the development of MAbs as a therapy for COVID-19. The first human research to treat COVID-19 is now underway, employing LY-CoV555 neutralizing MAbs against the spike protein, and is being conducted by the drug maker "Lilly." The neutralizing antibody LY-CoV555, at a dosage of 2800 mg, appeared to hasten the normal fall in viral load, but the two doses (700 mg and 7000 mg) did not. Bamlanivimab and Casirivimab-Imdevimab are new virus-neutralizing MAbsthat have just been approved for the treatment of mild to moderate COVID-19 infected outpatients who are at risk of progressing to a severe infection. Early therapy may also be effective in halting the development of infection in highly infected patients. However, FDA granted an emergency use authorization (EUA) forImdevimab and Casirivimab to be used jointly in adults and children with mild to moderate COVID-19 [24,25].

New SARS-CoV-2 viral variants have just been discovered. Mutations in the virus's DNA give rise to these variations. MAbs are still effective against the B.1.1.7 form of SARS-CoV-2. Certain mutations, though, may produce alterations in the spike protein, which might impair the efficacy of presently offered MAbs[26].

MAbs treatment has recently acquired a lot of attention. MAbs recognize particular epitopes in the target antigen and bind to them. Initially, MAbs were only used to create diagnostics; therapeutic applications were limited by the immunogenic potential and low effectiveness associated with murine antibodies due to the absence of effector function. Following that, modified antibodies containing a murine variable domain and a human constant domain were developed and demonstrated to have fewer side effects while maintaining binding ability, leading to the approval of chimeric MAbs for a variety of indications, including infectious diseases, genetic diseases, tumor, allergic conditions, and so on [27]. MAbs are also used for other diseases for the treatment (Figure 3) like autoimmune diseases, infectious diseases, tumors, metabolic disorders, etc.

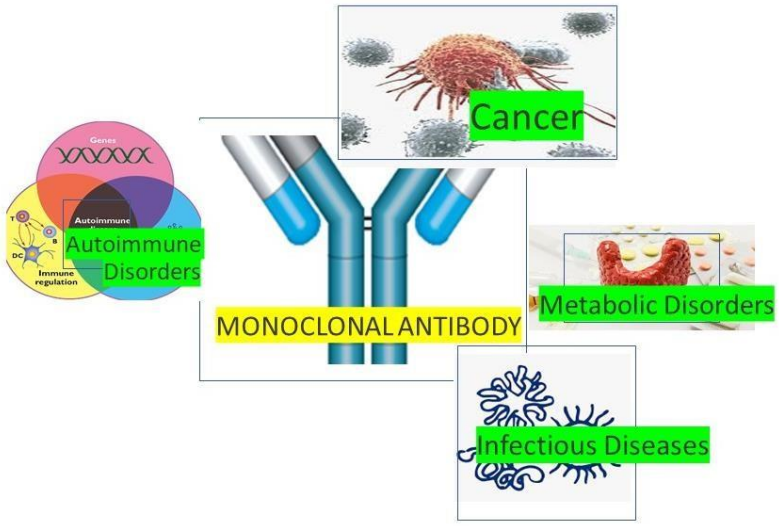

Figure 3: Some other areas for therapeutic applications of MAbs.

In 1997, the first anticancer MAb, rituximab, was authorized for usage globally, ever since, more than 35 MAbs have been licensed for clinical use [28].Recent advancements in genetic engineering have created the opportunity to deliver therapeutic use of MAbs by discovering novel targets with higher effectiveness for clinical usage. Infectious illnesses, as carriers for harmful chemicals delivery to tumors, or as instruments for detecting, finding, and targeting neoplasms have all benefited from their usage in immunoprophylaxis or immunotherapeutics. Their therapeutic uses include human and animal illness treatment, vaccine production, immune response suppression, and hormone purification [29].

CONCLUSION

Antibodies have replaced large libraries of small compounds as the foundation of the pharmaceutical sector. MAbs offer superior target selection compared to small compounds, resulting in reduced toxicity due to binding to non-targets. Because of their selectivity and versatility, MAbs are an appealing alternative for the production of novel treatments and molecular targeted therapies against a broad variety of illnesses. MAbs may now target two or even more sites at the same time, increasing their clinical efficacy.

The therapeutic era of MAbs is yet in its early stages. The fast progress achieved in recent decades toward the creation of effective therapeutic MAbs, mostly for oncology and immunological disorders, presents several challenges about the field's foreseeable paths. A significant concern is if there are any signs of a paradigm shift that might lead to fundamentally new treatments, similar to what happened two-three decades earlier and resulting in an outburst of MAbs medicines authorized for clinical usage in the previous decade.

MAbs might eventually be utilized to treat a wide range of diseases, including drug addiction, malignancy, allergies, infectious agents, septicemia, and toxicity, thanks to such encouraging findings. "The therapeutic use of MAbs, although currently restricted in scope," Heddy Zola said in 1995, "promises to overcome its considerable constraints and achieve the possibilities prophesied by its proponents." The industry for MAbs has exploded in recent years. Furthermore, given the vast number of MAbs presently in production and pharmaceutical firms' ongoing interest, the MAbs market is projected to increase in the coming years.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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ETHICAL APPROVAL

Not Required.

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