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Review

Monoclonal War: The Antibody Arsenal and Targets for Expanded Application

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Abstract: Advancements in sequencing and screening technology have made monoclonal antibodies more accessible, cost-effective, and precise. These drugs effectively target pathogens and cancer cells and even regulate metabolic pathways by focusing on specific intermediates. Monoclonal antibodies play a key role in mitigating a rise in occupation-related cancers, neurodegenerative disorders, and multidrug-resistant organisms. Here, we review the origins, mechanisms, and applications of this important drug class and explore future avenues for research.

Keywords: monoclonal antibody; immunometabolomics; antibody drug conjugates; immunotherapy

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1. Introduction

Monoclonal antibodies (mABs) were first developed using specialized mouse cells called hybridoma, which produce large numbers of identical immunoglobulins. The affinity of these antibodies for the desired antitope could be selectively enhanced through manipulation. The architects of this method suggested that these antibodies would have many clinical and therapeutic applications, and they won the Nobel Prize in Physiology and Medicine in 1984. However, progress was slow due to issues with non-specific interactions. Advancements in genetic engineering in the 1990s allowed for changes to be made to the primary sequence of mABs, thereby producing effective targeted therapy. Further manipulation reduced hypersensitivity reactions and long-term toxicity. Once these hurdles were cleared, several mAB treatments were quickly developed and approved by the FDA. The novel mAB treatments displayed specificity and a reduction in off-target effects. They bypassed the cytochrome P450 system and thus had fewer interactions with other medications. These attributes made mABs more attractive than small biologics, an alternative drug treatment that was also in expansion. Muromonab was approved in 1986 as the first mAB; it was used to treat graft rejection, but it displayed significant toxicity typical of the early mAB therapies. This class represents a major proportion of new drugs that are both in development and approved each year.

2. Methods

A comprehensive literature review was conducted to review the subject of monoclonal antibody therapies. Relevant Pubmed® articles published within the last five years with a Q1 quartile score were included in the analysis.

3. The Biological Role of Antibodies in the Normal Human Immune Response

Antigens are proteins found on the surface of cells, viruses, and non-living agents; they may be toxins, chemicals, or drugs that are foreign to the body. These moieties give

every non-self-agent a specific marker. Antibodies are immunoglobulins produced by B-cell lymphocytes following exposure to an antigen (Figure 1). The body stores the "codes" to these antibodies—an immunologic memory—to produce a quick immune response during the following encounter with that pathogen.

The immune system has two parts that work in unison to eliminate foreign antigens. The innate immune response is the initial, non-specific defense against harmful foreign substances. It is inherent, natural, and programmed from birth. Innate immunity involves constitutively present cells, like macrophages and natural killer (NK) cells, which rapidly eliminate antigens. In contrast, the adaptive immune response requires time to generate specific cells that target unwanted substances.

The adaptive immune response is an antibody-mediated process in which T-cells activate B-cells to produce millions of specific antibodies to neutralize antigens. These antibodies can react at any physiological location including the skin, internal organs, and mucous membranes [1].

Manipulation of this intricate inflammatory system allows for antibody therapies with wide applications. Early detection of a newly encountered pathogen can prevent an infection for which the host lacks immunity. Antibodies can be administered to immunocompromised individuals whose bodies are not producing enough of their own [2]. They can also be engineered to fight malicious cells in conditions like cancer and autoimmune disease [3].

Antibodies exert their neutralizing effects by inducing conformational changes that hinder the binding of their target antigen to coreceptors or growth factors. An antibody molecule consists of four polypeptides, including two identical heavy chains and two identical light chains, forming a Y-shaped structure with three functional domains. Specifically, two antigen-binding fragments (Fabs) bind to a specific molecular target, while a crystallizable fragment (Fc) binds to Fc receptors, facilitating biological activity. Variations in these regions govern the characteristics of the antibody–antigen interaction, such as the specificity, affinity, and overall activating or inhibitory effects [4].

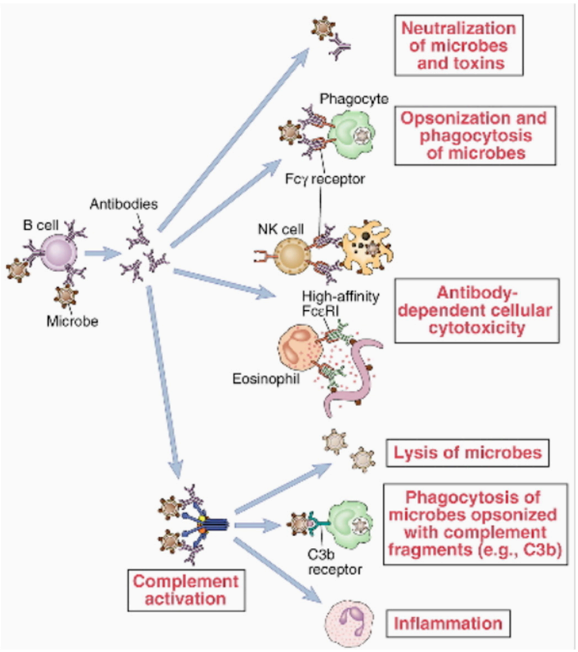

Figure 1. Actions of endogenous antibodies [5] Immune activation by pathogenic stimulus causes B-cells to produce antibodies. These circulate in blood and lymph to find the pathogen at any location in the body. Antibodies can directly neutralize the target, mark it for phagocytosis, or activate complement elements that likewise bind and restrict the pathogen or mark it for destruction.

A mechanistic understanding of antibody affinity is necessary to exploit interactions with viral invasive proteins and bacterial toxins as well as endogenously produced harmful

stimuli [6]. For example, streptococcus has developed the ability to bind antibodies at their Fc regions, impeding their interactions with receptors. A bacterial factor called Protein L demonstrates this capability and can bind to antibodies of all subclasses. These bacterial factors have proven valuable in affinity-based antibody purification, a highly efficient method that has streamlined therapeutic development [4].

Subtle considerations define whether the immunogenic effect of antibody binding will have a protective response or result in harmful inflammation. A promising treatment for IgA nephropathy involves an anti-APRIL immune response- an important signaling molecule leading to the production of aberrant IgA1 in the main pathogenesis pathway. By stimulating controlled immune inhibition of the molecule, the more devastating autoimmune response that occurs as a result of the disease is mitigated [7].

4. Production of mABs and Therapeutic Dynamics

Monoclonal antibodies were first engineered using mouse antibodies, followed by human/mouse chimeric formulations, and finally, fully humanized antibodies in the present. Drugs from these stages are identified by the suffixes: -zumAB, -ximAB, and -umAB, respectively. Examples include TranstuzimAB, which is used to treat breast cancer, and RituximAB, a therapy for B-cell non-Hodgkin's lymphoma and other inflammatory disorders. A new naming system was employed in 2021 to avoid confusion as the number of mAB drugs has rapidly expanded [8]. A comprehensive database of mAB and related therapies, some of which we will discuss, called the IMGT/mAB-DB was started in 2010 and is currently available at https://www.imgt.org/mAb-DB/ [9] (accessed on 11 September 2023).

Generating antibodies that can be programmed for a specific target was the next logical step (Figure 2). This targeted therapy proved useful in targeting cancer cells in solid and well-defined tumors as many cancers have monoclonal cell lines. Other conditions treated with mABs include inflammatory bowel disease and autoimmune diseases like rheumatoid arthritis. More applications of mABs are being explored as genetic engineering techniques improve [10]. Today's mABs are mass-produced using recombinant DNA techniques and optimized expression systems [6,11]. High-throughput screening and computerized assays have allowed for research into new applications to be conducted more rapidly than ever before [11,12]. Furthermore, the integration of computational pharmacology and quality by design approaches that take the scaling up process Into consideration from drug conception is leading to better outcomes for specificity and the cost of market products [13].

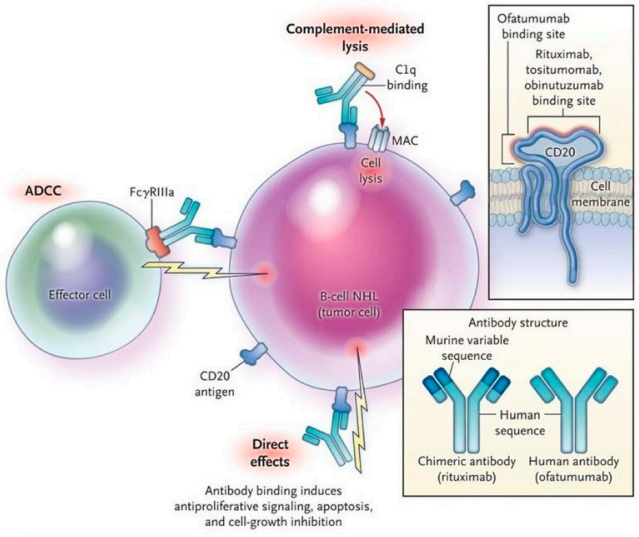

Figure 2. Monoclonal antibodies utilized for targeted therapy [14] Antibodies specific for cell surface markers like the tumor-specific antigen CD20 can be created. Binding of these to the target tumor cells makes these recognizable by the immune system mediating destruction. mAB binding also has direct effects on cell signaling that inhibit tumor growth.

One of the many mechanisms of action of mABs is their direct binding to a pathogen and preventing it from entering host cells via steric hindrance. A similar mechanism allows mABs to block cellular signaling molecules, which disrupts replication and anti-apoptotic factors in various cancers [15]. While this small disruption may hinder growth, the critical response is the further interaction of the mAB Fc region with host immune cells, which causes major counteraction to malignant cells [16]. Phagocytes, dendritic cells, macrophages, and neutrophils are all recruited to enact a feed-forward response with further antigen presentation and cytokine production. The Fc interaction also recruits natural killer cells and increases opsonization. Lastly, the activity involving the Fc region results in the formation of the membrane attack complex (MAC). The Fc–host interaction has multiple innate effects resulting in targeted destruction as well as local and systemic responses. Margetuximab, a derivative of Trastuzumab approved by the FDA in 2020 for treating adult metastatic HER2-positive breast cancer, is one of several drugs that exploit alterations in the Fc region [17]. Advancements in genetic engineering have produced drugs like these that exploit small mutations and lead to large pharmacodynamic variability without significantly altering the broader chemistry [18]. Precise changes in pharmacodynamics can thus be made without requiring a large shift in protocol or existing manufacturing practices [19]. Proteomic and gene-editing technologies allowing for glycol-moiety addition or the induction of point mutations at the Fc region could be an avenue for producing more personalized treatments as well as helping overcome a bottleneck leading to a new source of highly specific multimodal drugs.

5. Examples of Antibody Treatment Mechanisms Applied in Current Disease

The first applications of mABs were in cancer treatment, where they were originally used as a diagnostic tool before being established as an effective pharmaceutical. RituximAB was approved in 1997 as the first antitumor mAB [20]. Researchers continue to investigate the mechanisms behind these treatments to expand their application and effectiveness. Unconjugated mAB therapies for cancer are based on the same principle of stimulation of immune effector processes. The effect of the mABs is not primarily through interaction with tumor cells, but rather through the involvement of secondary processes that activate the host's innate immune response and complement activity. This is a departure from the previous theory that mABs directly inhibited growth factor signaling and that future development should improve the host–mAB interaction by strengthening the Fc–FcR interaction. However, there is still some mechanistic variance that must be examined.

A cancer that exhibits a well-defined monogenic cell line along with a mutated protein is a favorable situation [16]. This mutated surface molecule differs greatly from any protein found in healthy cells and is thus a favorable therapeutic target. Human epidermal growth factor receptor 2 (HER2) breast cancer is an example that offers an excellent response to mAB therapy. However, this is an isolated case; in general, tumor-associated proteins are evasive and hard to distinguish, thus extensive studies into the pharmacodynamics of any agent are required to determine off-target toxicity [21]. Unfortunately, few proteins and immune markers are known to be large enough mAB targets, hindering lead-based design and the discovery of novel pathways. Improvements in mAB specificity, based on new developmental techniques, are leading to expanded potential in high-throughput screening (HTS) and targeted approaches. A rapidly developing understanding of system biology has also contributed to a design approach utilizing computational and data analytic methods for focused screening; a departure from classic library screening [22,23].

Another application of mABs has been in fighting infections [24]. Many bacteria produce exotoxins, which are easily isolated and combatted. The mABs bind bacterial toxins in vivo, decrease bacterial virulence, and reduce clinical symptoms. Current research is underway to target the highly conserved bacterial membrane proteins. There has also been a growing interest in using mABs to target hepatitis B virus (HBV) [25] because of their potential advantage over existing therapies for HBV. Monoclonal antibodies neutralize HBV by targeting key epitopes on the surface of the virus that are essential for its

infectivity [25,26]. Thus, mABs can help prevent it from infecting new cells and spreading throughout the body. This is in contrast to existing HBV therapies, which primarily focus on suppressing viral replication via genetic alteration rather than preventing spread via a physiologic response [27]. Monoclonal antibodies may also induce other immune responses against HBV. They are known to trigger the production of other antibodies that bind and clear the virus from infected cells. They can activate complement-mediated cytotoxicity, which leads to the destruction of infected cells. In addition, mABs can also stimulate phagocytosis, whereby infected cells are engulfed and destroyed by immune cells. Clinical trials have shown that mABs are safe and well tolerated in humans, can significantly reduce viral load, and have even induced long-term remission from HBV infection in a few cases [28]. The above mechanisms suggest that mABs may one day play a role in the treatment of HBV; however, more clinical research is needed.

6. Advances in Development and Emerging Treatments

Cancer is a devastating disease that affects millions of people worldwide. The currently available treatment options are associated with severe side effects and poor efficacy. There is a great need for more effective and less toxic cancer therapeutics; antibody–drug conjugates (ADCs) are a promising new class of cancer therapeutics in terms of safety and efficacy (Figure 3) [29]. The ADC is a human monoclonal antibody conjugated with a cytotoxic small molecule payload via a linker. It shows improved efficacy, reduced toxicity, and effective pharmacokinetics compared to other cancer drugs. The ADC is administered into the blood, where the antibody component binds to cancer-specific surface antigens. Endocytosis of the ADC releases the cytotoxic payload, which disrupts DNA regulatory proteins and causes cancer cell death [30].

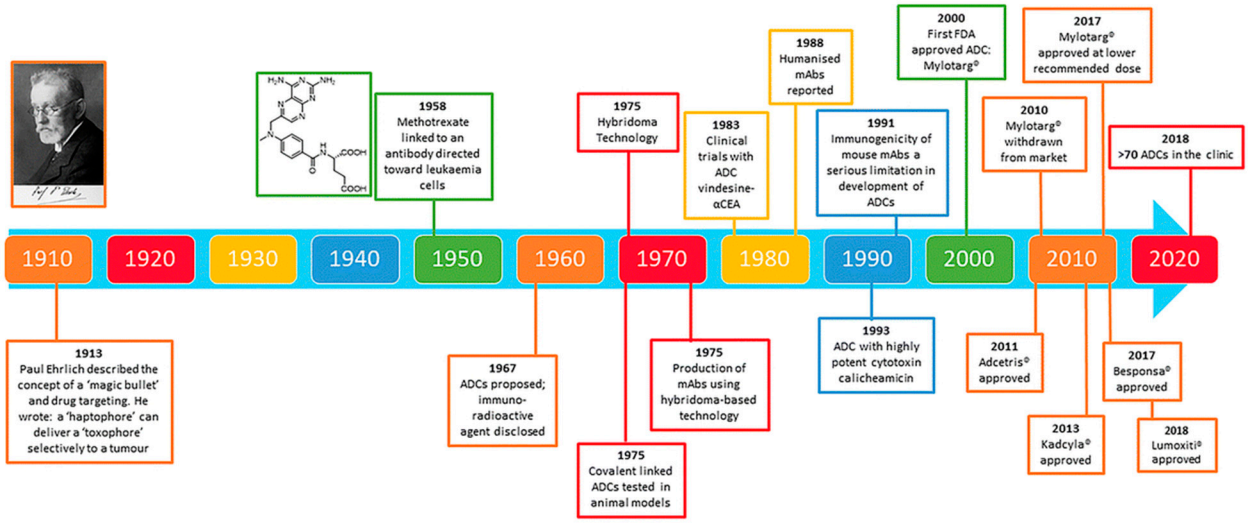

Figure 3. Timeline of mAB and ADC development [31].

A challenge in designing ADCs is the trade-off between antigen affinity and tumor penetration. Antigen affinity ensures that the ADC binds specifically to cancer cells. High antigen affinity can lead to poor tumor penetration as the cells do not internalize the ADC and fall short of the target effector. Utilizing site-specific conjugation for constructing homogeneous ADCs improves their design. This technology uses an enzyme to attach the antibody and payload components, resulting in a more stable and efficient ADC [11,32]. Consequently, the antibody–drug conjugate is a promising cancer therapy that can potentially improve clinical outcomes.

Gemtuzumab ozogamicin, Brentuximab vedotin, Inotuzumab ozogamicin, Moxetumomab pasudotox, and Polatuzumab vedotin are examples of antibody–drug conjugates (ADCs) that have successfully received approval for the treatment of various hematological malignancies [33]. These ADCs have demonstrated remarkable efficacy in targeting specific

antigens associated with different blood cancers. Gemtuzumab ozogamicin targets the CD33 receptor and is approved for relapsed or refractory acute myeloid leukemia (AML). Brentuximab vedotin targets the CD30 receptor and is approved for treating Hodgkin lymphoma and systemic anaplastic large-cell lymphoma. Inotuzumab ozogamicin targets the CD22 receptor and is approved for relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) [34]. These ADCs have significantly improved the treatment landscape for hematological malignancies by providing targeted therapies with enhanced efficacy and reduced toxicity compared to the traditional treatment approaches [35].

7. Obstacles in Development

New technologies are being used to further explore single primary B-cell retrieval, a method used to identify antigen-specific mABs [36]. Considerable obstacles still need to be overcome to simplify this process and make further progress. It takes a significant amount of time to create hybridoma cells, harvest their antibodies, and identify the rare antibody binders used in this technique [37]. Some methods are limited by functional barriers, such as the high cost of screening for antibodies with high throughput [27,38]. Other methods are prone to technical shortcomings. For example, there is a current shortage of fluorescently labeled antigens for B-cell sorting, with low-quality products displaying low affinity [39]. Maintenance issues also dampen the effectiveness of this treatment due to the naturally short half-lives of the monoclonal antibody proteins; they typically range between a few hours and a few days. Preservation includes keeping the mAB proteins stable during manufacturing, transport, and storage, when they are most prone to aggregation and denaturation [40].

Monoclonal antibodies for cancer therapy are commonly used to selectively inhibit specific molecules involved in tumor growth. The efficacy of mABs alone may be limited when relapses occur, and the cancer cells have developed resistance to treatment. Researchers have explored Antibody-Dependent Cell Cytotoxicity (ADCC) as an additional therapeutic strategy to overcome the challenge of resistance. ADCC involves activating NK cells, a type of lymphoid cell that plays a vital role in immune surveillance against cancer cells. NK cells can recognize and eliminate metastatic growth by inducing direct cell death [41]. Combining NK cell adoptive immunotherapy with mAbs has emerged as a promising approach to overcoming treatment resistance [42].

8. Autoimmune Neuropathies as an Example of the Challenges in the Current Research

Autoimmune neuropathies are a group of disorders characterized by damage to the nervous system due to an overactive immune response [43]. These disorders affect various neuronal cell lines, localize to both the autonomic and peripheral nervous systems, and can present with psychological symptoms, motor symptoms, or a combination of symptoms. Variable symptoms can make them hard to diagnose or differentiate from neurological tumors. However, they are also highly associated with neoplasms. Examples include Guillain–Barre syndrome, which classically presents as ascending paralysis, and multiple sclerosis, which often presents with impaired coordination and eventual loss of movement control [44]. Autoantibody detection along with CSF analysis are key diagnostic tools [45]. These conditions are treated with exogenous high-dose intravenous immunoglobulin (IVIg) therapy, but there is an increasing shortage of IVIg worldwide [46]. B-cell-depleting monoclonal antibodies like rituximab have shown promise in treating some forms of autoimmune neuropathy, but these drugs are not always effective or well tolerated [47].

Recent evidence supports the involvement of the complement system in the development of chronic autoimmune neuropathies, suggesting that therapies targeting the complement system could effectively address these conditions. Of note, eculizumab has been shown to remarkably improve symptoms and outcomes in patients with myasthenia gravis [48]. Rituximab is under investigation as a therapeutic option for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Preliminary findings suggest it is a potential modulator of the complement cascade and may halt disease progression [49,50].

New Fc engineering techniques are in process that may improve the efficacy of monoclonal antibody drugs [20,51]. Bruton's tyrosine kinase (BTK) inhibitors are a new class that has shown promise in treating B-cell-related diseases. Monoclonal antibodies targeting Fcγ receptors are also in production as potential treatments for autoimmune neuropathies. There is a need for more effective and tolerable therapies for autoimmune neuropathies, as well as further clinical research on combined therapies (Figure 4) [52].

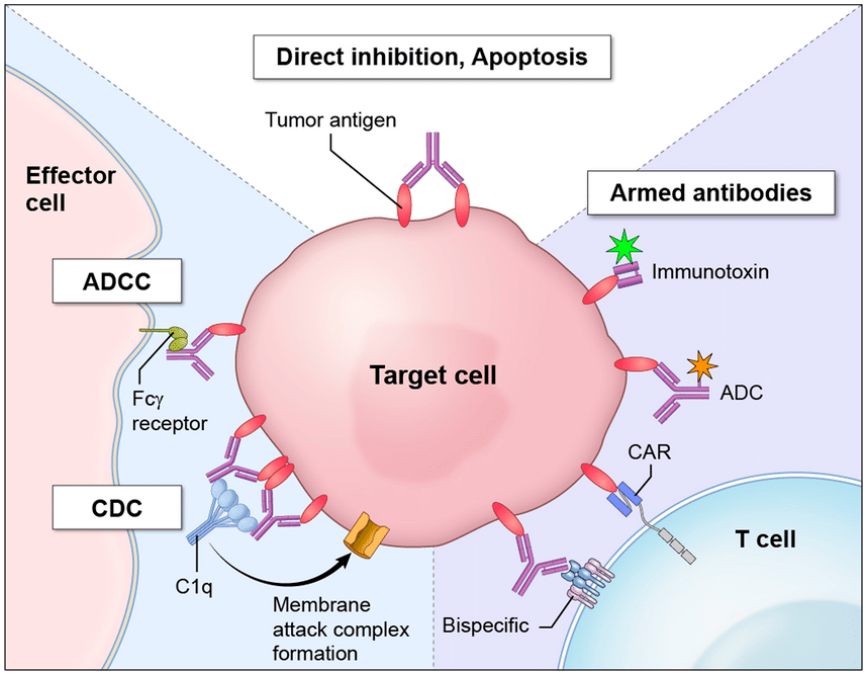

Figure 4. Various Strategies for Producing mAB Pharmacologic Effects [53].

9. Addressing Challenges and Future Directions: mABs as the Therapeutic Swiss-Army Knife

The development of mAbs presents specific challenges, particularly for high-concentration mAbs administered via subcutaneous injection. The elevated protein concentration in these mAbs poses formulation challenges due to the propensity for protein–protein interactions, leading to increased viscosity and self-aggregation [54]. These factors can affect the long-term stability and injectability of the drug [55]. Kinetic studies and modeling data enable the optimization of dosage formulation and play a crucial role in understanding how aggregation may occur during storage [56]. Achieving a therapy with the desired effect that is also practical in storage and administration is a complex engineering task requiring careful consideration for each specific therapy [57]. These challenges contribute to the extended timelines observed for the development of many therapies in the field.

Different routes of administration and doses of mABs are under examination in order to target specific sites in the body [58]. Therapies that can utilize cellular machinery to reach intracellular transport are of particular interest and can more effectively reach the brain [59]. Current therapies that target TAU protein and a-synuclein are being re-applied to treat Parkinson's and Alzheimer's diseases; however, the dose required to reach therapeutic levels is challenging in terms of cost and availability [59,60]. Bispecific antibodies with an affinity not only for the therapeutic target but also for transporters spanning the brain parenchyma, such as transferrin receptors, can serve as a "trojan horse" to deliver the construct [61]. By this mechanism, preliminary studies showed significantly increased levels of these antibodies in the brain versus antibodies targeting only the endpoint receptor [4,62].

Monoclonal antibodies are known to impact pharmacodynamics by engaging specific cellular pathways despite not exhibiting significant interactions with pharmaceutical compounds. This disruption of therapeutic effects can cause the formation of Anti-Drug Antibodies (ADAs) which directly target the metabolic pathways of the drug and result in

potentially harmful poly–drug interactions [21]. While mAb therapies are unlikely to affect a patient's other medications, there is the potential for significant and adverse immunogenic reactions while using other medications to treat coexisting conditions that are similar to or related to the targeted disease entity. The initially remarkable properties of mAbs can exhibit drastically altered interactions in some instances. ADCs and combined therapies hold promise for multifactorial conditions, but challenges emerge with the additional layers of pharmacodynamic complexity [63].

The ADAs, which result from the use of mABs, are currently being explored as a therapy for substance use disorders. A mAB therapy for treating methamphetamine addiction was the first avenue researched with the development of biosynthetic chimeric mouse/human antibodies against methamphetamine [64]. The bulky antibody binds the illicit substance and blocks it from crossing the blood–brain barrier, thereby preventing the psychoactive effects and promoting its excretion. Test subjects given a prophylactic antibody had a lasting aversion to the drug, which led to a decline in relapses. Higher therapeutic adherence was achieved as fewer euphoric effects were experienced when using methamphetamine [65]. Monoclonal antibody therapy has been highlighted as having a potential role in fighting the American opioid crisis [66].

Developing antibodies targeting and disabling opioid receptors has been proposed as a strategy to prevent opioid use and reduce the risk of overdoses [67]. Structure-based techniques serve as the current gold standard in targeted drug design. Researchers design small molecules that enhance the binding of desired downstream signaling proteins while inhibiting the binding of proteins associated with adverse effects by utilizing high-resolution receptor structures [68]. Creating "designer drugs" that enhance g-protein binding to the mu-opioid receptor while inhibiting beta-arrestin binding is believed to enable the analgesic effects of opioids without the risk of nervous and respiratory system depression [69]. These promising techniques rely heavily on structural methodologies like X-ray crystallography and cryogenic electron microscopy (cryo-EM), which are time-consuming, expensive, and require extensive manpower [70]. Alternatively, employing high-throughput methods to identify mAbs that achieve similar effects as structurally designed drugs may offer a faster and more accessible solution to addressing the challenges of substance use disorder and overdose.

Researchers at the University of Cincinnati are developing a mAb as a potential treatment for cocaine use disorder [71]. Effective treatments to reduce urges, withdrawal symptoms, and dependency are currently lacking for this condition. The mAb-based therapy aims to mitigate addiction by sequestering cocaine metabolites and preventing them from reaching the bloodstream even if use of the substance is continued [72]. The user fulfills the psychological habit, but the body's dependence subsides without a physical effect [73]; research showed this led to cessation of the drug in a majority of trials. Sequestering the drug also inhibits its harmful, oxidizing effects on the cardiovascular and central nervous systems. While these therapies addressing the action of various narcotics are similar in their desired outcome, prevention of drug stimulus leading to cessation, they represent diverse strategies in mAB therapeutic development and display the all-in-one quality of mAB applicability.

Monoclonal and therapeutic antibodies are becoming an increasingly integral part of network pharmaceuticals. Such therapies combine technologies like genetic vaccines with nanoliposome delivery constructs for immunomodulatory responses [74]. Monoclonal antibodies can act as a targeting system when conjugated to the surface of a delivery platform like a lipid nanoparticle; they instill properties to the construct such as evasion of improper immune interactions and greater recognition and uptake at the target site [75]. A passenger vehicle can serve as an analogy of how these sought-after "magic bullet" pharmaceuticals might function. If an mRNA drug cargo was the passenger and a nanoparticle carrier the vehicle, conjugated mABs would be the navigational system. Conversely, new mRNA therapeutics can code for particular mABs, leading to their in vivo production at desired target sites [76]. The development of such therapeutics is gaining research focus as in silico

molecular modeling and Physiologically-Based Pharmacokinetic (PBPK) prediction become increasingly accurate and an essential component of the developmental pipeline.

10. Conclusions

Monoclonal antibodies act as potent modulators of biological pathways throughout the body. Looking ahead, there is the possibility of developing mAb-based vaccines like constructs capable of sequestering and eliminating harmful elements upon entry into the body. Further advancements in metabolomics look to develop mAb formulations that enhance the pharmacological effects of drugs by complementing their mechanisms. Progress is needed to improve the efficiency of producing mAbs, reduce costs, enhance specificity, and gain a deeper understanding of their interaction pathways. Exploring the development of bifunctional mAbs with multiple targets represents a promising next step as it could enhance existing applications and expand the therapeutic potential for new diseases [77]. The application of multi-omic platforms in analyzing multifactorial pathologies presents an integrative approach that offers a fresh perspective on the potential of mAB therapies and a broader understanding of fundamental biologic mechanisms.

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