Therapeutic Monoclonal Antibodies: Clinical Applications

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Abstract: Diagnostic and therapeutic monoclonal antibodies (mAbs) have a broad application prospect, conducive to mass production by optimizing the quality of monoclonal antibodies and improving productivity. The number of monoclonal antibodies approved for the treatment and use has increased significantly over the years. Some improvements and modifications have been made given monoclonal antibody's side effects and limitations. These improvements facilitate monoclonal antibodies in various therapeutic applications, from treating noncontagious diseases such as cancer, like breast cancer, to using monoclonal antibodies to cure infectious diseases caused by viruses, such as viruses Covid-19 and its causing agent SARS-CoV-2. This paper reviews monoclonal antibody's clinical application, focusing on these two main categories and discussing its potential future development trend.

1 INTRODUCTION

Monoclonal antibodies are homologous antibodies produced by single clone hybridoma cells that only recognize a specific epitope. Monoclonal antibodies have the properties of general antibodies; monoclonal antibodies are a type of globulin produced by the proliferation and differentiation of B cells into plasma cells. Such as pathogens) specifically bind, and exert an immune effect under the participation of other immune molecules and cells. In addition to the general properties of antibodies, monoclonal antibodies also have their particularities. Monoclonal antibodies have mouse immune spleen cells (B cells) and immortal myeloma cells fused together to form a hybridoma cell. This hybridoma cell not only has the ability to reproduce indefinitely but also has the ability to secrete antibodies. Therefore, after in vitro culture, antibodies can be secreted indefinitely. Clinically, such as the application of diphtheria exotoxin monoclonal antibody to treat Corynebacterium diphtheriae; the application of anti-endotoxin lipid A monoclonal antibody to treat G~bacterial sepsis, etc., using a monoclonal antibody as an affinity column can separate and purify the content of extremely low solubility Antigens such as hormones, cytokines, and tumor antigens that are difficult to purify; open up a new way for substance purification; prepared monoclonal antibodies to recognize specific receptors on the cell surface, and couple anti-tumor drugs (such as toxins or radioactive substances). Connect to it to build biological missiles to overcome human diseases-tumors.

Monoclonal antibodies are vital in tumor diagnosis and treatment. It is of great significance to use new secretory antigens that can promote tumor growth or metastasis as antibody blocking targets (Scott, 2012). Monoclonal antibody-targeted therapy for tumors is: monoclonal antibodies against tumor antigens are attached to chemotherapy or radiotherapy agents, and use the targeting effect of the monoclonal antibody to carry the drug or radiotherapy substance to the target organ and directly kill the target cell. In addition, radio immunoimaging can be realized to aid tumor diagnosis by linking the radio markers with monoclonal antibodies and applying them to patients. Although monoclonal antibodies against tumor-specific antigens remain to be studied, monoclonal antibodies against tumor-associated antigens such as alpha-fetoprotein, tumor basic protein and

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carcinoembryonic antigen have been used in clinical trials for a long time. With the application of lymphocytic hybridoma technology, many hybridoma cell lines resistant to human tumor markers have been established. Radionuclide-labeled monoclonal antibodies can be used for in vivo diagnosis, and combined with X-ray tomography technology, it can make a quantitative diagnosis of the size of the tumor and its metastasis. At present, monoclonal antibodies have their limitations in the diagnosis and treatment of tumors. Monoclonal antibodies are mainly murine-derived antibodies, which are satisfactory as in vitro diagnostic reagents (Abès, 2011). If murine-derived monoclonal antibodies are used in humans as biological preparations, the heterogeneous proteins in the serum of heterogeneous animals can cause allergic reactions and even life-threatening (Marabelle, 2015). Human monoclonal antibodies or humanized antibodies are important for disease treatment. Although there are reports that the culture of these cell lines is very unstable, the human chromosomes in the fusion cells are often selectively lost, making cell lines difficult to cultivate. Maintain cultivation. Therefore, the preparation of human monoclonal antibodies is a problem that needs to be solved urgently, but no significant progress has been made in this regard.

Prospects Various preparation technologies of monoclonal antibodies are changing with each passing day, but they still have their own advantages and disadvantages and require resource integration (Jahanshahlu, 2020). The library of antibody library technology can be derived from immunized wild-type or transgenic animals, or it can be derived from a single B cell sorted out from a patient who has recovered from a specific disease. In short, several preparation techniques can be used interchangeably (Cruz-Teran, 2021).

This article mainly describes the progress and problems of monoclonal antibodies in tumor diagnosis and treatment and new coronavirus vaccine research. With the continuous progress and development of research technology, monoclonal antibody is expected to achieve a breakthrough in tumor diagnosis and treatment, and will also be better applied to the development of vaccines against new coronaviruses (Anti-SARS-CoV-2 neutralizing monoclonal antibodies: clinical pipeline – PubMed, 2021).

2 CLINICAL APPLICATIONS: IN CANCER TREATMENT

Antibody-based cancer treatment has grown well-established over the last 20 years, and it is currently one of the most effective and critical techniques for treating people with solid tumors and blood cancers (Bayer, 2019).

2.1 For Oncology Indications, Around 30 mAbs Have Been Received

A wide variety of new therapeutic antibodies are being evaluated in early and late-stage clinical studies. When compared to traditional chemotherapeutic drugs, most antibodies that have been authorized have different, and frequently lesser side effects.

Chemo therapies based on monoclonal antibodies (mAbs) began to appear.

By selectively binding an antigen on a malignant cell, mAbs might decrease non-specific toxic effects, identify malignant cells, and either change cellular signaling pathways toward a therapeutic outcome or activate an immune system response against with the cancer cell.

Antibody-drug conjugates (ADCs) are an immune conjugation made up of a cytotoxic medication (the payload) linked to a monoclonal antibody via a biochemical linker. The ADC is intended to specifically convey the ultra-toxic load direct to the tumor cells or tissues (Chau, 2019).

Five ADCs have been approved for use in the market, while more than 100 are being studied at various levels of clinical testing.

The ADC is now being used in breast cancer therapy in a variety of forward ways. This Review will use triple-negative breast cancer (TNBC) as an example to present the properties of mAbs therapy. TNBC lacks the expression of progesterone receptor, estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2), and belongs to the invasive breast cancer subtype. Traditional and growth factor receptor or endocrine targeted therapies do not work for women with TNBC. The predominant therapeutic technique for patients is a mix of radiotherapy, surgical intervention, and systemic chemo.

These therapeutic methods provide little clinical benefit, and varieties of side effects such as neutropenia and cardiotoxicity are common. Even with therapy, initial TNBC cancers often distant organ metastasis such as the the brain and lungs, causing the low overall survival seen in TNBC

patients. Small molecule antagonists targeting DNA double strand damage repair pathways in TNBC have demonstrated to be a potential option for enhancing TNBC survival rates. The FDA has authorized two poly ADP-ribose polymerase (PARP) antagonists, talazoparib and olaparib, for the therapy of HER2 negative later-stage cancer cases containing germ line changes in the breast tumor vulnerability gene 1/2 (BRCA1/2).

The progression-free survival (PFS) was 7 months for TNBC patients undergoing olaparib, compared to 4.2 months for patients who received single-agent chemo (ClinicalTrials.gov Identifier NCT02000622). In compared to chemotherapy- treated clients, PFS for TNBC patients undergoing talazoparib was prolonged by around 90 days (ClinicalTrials.gov Identifier NCT01945775).

Though PARP inhibitors exhibited therapeutic effectiveness as targeted therapies for TNBC, client survival improved only marginally. Taken all together, Additional treatments are desperately required, which suited to the therapy of TNBC, to stop the invasive disease's fast clinical progression.

Current cancer immunotherapy research on the field of meeting the unmet clinical need in TNBC presents a significant possibility. In the realm of TNBC, programmed death-ligand 1 (PD-L1) is a famous regulatory molecule that has recently attracted consideration as a prospective immuno-biological cancer therapy target.

The atezolizumab with the chemotherapeutic drug nab-paclitaxel, an anti-PD-L1 monoclonal antibody, the FDA authorized the conjunction for the therapy of locally advanced, PD-L1positive unresectable, or metastatic TNBC. The TNBC patient, whose median overall survival for PD-L1 positive was approximately 10 months longer than for those taking a placebo plus nab-paclitaxel , received atezolizumab with nab-paclitaxel.

After that, sacituzumab govitecan, the first ADC (antibody–drug conjugate), was approved for the therapy of metastatic TNBC. These ground-breaking approvals have paved the way for a new era of immunotherapy in TNBC (Dees, 2021). 86% Bispecific antibody treatment strategies in the clinical pipeline, which are authorized for oncology treatment, reached. The progress of DNA recombinant technology has led in the manufacturing of a plethora of cancer-targeting bispecific antibodies in a variety of configurations.

A bispecific antibody, conventional bivalent IgG-like, produced employing knobs into holes technology, has a fragment crystallizable region (Fc region) which is suitable of regulating regulatory activities, as well as fragment antigen-binding (Fab) regions which can detect and recognize multiple antigens. Even though some bispecific antibody models include a muted Fc region, there are certain bispecific antibody forms that do not have an Fc region at all.

Diabody, dual-affinity retargeting (DART), bispecific killer cell engager, and bispecific T cell engager (BiTE) are examples of Fab-based bispecific antibody constructions. The predominantly sum of bispecific antibodies in medical studies for cancer therapy have a process of the dual interaction of cancer cells and immune cells, and are usually structured as BiTEs. The blinatumomab, for bispecific antibody development has created a medical precedent in cancer treatment, which is a treatment of B cell tumors situated the first-in-class BiTE.

2.2 Therapeutic Monoclonal Antibodies (mAbs) Targeting the ERBB Family of Proteins Have Shown to Be Effective in Patients with Solid Tumors

There are many types of tumor-associated antigens that therapeutic mAbs detect. CD30, CD20, CD52, and CD33 are hematopoietic differentiation antigens, which are glycoproteins that are normally linked with a CD grouping. Both malignant cells and Normal include cell surface differentiation antigens, which are a broad array of carbohydrates and glycoproteins. Growth factors receptors and growth factor are often antigens engaged in differentiation signaling and growth.

United therapy with immune checkpoint suppressant, and a mass of TNBC targets such as Ephrin receptor A10 (EphA10), Trophoblast Cell-Surface Antigen 2 (Trop2), carcinoembryonic-antigen-related cell-adhesion molecule 5 (CEACAM 5), Epithelial cell adhesion molecule (EpCAM), P-cadherin, mesothelin, and EGFR have all been integrated into immune cell-redirecting bispecific antibody constructions. Furthermore, several receptors on TNBC cells, such as EGFR, Notch and HER3, can be recognized by bi-specific antibodies.

Bispecific antibodies have been developed as potential therapies for malignant tumors by transferring the cytotoxic effects and load of the immune system to cancer cells, or by simultaneously activating two functional receptors of a tumor cell. A fab - like bispecific antibody was found to participate in CD16 (FcRIII). A typical antibody-dependent cytotoxicity (ADCC) mechanism is triggered when a

stimulating receptor CD16, widely observed on NK cells, connects to the Fc region of an antibody conjugated to a target antigen.

Human epidermal growth factor receptor 3 (HER3), extracellular signal - regulated tyrosine kinase, and also another a bispecific diabody-Fc integration protein marking EGFR found on TNBC cells, was recently developed. The assay methods of cell culture in vitro monolayer and more complicated, physiologically associated 3D perfect sphere models proved that the EGFR ×HER3 bispecific antibody effectively inhibited TNBC cellular proliferation. Furthermore, in an murine models with orthotic MDA-MB-468 TNBC, the EGFR× HER3 bispecific suppressed growth and the survival of TNBC cancer stem cells (CSCs).

Positively, HER3 and Multi-specific EGFR identification has shown clinical effectiveness and safety in other cancers like as colorectal cancer and head and neck cancer identifier. In some other research, dual HER3 and EGFR blockade has been seen to increase TNBC cell sensitivity to phosphatidylinositol 3-kinase (PI3K) inhibitors, revealing the need for more research into combination treatment for TNBC.

Interestingly, EGFR Notch bispecific antibodies augmented the response to therapy of TNBC cells to PI3K inhibition, as demonstrated by a significant decrease in TNBC CSC communities. The same phenomenon was found with EGFR × Notch bispecific antibodies.

Recently, an innovative technique for delivering immune response therapeutic approaches to TNBC cancers using lipid-coated phosphate and calcium nanoparticles was established (LCP NPs). The LCP NPs were not only designed and synthesized on the outside with a PEG × EGFR bispecific antibody but was also added with cell apoptosis siRNA and indocyanine green on the inside of nanoparticle.

Consequently, LCP NPs chemically modified with PEG × EGFR bispecific antibodies function in TNBC cancer cells with EGFR-expressing, when exposed to near-infrared radioactivity in vitro, and removed TNBC tumors completely and induced cell death in TNBC cells in vivo. One study shows that bispecific antibodies can be used in photothermal therapy/a gene therapy-based nanoparticle platform to cure TNBC tumors.

Table 1: Tumor-associated antigens targeted by therapeutic monoclonal antibodies.

Antigen category	Examples of antigens	Examples of therapeutic mAbs raised against these targets	Tumor types expressing antigen
Haematopoietic differentiation antigens	CD20	Rituximab	Non-Hodgkin's lymphoma
		Ibritumomab tiuxetan and tositumomab	Lymphoma
	CD30	Brentuximab vedotin	Hodgkin's lymphoma
	CD33	Gemtuzumab ozogamicin	Acute myelogenous leukemia
	CD52	Alemtuzumab	Chronic lymphocytic leukemia
Glycoproteins expressed by solid tumors	EpCAM	IGN101 and adecatumumab	Epithelial tumors (breast, colon and lung)
	CEA	Labetuzumab	Breast, colon and lung tumors
	gpA33	huA33	Colorectal carcinoma
	Mucins	Pemtumomab and oregovomab	Breast, colon, lung and ovarian tumors
	TAG-72	CC49 (minretumomab)	Breast, colon and lung tumors
	CAIX	cG250	Renal cell carcinoma
	PSMA	J591	Prostate carcinoma
	Folate-binding protein	MOv18 and MORAb-003 (farletuzumab)	Ovarian tumors
Glycolipids	Gangliosides (such as GD2, GD3 and GM2)	3F8, ch14.18 and KW-2871	Neuroectodermal tumors and some epithelial tumors
Carbohydrates	Le^y	hu3S193 and IgN311	Breast, colon, lung and prostate tumors
Targets of anti-angiogenic mAbs	VEGF	Bevacizumab	Tumor vasculature
	VEGFR	IM-2C6 and CDP791	Epithelium-derived solid tumors
	Integrin αVβ3	Etaracizumab	Tumor vasculature
	Integrin αVβ31	Volociximab	Tumor vasculature
Growth and differentiation	EGFR	Cetuximab, panitumumab, nimotuzumab and 806	Glioma, lung, breast, colon, and head and neck tumors

signaling	ERBB2	Trastuzumab and pertuzumab	Breast, colon, lung, ovarian and prostate tumors
	ERBB3	MM-121	Breast, colon, lung, ovarian and prostate, tumors
	MET	AMG 102, METMAB and SCH 900105	Breast, ovary and lung tumors
	IGF1R	AVE1642, IMC-A12, MK-0646, R1507 and CP 751871	Glioma, lung, breast, head and neck, prostate and thyroid cancer
	EPHA3	KB004 and IIIA4	Lung, kidney and colon tumors, melanoma, glioma and haematological malignancies
	TRAILR1	Mapatumumab (HGS-ETR1)	Colon, lung and pancreas tumors and haematological malignancies
	TRAILR2	HGS-ETR2 and CS-1008	
	RANKL	Denosumab	Prostate cancer and bone metastases
Stromal and extracellular matrix antigens	FAP	Sibrotuzumab and F19	Colon, breast, lung, pancreas, and head and neck tumours
	Tenascin	81C6	Glioma, breast and prostate tumors

CAIX, carbonic anhydrase IX; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; EPHA3, ephrin Receptor A3; FAP, fibroblast activation protein; gpA33, glycoprotein A33; IGF1R, insulin-like growth factor 1 receptor; Le^{y}, Lewis Y antigen; mAbs, monoclonal antibodies; PSMA, prostate-specific membrane antigen; RANKL, receptor activator of nuclear factor-kB ligand; TAG-72, tumor-associated glycoprotein 72; TRAILR, tumor necrosis factor-related apoptosis-inducing ligand receptor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

3 CLINICAL APPLICATIONS: IN INFECTIOUS DISEASES

As of recent years, at least 20 neutralizing monoclonal antibodies (mAbs) medicines are now in late-stage clinical studies or have been permitted for use in treating a variety of transmittable diseases, including influenza viruses, Ebola, respiratory syncytial viruses (RSV), and others (Wrapp, 2020). Targeting SARS-CoV-2 as the causative agent of COVID-19 has been a hot research topic since the pandemic. Monoclonal antibodies against SARS-CoV-2 have the potential to be employed for both infection prevention and treatment. SARS-CoV and MERS-CoV monoclonal antibodies have already been shown to be beneficial in animal models (Taylor, 2021).

There were no approved COVID-19 preventative vaccinations or therapies when the outbreak began. Blocking mAbs are among the finest candidates for neutralizing viral infection due to their exceptional antigen specificity. The researchers aimed to locate and manufacture blocking monoclonal antibodies from memory B-cell libraries of newly cured individuals to counteract the virus from entering healthy host cells. Similar to SARS-CoV, which caused an outbreak of SARS in 2002-2004, SARS-CoV-2 also uses a high-glucose homologous trimer spike (S) protein to bind to receptors and virus entry (Zhou, 2020). Two subunits, S1 and S2, constitute the S protein of SARS-CoV-2 and undergo drastic conformational changes that expose the critical residues of the receptor-binding domain (RBD) binding to the receptor, thereby enabling the binding of the host cell receptor human angiotensin-converting enzyme 2 (hACE2), which SARS-CoV and SARS-CoV-2 share. S protein is metastable, and RBD binding to the hACE2 receptor may promote S2-mediated viral host membrane blending and viral entrance, as S1 protein is detached from S2 protein. RBD is an exposed mark for neutralizing antibodies because it is involved in SARS-CoV-2 access into healthy host cells. An S1-targeting monoclonal antibody made from genetically modified mice immunized with the expression of human Ig differential chains has recently been shown to counterbalance SARS-CoV-2 and SARS-CoV contagion; it is, however, neutral of the RBD-HACE2 connection being blocked due to unknown reasons (Cohen, 2021).

The researchers primarily looked for antibodies to SARS-CoV-2 S1 protein IgG in blood serum from individuals who had lately survived from COVID-19. Using an enzyme-linked immunosorbent assay (ELISA), they discovered that the majority of the 26 recovered COVID-19 patients were capable of

producing a high quantity of SARS-CoV-2 S1-specific IgG antibodies. Relatively low anti-S1 IgG antibody responses were only found in 3 patients. They also discovered that SARS-CoV-2 IgG antibodies explicit to RBD were detected in all of the affected individuals. Researchers successfully manufactured two human neutralizing monoclonal antibodies utilizing SARS-CoV-2 RBD-specific memory B cells obtained from patients who recovered from the disease. These two monoclonal antibodies attach to SARS-CoV-2 RBD and disrupt the connection between SARS-CoV-2 RBD and the hACE2 receptor, thereby neutralizing SARS-CoV-2 S protein pseudovirus contamination (Chen, 2020).

Passive vaccination uses antigen-specific monoclonal or polyclonal antibodies derived from animal or human blood sources. Two significant uncertainties in passive immunization may also exist in neutralizing monoclonal antibodies: first, whether they could potentially affect long-term physical immunity as prevention or treatment. It is unclear if the existence of circulating neutralizing monoclonal antibodies affects protective immunity via infection memory or vaccination, given the high doses used and antibody half-lives. Rodent and primate models of RSV infection suggest that passive antibody transfer does reduce the development of the recipient's human immunity. Nevertheless, long-term memory is still adequate to defend the host from second-time reinfection, thanks to the presence of an undamaged T-cell memory chamber (Marovich, 2020). Second, will the mutation of resistant virus affect the therapeutic effectiveness? Clinical evidence suggests that SARS-CoV-2 spikes (S) protein mutations can evade polyclonal serum, resulting in lower convalescent plasma neutralization activity against particular viral variants. As a result, monoclonal antibodies may require a mixture therapy of monoclonal antibodies to boost clinical efficacy and prevent treatment failure in the future, depending on the source of infection and the targeted epitope (Crowe, 2001).

It is essential to notice that Taylor also proposed that "due to the vast number of persons sick and the high intensity of virus transmission among humans, the COVID-19 pandemic poses a bigger risk of escape mutations than the Ebola outbreak did", which was later approved by the case of Delta variant and Omicron variant.

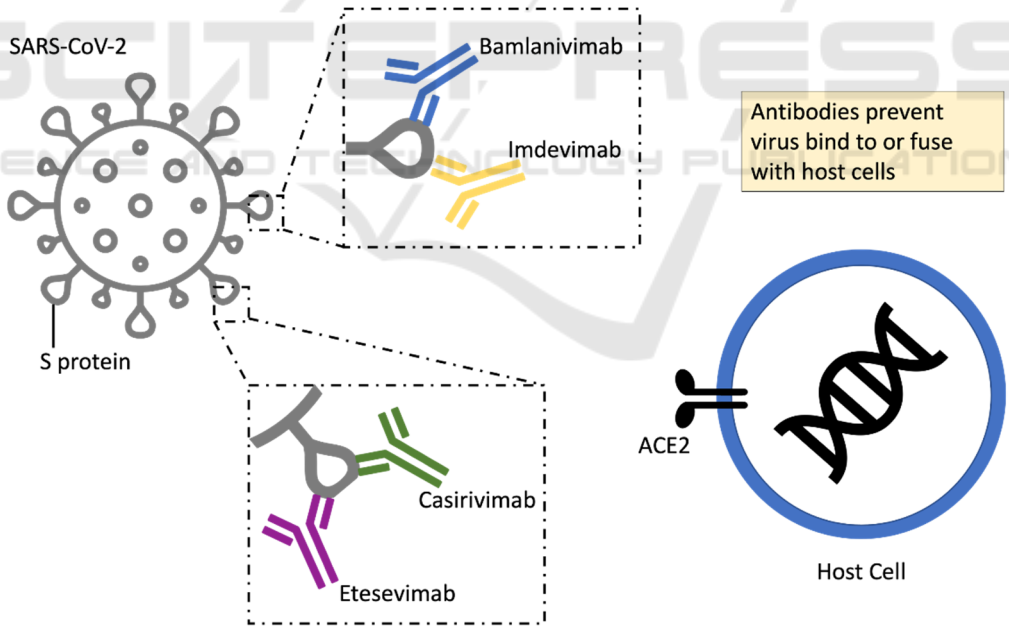

Figure 1: Neutralizing mAbs inhibit SARS-CoV-2 by binding to the spike (S) protein.

RT-PCR as a proxy for viral infection or viral replication scale for SARS-CoV-2. According to the findings, the monoclonal antibody serves as an antiviral agent, reducing viral load in the nasopharynx. The effect of monoclonal antibodies and other medications on viral load could be a crucial criterion for designing therapies to treat early COVID-19 infections (Crowe, 2001).

An effective vaccine is necessary to cure the epidemic. The functional and active evaluation of several COVID-19 vaccine candidates is expected to shorten the vaccine development process from years

or even decades to 12 to 18 months. Monoclonal antibodies offer another way to prevent COVID-19. Passive monoclonal antibody infusion as a prophylactic treatment before or after exposure provides immediate protection from an infection that can last weeks or even months. To extend the possible protection, the new technique that can modify the antibody Fc region to extend the half-life of the monoclonal antibody by up to several months, depending on the concentration of the desired monoclonal antibody. Even after an uninfected person has been vaccinated, the benefits of passive immunization can be seen during the period it will take for the immune system to establish an immune response using the mRNA information carried by the vaccine. Neutralizing monoclonal antibodies is especially helpful in health care facilities, homes, and kindergartens where people with low immunity gather because outbreaks are common and devastating. During epidemics, nursing home patients are given monoclonal antibodies. They may help slow the disease's course during early infections that go untreated. Furthermore, the elderly and those with underlying problems may not have a sturdy protective response to vaccination, necessitating the use of monoclonal antibodies to give protection (Taylor, 2021).

4 CONCLUSION

The attention of therapeutic monoclonal antibodies is increasing year by year. Their high specificity for antigen can offer various applicable medical treatments, and the emergence of molecularly targeted drugs has made the growth of a new generation of therapeutic medications possible. In this review paper, human monoclonal antibodies are introduced as homologous antibodies produced by single clone hybridoma cells, produced by the proliferation and differentiation of B cells. The clinical application of mAb therapies can be separated into two main categories, cancer treatment, and infectious diseases medicine. The most successful class of antibodies targeting the ERBB family is the usage of therapeutic mAbs on patients with solid tumors, and one of the examples in breast cancer. Focusing on treating infectious diseases, the efficacy of mAb therapies targeting SARS-CoV-2 was discussed as the causative agent of Covid-19 and its advantage compared to CPT. In future studies of mAb therapies targeting SARS-CoV-2, several combination therapies are under clinical trials, like bamlanivimab and etesevimab, which are expected to overcome or prevent antibody resistance.

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