Chapter 5

Biotechnological Therapeutics: Advances and Future Outlook

Pakize Canturk[1]

Abstract

In today's world where current medical treatments have reached their peak, many highly effective drugs have been developed with various technologies and unfortunately, despite the development of sophisticated drugs, there are still incurable diseases in the world. However, due to the lack of sufficient funds on a global scale and the inability to access treatments due to the inadequacy of various health policies, many patients cannot be provided with the magnificent fountain of life called "treatment". To some extent, even the limited focus area on developing new scientific perspectives can be compatible with this sad result. The development of biotechnological drugs and their prominent applications in current treatments are increasingly receiving investment and are considered worthy of attention. In addition to the traditional production of many drugs used in treatment, technological developments inevitably change the fate of drug development. In this section, by giving a little favor, examples were presented where biotechnological drugs seem to have won the war against conventional drugs.

1. Introduction

Many conventional drugs have been developed and used in the treatment of various diseases, but some of these diseases are so challenging that since no effective drug has yet been found for their treatment, we have long since chosen to resort to various alternative drug development methods. In fact, as the treatment of incurable diseases becomes more complex, we expect more efficiency from biotechnological drug development methods.

1 Asst. Prof., Sivas Cumhuriyet University, Faculty of Pharmacy, Department of Pharmaceutical Biotechnology, Sivas, Turkiye, E-mail: pcanturk@cumhuriyet.edu.tr, ORCID: 0000-0001-8623-784X

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Biotechnological therapeutics can be broadly classified into recombinant protein–based therapeutics, including growth factors, hormones, enzymes, and cytokines; monoclonal antibodies (mAbs) and antibody derivatives such as humanized, fully human, and bispecific antibodies as well as antibody-drug conjugates; nucleic acid-based therapies encompassing mRNA therapeutics, siRNA and antisense oligonucleotides, and CRISPR-based platforms; cell and gene therapies including CAR-T cell therapies and gene replacement or gene-editing approaches; and vaccines developed using biotechnological methods, such as mRNA vaccines (Crommelin et al., 2013; Dey et al., 2024). Many of these biotechnological therapeutics can be considered groundbreaking applications in their own right. For example, monoclonal antibody–based therapeutics and their derivatives demonstrate how recombinant and engineered proteins can be translated into effective, rapidly deployable treatment options, particularly in disease areas where conventional pharmacological approaches are insufficient. Likewise, CRISPR-based platforms-within the broader category of nucleic acid–based and gene-editing therapies-highlight the potential of highly precise, target-specific interventions that extend the therapeutic landscape beyond traditional modalities (Huber et al., 2026; Rajewsky, 2019).

2. Current Advances in Biotechnological Therapeutics

2.1. Monoclonal Antibodies

Monoclonal antibodies (mAbs) have emerged as highly effective therapeutic agents for the treatment and management of a wide range of chronic diseases, including cancer, cardiovascular disorders, immune-mediated conditions, and neurological diseases (Colwill et al., 2025; Lee et al., 2025; Saha et al., 2025). MAbs can also target cytotoxic small molecules (e.g., ADCs) and can affect the immune system by either strengthening or suppressing it (Mould & Meibohm, 2016). Monoclonal antibodies represent one of the leading modalities in biotechnological drug development, with multiple factors influencing the design and optimization of their production processes. The development of mAb manufacturing processes must address several critical control parameters, including product purity, stability, scalability, compatibility with large-scale manufacturing protocols, and reliable raw material supply, all of which contribute substantially to overall production costs. Aggregation represents a critical degradation pathway for therapeutic proteins such as antibodies and remains a central challenge in antibody developability and formulation. Advanced molecular simulation approaches, when accurately interpreted, enable the identification of

aggregation-prone regions and physicochemical liabilities that can compromise stability. Furthermore, the increasing resolution of structure-based simulation and interaction analyses supports rational antibody engineering, facilitating improved developability profiles while enhancing target binding and functional performance. Moreover, practical limitations-such as expression system performance and cost constraints-necessitate continuous refinement of laboratory and industrial strategies to achieve efficient and optimal mAb production (Chennamsetty et al., 2009; Shukla et al., 2017).

The number of monoclonal antibodies (mAbs) has been steadily increasing in recent years; as of 2021, 118 therapeutic monoclonal antibodies (mAbs) have been approved for the European market, with over 294 mAbs reported to have been approved in total (Chiu & Gilliland, 2016; Gogesch et al., 2021). The use of monoclonal antibodies (mAbs) and other biological drugs in the treatment of many diseases is constrained by several factors, one of which is the limited incorporation of patients' genetic profiles into treatment decision-making. In this context, prioritizing therapies tailored to individual genetic characteristics has been proposed as a more effective strategy. Accordingly, pharmacogenomics holds significant potential to inform mAb dose optimization, reduce interpatient variability, and substantially influence therapeutic efficacy and drug response (Lee et al., 2025; Okusanya et al., 2025).

Monoclonal antibodies (mAbs) constitute one of the largest and most extensively utilized classes of biological therapeutics across a broad range of clinical indications. The antigen-binding sites of mAbs are formed by the variable domains of the heavy (HC) and light (LC) chains, which collectively determine antibody specificity and binding affinity. The Y-shaped constant region of the antibody, referred to as the Fc (fragment crystallizable) domain, is composed of two glycosylated heavy-chain constant domains and mediates effector functions through interactions with immune receptors and complement components. The variable (V) regions of the Fab fragment constitute a critical determinant of antigen or target recognition. The antigen-binding site is formed by the spatial convergence of six hypervariable complementarity-determining regions (CDRs), with three contributed by the heavy chain and three by the light chain, collectively defining binding specificity and affinity (Chen & Zhang, 2021; Chiu & Gilliland, 2016).

With technological advancements enabling the development of higher-level MAbs, innovations in MAbs such as antibody-drug conjugates (ADCs), fusion proteins, and other derivatives with high affinity and efficiency are

expected for the development of therapeutic monoclonal antibodies (Mould & Meibohm, 2016). In recent years, numerous studies have been conducted on the modification of mAb structures, revealing the numerous advantages that can be gained through changes in the mAb structure. mAbs used in cancer treatment are responsible for recognizing cell surface proteins in target cells. They then aim to kill target cells through multiple mechanisms involving interaction with effector Fc gamma receptors. Therefore, researchers have developed extensive and elegant modification capabilities to fine-tune Fc functions by strengthening or weakening the effector functions of mAbs (He et al., 2025; Kang & Jung, 2019).

Expanding the number of molecular targets can substantially influence both the efficacy and functional limitations of antibody constructs. In this context, the development of bispecific antibodies (BsAbs) has emerged as a successful strategy to enhance therapeutic performance. BsAbs are engineered antibodies that contain two distinct antigen-binding domains capable of recognizing either two different antigens or two separate epitopes on the same antigen, thereby enabling simultaneous modulation of multiple disease-driving pathways. Owing to their capacity for concurrent target engagement, BsAbs offer unique therapeutic advantages and have gained increasing prominence across a wide range of clinical applications (Chiu & Gilliland, 2016; Ma et al., 2021). Bispecific antibodies appear to be a highly preferable option compared to monoclonal antibodies due to their lower resistance rates under cytotoxic effects, tumor formation, and infection conditions, as they target two different antigens (Ma et al., 2021). Figure 1 illustrates the mechanism of action of a bispecific antibody in a simplified manner.

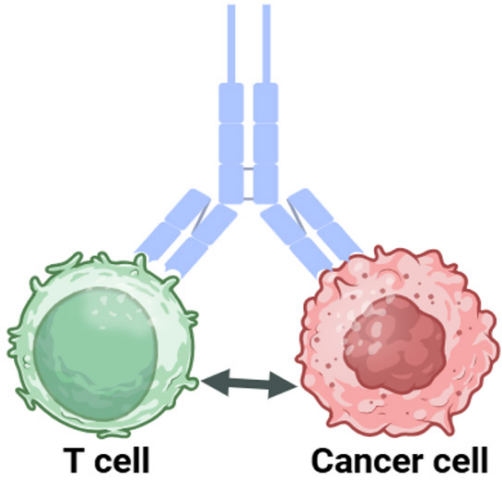

Figure 1. An example illustrating the mechanism of bispecific antibodies, specifically Catumaxomab, was adapted from Ma et al. with modifications (Ma et al., 2021). Figure created with BioRender.com

2.2. RNA-based Therapies

RNA molecules offer compelling alternatives and new treatment possibilities in the field of biotechnological drug development. The therapeutic versatility of RNA interference (RNAi) has catalyzed its application across a broad spectrum of human pathologies. Significant clinical progress is currently being made in leveraging RNAi-based platforms to target the molecular drivers of neurodegenerative disorders, infectious diseases, various malignancies, and cardiovascular diseases (Parsamanesh et al., 2024). Modern transcriptomic intervention strategies encompass a broad range of oligonucleotide-based modalities. These include RNA interference (RNAi) platforms, such as small interfering RNA (siRNA), microRNA (miRNA), and short hairpin RNA (shRNA), alongside other sophisticated approaches like antisense oligonucleotides (ASOs). While these tools differ in their intracellular processing and molecular structures, they collectively offer unprecedented precision in modulating gene expression at the post-transcriptional level (Germain et al., 2023; Liu, 2024). With these

characteristics, ribonucleic acid (RNA) therapeutics provide an effective and targeted treatment option when existing therapies suffer from target selectivity or low efficacy (Torrisi et al., 2026).

RNA interference (RNAi) is fundamental to a variety of biological processes, ranging from post-transcriptional gene regulation to the defense against RNA virus infections. A critical function of the RNAi pathway is the suppression of transposable elements (TEs)-genomic sequences capable of causing deleterious mutations if left unregulated. Dicer proteins facilitate this by identifying and cleaving TE-derived transcripts, thereby initiating gene silencing. Beyond its role in genomic stability, Dicer acts as a cellular sentinel, recognizing endogenous double-stranded RNA (dsRNA) to trigger a precise inhibitory response that maintains cellular homeostasis (Cornec & Poirier, 2023; Jadhav et al., 2024; Wang & Li, 2024). Following the early demonstration of antisense oligonucleotide–mediated viral inhibition by Stephenson and Zamecnik in 1978, RNA-based therapies gradually advanced toward clinical application. In 2018, patisiran became the first RNA interference (RNAi)-based drug to receive approval from both the FDA and the European Commission for the treatment of hereditary amyloidogenic transthyretin (hATTR) amyloidosis with polyneuropathy. This milestone was followed by the FDA approval of givosiran for adult patients with acute hepatic porphyria (AHP) (Hu et al., 2020; Torrisi et al., 2026). During the COVID-19 pandemic, RNA-based drugs and vaccines gained global prominence as effective therapeutic and preventive tools. The urgent need for rapid development and deployment underscored the potential of RNA technologies. In parallel, their versatility across multiple indications became increasingly clear, contributing to a growing pipeline of RNA-based therapeutics entering clinical development (Hu et al., 2020; Sparmann & Vogel, 2023).

Chemically synthesized siRNAs represent a highly promising therapeutic modality, characterized by their streamlined and rapid production. Beyond their ease of manufacture, these therapeutics offer a distinct mechanism of action by selectively silencing disease-associated genes at the post-transcriptional level (Ebenezer et al., 2025). The versatility of RNA-based drugs has fueled a broad expansion of their therapeutic reach. Notably, these agents can be programmed to target specific oncogenes or disrupted signaling pathways, allowing for highly individualized treatment strategies. This capability underpins the development of personalized mRNA vaccines, which are meticulously optimized based on the genetic characteristics of a patient's tumor (Hu et al., 2020; Rossi & Rossi, 2021).

Recent investigative studies highlight the clinical evaluation of Alnylam's cemdisiran and Regeneron's pozelimab as a dual-action therapy for paroxysmal nocturnal hemoglobinuria (PNH). By combining pozelimab-a monoclonal antibody-with the siRNA cemdisiran, researchers aim to target distinct components of the complement cascade. This combinatorial approach suggests a synergistic potential to modulate inflammatory responses and complement activation more robustly than monotherapy. By extension, this therapeutic synergy may prove effective in other pathologies driven by complement dysregulation, including atypical hemolytic uremic syndrome (aHUS), age-related macular degeneration (AMD), and various autoimmune disorders (Ebenezer et al., 2025).

Next-generation platforms, such as CRISPR-Cas13, are poised to revolutionize the landscape of RNA-targeted interventions by providing unprecedented precision in transcriptomic modulation. A particularly compelling frontier in this field lies in the development of combinatorial therapies. By integrating RNA-interference (RNAi) with biomaterial engineering or regenerative cell-based therapies, researchers can create synergistic platforms that address complex pathologies-such as the inhibitory environment of the injured spinal cord-through multiple therapeutic axes (Chudakova et al., 2025). Despite its immense potential, the clinical translation of RNA-based therapeutics is hindered by significant pharmacological barriers. These challenges primarily include suboptimal pharmacokinetic profiles, the inherent difficulty of achieving efficient intracellular delivery across biological membranes, and the risk of triggering adverse immune-related toxicities. Overcoming these hurdles is essential for ensuring that RNA drugs can reach their intended targets without inducing systemic inflammatory responses (Sparmann & Vogel, 2023).

2.3. Innovations in Gene Therapy; CRISPR

CRISPR-based gene therapies, leveraging the programmable nature of CRISPR-Cas (clustered regularly interspaced short palindromic repeats (CRISPR)-associated proteins) nucleases, represent a transformative approach to modern medicine. These systems facilitate precise genetic modifications-including gene disruption, the correction of pathogenic defects, or the introduction of novel cellular functions-to address a wide array of severe pathologies. However, the successful clinical adoption of these tools is contingent upon rigorous evaluations of their long-term safety profiles, immunogenic potential, and the development of high-resolution regulatory frameworks to ensure precise and predictable genetic outcomes (Banerjee et al., 2021; Huber et al., 2026; Ji et al., 2025). Originally discovered as

adaptive immune mechanisms in prokaryotes, CRISPR-Cas9 established the foundation for programmable genome editing by enabling efficient, site-specific DNA cleavage. Since its inception, the field has expanded to include over 300 characterized CRISPR-Cas systems, including the structurally and functionally distinct Cas12 and Cas13 families. The development of engineered Cas variants has further refined editing specificity, significantly reducing off-target effects. While CRISPR-based gene therapies have transitioned into clinical trials for a variety of pathologies, critical challenges-specifically regarding delivery efficiency, molecular precision, and long-term safety-must be fully addressed to ensure clinical success (Gasiunas et al., 2012; Ji et al., 2025).

The clinical success of CRISPR therapies is heavily dependent on overcoming delivery-related hurdles. While viral systems like AAV and lentivirus are widely utilized, they present a complex risk profile characterized by limited cargo size and host immune activation. A major concern remains the lack of control over the duration of Cas expression; prolonged presence of the editor can lead to cumulative off-target activity. Moreover, the threat of insertional mutagenesis-where the vector integrates into the host genome in an unintended manner-highlights the urgent need for more precise, transient delivery mechanisms (Ji et al., 2025; Saha et al., 2019). The limitations of the CRISPR-Cas9 system-namely its susceptibility to off-target effects and the challenges associated with non-specific delivery-have necessitated the diversification of the genome-editing toolkit. While Cas9 remains the dominant platform, non-nuclease technologies are gaining attraction as safer or more controlled alternatives.

Triplex-forming peptide nucleic acids (PNAs) represent a notable advancement in this category; these synthetic analogs can bind with high affinity to double-stranded DNA, creating triplex structures that stimulate site-specific gene correction without the double-stranded breaks typically required by CRISPR-based systems (Saha et al., 2019). While many current gene-editing techniques utilize donor templates to facilitate precise sequence correction, recent evidence suggests that peptide nucleic acids (PNAs) possess an intrinsic propensity to aggregate with single-stranded DNA (ssDNA) donor templates. This clustering phenomenon can manifest as false-positive signals in PCR-based readouts, potentially leading to the overestimation of editing efficiencies. Interrogating and mitigating such artifacts is critical for the rigorous development of optimized gene-editing agents (Ho et al., 2021). The advent of CRISPR-Cas9 technology has significantly transformed the landscape of epigenetics, offering a sophisticated toolkit for both genomic and epigenomic manipulation. Leveraging its inherently modular design,

Cas9 can be adapted-typically through the use of catalytically inactive 'dead' Cas9 (dCas9)-to serve as a scaffold for various epigenetic modifiers. This multi-processing capability facilitates the precise and dynamic modulation of epigenetic states within living cells. By enabling site-specific alterations to DNA methylation or histone acetylation, these tools allow researchers to interrogate the functional consequences of epigenetic regulation in real time, providing unprecedented insights into gene-regulatory networks (Pulecio et al., 2017).

Among the diverse strategies within biotechnological drug development, Chimeric Antigen Receptor (CAR) T-cell therapy has emerged as a transformative modality. While its clinical application is currently focused on lymphomas in select regions and is occasionally complicated by adverse events-specifically cytokine release syndrome (CRS) and neurotoxicity-it represents a vital therapeutic alternative for patients refractory to conventional treatments**.** The study by Stadtmauer et al. is particularly noteworthy, as it lays the groundwork for future research into CRISPR-engineered cancer immunotherapies. In this phase I clinical trial, the authors evaluated the safety and feasibility of CRISPR-Cas9-mediated gene editing in three patients with advanced malignancies. They extracted T lymphocyte cells from the patients and used the CRISPR-Cas9 system to modify three genes (TRAC, TRBC, and PDCD1) to enhance antitumor immune responses. In addition, a cancer-specific transgene, NY-ESO-1, was introduced to enable tumor recognition. The edited T cells were subsequently infused back into the patients, were well tolerated, and demonstrated sustained persistence for an approximately nine-month period (Stadtmauer et al., 2020). One of the notable factors in this study is the absence of any clinical toxicity associated with genetically engineered T cells. Bone marrow and tumor biopsies showed that T cells migrated to tumor sites in all three patients, but residual tumor tissue was detected in tumor biopsies in both myeloma patients. Nevertheless, the genetically engineered T cells were shown to be effective on their target. As summarized in Figure 2, cancer cell elimination mediated by CRISPR-edited T cells is driven by enhanced anti-tumor effector function, resulting in increased cytotoxic activity against tumor cells.

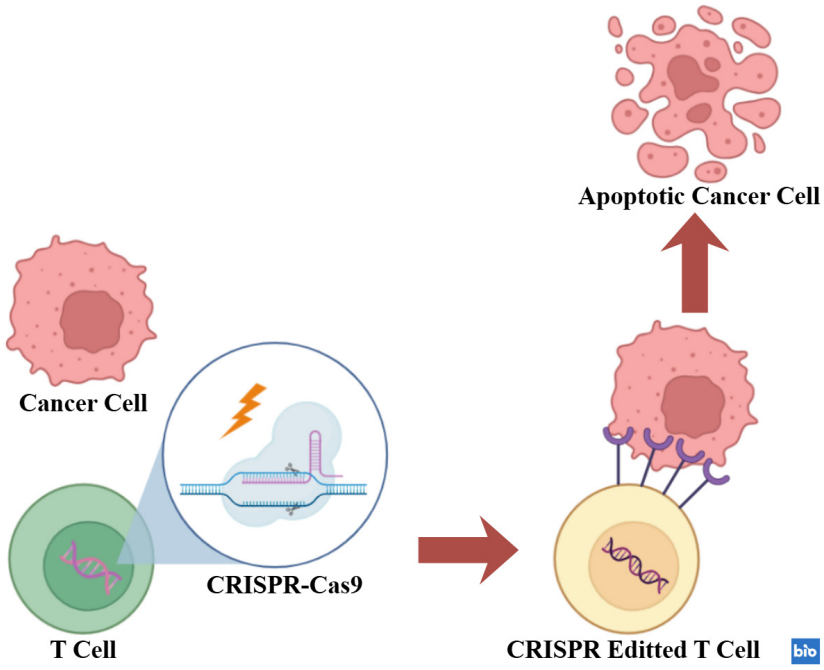

Figure 2. Schematic illustration of cancer cell elimination mediated by CRISPR-edited T cells. This approach enhances T-cell cytotoxic activity by genetically reprogramming T cells to mount an improved anti-tumor immune response. The figure was adapted and simplified from Stadtmauer et al. (2020). Figure created with BioRender.com

3. Discussion

Biotechnology-based therapeutic products have a wide range of clinical applications, including gene therapies, CAR-T cell therapies, RNA-based therapeutics, nucleic acid vaccines, recombinant proteins, and monoclonal antibodies. These modalities have achieved significant clinical success across oncology, immunological and infectious diseases, neurological disorders, and autoimmune conditions. Among biotechnological drugs, monoclonal antibodies are the first that come to mind due to their prominent applications.

Monoclonal antibodies (mAbs) are a key class of biotechnological therapeutics, with production process design shaped by multiple technical and economic factors. Limitations such as expression system efficiency and production costs require continual optimization of mAb manufacturing strategies. Detailed investigation of adverse immune-mediated drug reactions to monoclonal antibodies (MAbs) in humans is necessary; when

examining the formation of anti-drug antibodies (ADAs) in drug-treated animals, pharmacological studies designed with short timeframes yield more favorable results than toxicological analyses conducted over longer periods. Furthermore, while preclinical pharmacology studies often require animal models of a specific disease or condition, toxicology studies may not fully conform to these models, encouraging interdisciplinary collaboration (Mould & Meibohm, 2016). By targeting immune mediators including cytokines, integrins, and lymphocyte trafficking pathways, monoclonal antibodies (mAbs) have emerged as effective therapeutic agents for inflammatory bowel disease, a disorder associated with a substantial reduction in quality of life (Colwill et al., 2025). Closely related to monoclonal antibody production, biosimilar drugs have attracted considerable attention due to their potential to reduce manufacturing costs, and numerous biosimilar candidates are currently undergoing regulatory approval processes. Furthermore, the globalization of biological manufacturing enables countries to establish local production capabilities, thereby improving accessibility and supporting more sustainable healthcare systems (Chennamsetty et al., 2009; Dey et al., 2024).

RNA therapeutics are designed to modulate gene expression and protein synthesis for disease prevention and treatment. While the development of RNA-based therapeutics necessitates precise computational and molecular interaction analyses, these agents provide significant advantages in safety, efficacy, and manufacturing efficiency. Their cost-effectiveness, along with favorable storage and distribution characteristics, underscores their growing importance. Notably, RNA-based drug development occupies a unique therapeutic niche, offering a viable pathway toward personalized treatments for a myriad of diseases that have historically remained refractory to conventional interventions (Torrisi et al., 2026). Complementing these advancements, advanced drug delivery systems serve as a cornerstone for maximizing therapeutic efficacy and ensuring precise target engagement. A critical imperative in this field is the optimization of intracellular transport and the stability of biotechnological agents. This is increasingly achieved through strategic chemical modifications or the integration of sophisticated structural frameworks.

The evolution of RNA delivery is perhaps most evident in the dramatic enhancements to both potency and metabolic longevity. Recent breakthroughs have successfully reduced therapeutic requirements to the microgram level while extending drug half-lives from minutes to several months. A hallmark of this progress is the development of GalNAc-siRNA conjugates, which permit infrequent subcutaneous administration-occurring

as rarely as twice annually-and offer expanding potential for targeted delivery to the renal, central nervous, and ocular systems (Ebenezer et al., 2025). Similarly, exosomes have emerged as robust vehicles for miRNAs, acting as pivotal mediators of gene expression within the oncogenic landscape. By exporting tumor-suppressor miRNAs, these vesicles can actively facilitate tumor progression; however, current strategies to modulate this biogenesis often disrupt essential physiological functions. Through the standardization of molecular profiling, exosomal miRNAs are poised to become highly precise, non-invasive biomarkers for cancer diagnosis (Thind & Wilson, 2016).

CRISPR technologies provide unique opportunities for both preventing and treating disease by directly correcting harmful genetic mutations. By utilizing targeted gene disruption or precise correction, CRISPR can effectively stop a disease from advancing or restore a gene's natural function. Despite this potential, researchers must still overcome critical hurdles, such as off-target effects and accidental DNA changes that could lead to genomic instability. Similarly, CAR T-cell therapy faces barriers beyond its high price point. A comprehensive assessment of its long-term success and safety profile is still required. To make this treatment more accessible to the general population, it is essential to develop the technical expertise and infrastructure-the 'know-how'-necessary to scale production and reduce costs.

Addressing the remaining challenges in biotechnological therapeutics will require the accelerated development of next-generation biotherapeutics, the integration of personalized and precision biomedicine, the adoption of AI-driven drug design and protein engineering strategies, and continued advances in delivery technologies. Together, these efforts are expected to drive more effective, accessible, and durable therapeutic solutions in the coming years. Perhaps it's time to focus on some "elegant biological details" to make monoclonal antibodies (mAbs) and other biological drugs more useful in treating many diseases. Especially when considering the development of personalized medicine, pharmacogenomics seems to have the potential to change mAb dose optimization. From this perspective, improving biological therapies based on individual genetic profiles that can significantly influence drug response has become one of the priority issues to be addressed.

In conclusion, despite substantial progress in addressing many of the challenges associated with biotechnological drug development, important limitations persist, including high manufacturing costs, logistical constraints related to storage and distribution, and the need to mitigate unwanted

immune responses. Nevertheless, the consistently promising clinical and translational outcomes achieved to date underscore the transformative potential of these therapies. Continued innovation in bioprocessing, formulation, and molecular design is therefore expected to further expand their accessibility, effectiveness, and long-term clinical impact.

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