Targeted Therapies for Rare Diseases: Innovations in Gene Therapy, Stem Cell Treatments, and Precision Medicine

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Abstract

The global prevalence of rare diseases is on the rise, with approximately 400 million individuals affected worldwide. These conditions, often treated with orphan drugs, pose significant challenges due to their limited availability, high costs, and the complexity of treatment. As research and funding for rare diseases increase, pharmaceutical companies are making strides in developing novel therapeutic approaches. This review examines the recent advancements in targeted therapies for rare diseases, with a focus on gene therapy, stem cell therapy, small nucleic acid drugs, enzyme replacement therapies (ERT), and exosome-based technologies. Special attention is given to the role of artificial intelligence (AI) in accelerating drug discovery, facilitating the identification of novel treatments, and optimizing personalized therapies. Clinical case studies, such as those addressing cystic fibrosis, spinal muscular atrophy, and Leber's hereditary optic neuropathy, are presented to highlight the transformative impact of these therapies on rare disease management. Additionally, the review discusses the integration of gene and stem cell therapies in treating the root causes of genetic disorders, moving beyond symptom management. It also underscores the importance of collaboration among researchers, healthcare providers, and regulatory bodies to overcome the challenges of rare disease treatment and improve patient outcomes. Despite significant progress, the review concludes by emphasizing the need for equitable access to these therapies to reduce healthcare disparities, ultimately advancing the future of personalized medicine and enhancing the quality of life for individuals with rare diseases.

Keywords: Rare Disease, Orphan Drugs, New Drug Development, Gene Therapy.

Significance | This review discusses the advancements in targeted therapies offer transformative potential for rare disease treatment, emphasizing precision medicine and equitable healthcare access.

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1. Introduction

Rare diseases, as defined by the World Health Organization (WHO), are conditions with a prevalence of 0.65–1% of the total population (Alessandrini et al., 2019). These illnesses, though individually uncommon, collectively affect an estimated 400 million people worldwide, with a prevalence ranging from 3.5% to 5.9% (Barkau et al., 2021). In China, rare diseases are characterized by strict criteria: affecting fewer than 140,000 individuals, a newborn incidence of less than 1 in 10,000, or a population prevalence rate under 1 in 10,000 (Bernuy-Guevara et al., 2020). Despite their rarity in individual patients, the cumulative burden of rare diseases is substantial. In China alone, over 20 million people are estimated to be living with rare diseases, with more than 200,000 new cases reported annually (Brunetti et al., 2020).

Globally, approximately 6,000 to 8,000 diseases are classified as rare, with 250 new conditions added to this list annually (Buss et al., 2012). China's First List of Rare Diseases includes 121 recognized conditions, with hemophilia, amyotrophic lateral sclerosis (ALS),

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epidermolysis bullosa, albinism, and spinal muscular atrophy (SMA) among the most prevalent (Chen et al., 2017). However, numerous diseases, including autosomal recessive genetic disorders, Cloves syndrome, and Gorham-Stout disease, remain excluded from China's rare disease database, reflecting the complexities in identifying and categorizing these conditions.

One of the most significant challenges in addressing rare diseases is the scarcity of effective treatments. Globally, nearly 4,000 rare diseases lack proper therapeutic solutions, and only 10% of rare diseases are treated effectively (Cheng, 2020). This deficit highlights an urgent need for innovative drug development. In China, a nation of over 1.4 billion people, the demand for research into rare disease treatments is particularly acute. Despite the low prevalence of individual rare diseases, the societal and healthcare burden is immense.

Many patients worldwide with rare diseases still suffer due to limited treatment options and delayed interventions. To address this gap, this study focuses on analyzing and summarizing recent advancements in therapeutic drugs and treatments for rare diseases. This includes reviewing marketed drugs, recent clinical trials, and promising drugs currently under development. By presenting these insights, we aim to provide valuable references for researchers and stakeholders in rare disease research, fostering further progress in addressing this critical global healthcare challenge.

2. Treatment methods for rare diseases

Treatment for rare diseases presents significant challenges for clinicians, particularly in terms of accurate diagnosis and timely intervention. One of the primary contributors to these diseases is genetic abnormalities, with hereditary disorders often requiring complex therapeutic approaches such as bone marrow transplantation, surgery, medication, dietary interventions, and other methods (Craven et al., 2013). The available treatment options for rare diseases are diverse and include gene therapy, antibody treatment, enzyme replacement therapy, stem cell therapy, small molecule drugs, and drug repositioning (Craven et al., 2013). Recent breakthroughs in gene therapy, stem cell therapy, and oligonucleotide therapy have brought about transformative changes in the treatment of numerous rare conditions, providing hope for individuals who previously had limited options.

2.1 Gene Therapy

Gene therapy has emerged as a groundbreaking experimental treatment for genetic disorders by altering human genes to treat or prevent diseases. According to (Dunbar et al., 2018), this technique utilizes various viral vectors, with adenoviral vectors being among the most commonly used. Gene therapy has shown significant progress in treating hematological disorders such as hemophilia, Gaucher disease, and hemochromatosis, as well as various cancers and rare genetic disorders (Finkel et al., 2021). Genetic inheritance plays a crucial role in the development of many rare diseases, with single gene mutations—either spontaneous or inherited—being the primary cause of these conditions (Finkel et al., 2021).

The development of gene therapies has provided new hope for treating rare diseases. For instance, Glybera®, developed by UniQure, became the first gene therapy approved by the European Medicines Agency (EMA) in 2012. Glybera® is used to treat lipoprotein lipase deficiency, a rare genetic disorder (Finkel et al., 2021). More recently, gene therapies like Valoctocogene Roxaparvovec, developed by BioMarin, have made significant strides in treating hemophilia A, with Phase III clinical trial data demonstrating promising results (Long et al., 2022). Similarly, Zynteglo, a gene therapy for beta-thalassemia by Bluebird, has been approved for use in Europe (Flaherty et al., 2012).

In China, while the number of domestically developed gene therapies is still relatively low, there have been notable advancements. For example, the AAV gene therapy EXG001-307, developed by Hangzhou Jiayin Biological, became the first gene therapy for type 1 spinal muscular atrophy (SMA) authorized for clinical use in China. As of now, there are approximately 40 gene therapy drugs available on the market, including those based on small nucleic acids, virus-based in vivo gene therapy, and in vitro gene therapy, with the majority addressing rare genetic disorders (Table 1).

These developments in gene therapy have opened new avenues for treating previously untreatable rare diseases, providing critical therapeutic options for affected individuals.

2.2 Stem Cell Therapy for Rare Diseases

Stem cell therapy has emerged as a promising treatment for a variety of rare diseases, particularly those involving genetic and hematological disorders. Hematopoietic stem cell transplantation (HSCT) is one of the most widely utilized stem cell therapies, offering potential for therapeutic interventions through immune modulation and providing vital educational support to the immune system. (Grilo & Mantalaris, 2019) define HSCT as a method that utilizes human stem cells to influence immune system function and to provide essential regenerative support. Several types of HSCT, including peripheral hematopoietic stem cell transplantation, bone marrow transplantation, umbilical cord blood transplantation, and fetal liver cell transplantation, are available, each with its specific indications and applications.

Among these, umbilical cord blood has garnered attention for its potential in treating rare diseases, with numerous clinical procedures demonstrating its therapeutic benefits. According to (Gui et al., 2020), umbilical cord blood stem cells (UCBT) have proven effective in treating various primary rare diseases. However, challenges remain, such as the risk of cytomegalovirus (CMV) infection and delayed immune reconstitution, which can complicate treatment outcomes (Haendel et al., 2020) Despite these

challenges, UCBT has shown promise in managing rare genetic disorders, such as lysosomal storage diseases (including mucopolysaccharide storage enzyme diseases, Gaucher's disease, and Niemann-Pick disease) and immunodeficiency syndromes, among others. Notably, UCBT has demonstrated therapeutic efficacy in rare conditions such as metachromatic leukodystrophy, chronic granulomatosis, and IgE syndrome, providing hope for patients with these life-threatening conditions (Hartin et al., 2020). Gaucher disease, an autosomal recessive lysosomal storage disorder caused by glucocerebrosidase deficiency, is another rare disease where stem cell therapy, in the form of HSCT, has shown potential. According to (Islami & Soleimanifar, 2020), enzyme replacement therapy (ERT) has been the standard treatment for Gaucher disease since 1984, but HSCT offers a more permanent and cost-effective alternative by providing a consistent source of enzymes. (Ji et al., 2019) highlight that HSCT can provide long-term benefits to patients with Gaucher disease at a fraction of the cost associated with ERT. In China, several clinical cases have demonstrated the successful use of cord blood stem cells for treating Gaucher disease, underscoring the growing recognition of stem cell therapies in rare disease management (Ji et al., 2019)

Moreover, recent advances in HSCT have been bolstered by the approval of new therapies, such as the FDA-approved PREVYMI oral and intravenous fluids, which help prevent CMV infections following hemodialysis (Jiang et al., 2011). This drug has enhanced treatment outcomes by improving infection control and increasing the success rates of hemodialysis, thus supporting the application of HSCT in rare disease contexts.

2.3 Antibody Therapy for Rare Diseases

Antibody therapy, also known as passive immunity, involves the administration of antibodies to help the body fight specific pathogens or diseases. These therapies are particularly valuable for treating rare conditions that require targeted immune responses. One of the pioneering therapies in this field was muronomab-CD3, the first monoclonal antibody (mAb) licensed for organ allograft rejection (Kulagin et al., 2019). Antibodies play a critical role in regulating cellular signaling systems, binding to specific proteins or cells, and delivering cytotoxic or neutralizing substances (Li et al., 2022). Their specificity makes them ideal for treating rare diseases, where the immune system needs to be carefully modulated.

Caplacizumab, the first nanobody therapy, was approved by the European Commission in 2018 for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP), a rare and life-threatening blood disorder (Li et al., 2020). Similarly, Soliris, a monoclonal antibody developed by Alexion Pharmaceuticals, was approved by the FDA in 2007 for the treatment of paroxysmal nocturnal hemoglobinuria, an extremely rare blood disorder. Over time, Soliris has expanded its indications to include atypical hemolytic uremic syndrome and myasthenia gravis, both of which are rare conditions linked to the complement system (Lim et al., 2017).

The key advantage of antibody therapies is their high specificity, which reduces the risk of off-target effects and ensures a more targeted treatment approach for rare diseases. The development of antibody therapies for rare diseases continues to evolve, with researchers increasingly prioritizing rare conditions for novel therapeutic interventions. With their precision and growing versatility, antibody therapies represent a crucial component of the evolving treatment landscape for rare diseases.

2.4 Enzyme Replacement Therapy (ERT) for Lysosomal Storage Disorders

Enzyme replacement therapy (ERT) has become a cornerstone in the treatment of lysosomal storage disorders (LSDs), a group of rare inherited diseases caused by enzyme deficiencies or defects within the lysosomes, leading to the accumulation of substrates that are normally broken down. The development of ERT for LSDs began in the early 1980s when (Liu, 2018) first pioneered the therapy for type 1 Gaucher disease, a rare and debilitating disorder. This groundbreaking approach served as a proof-of-concept, providing the foundation for subsequent ERT developments for other LSDs. The first recombinant enzyme replacement product, glucocerebrosidase (produced by Genzyme), received approval from the U.S. Food and Drug Administration (FDA) in 1994, marking a major milestone in the treatment of Gaucher disease (Liu, 2019).

Since then, ERT has expanded to treat various other LSDs, including Fabry disease, Pompe disease, and mucopolysaccharidoses (Long et al., 2022). The success of ERT for Gaucher disease set a precedent for treating other rare and complex disorders. In 2006, ERT was approved for Pompe disease, a condition that manifests in both late-onset and infantile forms. For patients with late-onset Pompe disease, ERT has shown significant benefits, particularly in improving motor and respiratory function (Lu & Han, 2022). More recently, in 2021, the FDA approved Nexviazyme, an ERT for the treatment of individuals with late-onset Pompe disease, extending treatment options for patients as young as one year old (Mays & Deans, 2016). These advancements underscore the therapeutic potential of ERT in managing LSDs, improving patients' quality of life, and prolonging survival.

Despite its success, ERT faces several challenges. One of the most significant barriers is the body's distribution of biologic drugs. The blood-brain barrier (BBB), which prevents many substances from entering the brain, presents a major obstacle for treating neurodegenerative LSDs. Additionally, the high cost of these therapies remains a concern, as ERT involves lifelong treatment for most patients, further straining healthcare systems (Mercuri et al., 2018). Furthermore, clinical trials for ERTs require carefully designed endpoints to assess their effectiveness. Identifying the

minimum clinically significant differences for these endpoints is crucial to ensuring that the benefits of ERT are measurable and meaningful to patients (Mingozzi & High, 2013).

3. Rare Disease Drug Development

The development of drug therapies for rare diseases—often referred to as "orphan diseases"—faces unique challenges. In many countries, including China, a significant number of rare diseases still lack approved treatments. According to (Mitchell et al., 2018), China has published a catalog of rare diseases, with 121 conditions listed. Of these, 105 diseases (87%) have no targeted drug therapies, highlighting the gap in treatment options for rare diseases. Furthermore, over half of the orphan drugs available in China are imported, emphasizing the reliance on foreign pharmaceutical innovations. This situation is compounded by the limited research and development (R&D) resources dedicated to rare disease drug development in China and other developing regions (Nguengang Wakap et al., 2020).

The scarcity of orphan drugs can be attributed to several factors. The relatively small patient populations for rare diseases make it difficult for pharmaceutical companies to estimate potential profits, which limits their incentive to invest in R&D for these conditions. Developing new drugs requires substantial financial investment, making it unappealing for profit-driven companies to prioritize orphan drugs over more common and profitable treatments. Additionally, the regulatory and clinical trial complexities associated with rare diseases further discourage the development of new therapies.

Recent advances in molecular biology, including the Human Genome Project, have opened new avenues for drug development. Today, the focus of research is expanding beyond traditional protein-based therapies (such as antibodies and enzymes) to include innovative approaches like nucleic acid-based drugs, gene therapies, stem cell treatments, and protein degradation agents based on PROTAC (proteolysis-targeting chimera) technology. These new modalities offer exciting prospects for the treatment of rare diseases, offering more precise and personalized approaches to therapy (Oprea et al., 2011).

The ongoing development of these new drug classes signals a shift toward more targeted and effective treatments for rare diseases. With the growing focus on molecular and genetic-based therapies, there is hope for improving the availability of orphan drugs and ensuring that individuals with rare conditions have access to the treatments they need.

3.1 Small Molecule Drugs in Rare Disease Treatment

For decades, pharmaceutical companies have prioritized the development of small molecule drugs, which have been at the forefront of medication discovery and innovation. These drugs, typically composed of low molecular weight compounds, can easily enter cells and interact with intracellular targets, making them highly effective for treating various diseases, including rare and complex conditions. The advent of artificial intelligence (AI) and machine learning (ML) technologies has revolutionized the drug discovery process, particularly in the realm of small molecules (Paiva & Crews, 2019). By leveraging vast datasets and using advanced computational methods, AI can rapidly identify promising compounds for treating rare diseases, a task that traditionally required time-consuming and resource-intensive experimental processes.

One significant application of AI in small molecule drug research is its ability to analyze and integrate large volumes of literature and databases to predict the efficacy of compounds. For instance, Benevolent Bio, a UK-based company, utilized the technology platform JACS to screen 100 compounds for their potential to treat amyotrophic lateral sclerosis (ALS). The platform successfully identified five promising compounds, of which four were shown to effectively treat motor neurodegeneration (Patel & Genovese, 2011). This highlights how AI-driven platforms are streamlining drug discovery for rare diseases, providing hope for more rapid development of therapeutic options.

Technological advancements in chemistry and biology, alongside improved drug screening methods, have further propelled the success of small molecule drugs. A prime example is Vertex Pharmaceuticals, which developed the CFTR modulator ivacaftor through in vitro screening to treat cystic fibrosis (CF) caused by the F508del mutation. Vertex continued to innovate by developing Trikafta, a triple combination therapy that targets both F508del alleles, and Orkambi, a diphasic formulation of lumacaftor and ivacaftor (Rahit & Tarailo-Graovac, 2020). These therapies exemplify how small molecules are being tailored to address the specific genetic mutations underlying rare diseases.

Lysosomal storage disorders (LSDs), a group of rare inherited diseases caused by defective enzymes, are another area where small molecules have made a significant impact. Zavesca and Cerdelga, two small molecule therapies developed by Actelion Pharmaceuticals and Genzyme, respectively, inhibit the biosynthesis of defective enzyme substrates in Gaucher disease, an LSD. These drugs provide a therapeutic alternative to enzyme replacement therapy (ERT), which is often costly, injectable, and limited in its ability to penetrate the central nervous system (CNS) (Schmidt & Thompson, 2020). These examples illustrate the growing role of small molecules in treating complex, rare diseases.

AI technologies are continuously enhancing the ability to discover new uses for existing drugs, especially for rare diseases with unclear etiologies. By employing deep learning methodologies and phenotypic screening, researchers can identify compounds with therapeutic potential that may otherwise remain undiscovered. This

represents a significant step forward in drug development for conditions with limited treatment options.

3.2 Small Nucleic Acid Drugs for Rare Diseases

In recent years, the field of small nucleic acid drugs has rapidly advanced, offering new and potent treatments for a range of rare genetic disorders. Small nucleic acid drugs, such as antisense oligonucleotides (ASOs), small interfering RNA (siRNA), and microRNA (miRNA), are composed of short, synthetic sequences of nucleotides designed to target specific genetic sequences (Schuessler-Lenz et al., 2020). These drugs work by modulating gene expression, making them a promising class of therapeutics for genetically inherited diseases.

One notable example is Nusinersen, the first FDA-approved drug for spinal muscular atrophy (SMA), a rare genetic disorder characterized by the progressive degeneration of motor neurons. Nusinersen functions by binding to the precursor mRNA produced by the SMN2 gene, altering the RNA splicing pattern to promote the expression of normal SMN proteins (Sharma et al., 2010). Another example is Milasen, an antisense oligonucleotide developed to treat Batten disease, which shares a similar mechanism of action to Nusinersen but has specific modifications to improve its efficacy (Sleijfer et al., 2013). These therapies demonstrate the growing potential of small nucleic acid drugs to treat rare genetic conditions that previously had no effective treatment options.

Among the 14 small nucleic acid drugs currently available worldwide, antisense oligonucleotides (ASOs) make up the majority, with four siRNA medications, nine ASO medications, and one nucleic acid aptamer (Table 2). The use of ASOs has been particularly successful in treating Duchenne muscular dystrophy (DMD), a rare and severe form of muscular dystrophy. Eteplirsen, an FDA-approved ASO, targets exon 51 of the DMD gene, and other ASOs, such as Golodirsen (2019), Viltolarsen (2020), and Casimersen (2021), target different genetic loci associated with DMD (South et al., 2019). These drugs offer new hope for individuals with DMD, a disease that was once considered untreatable.

Small nucleic acid drugs have emerged as a new class of therapeutics, following small molecule drugs and protein therapies, due to their ability to target disease-causing genetic mutations directly. They hold significant promise for treating rare disorders that were previously considered intractable. One of the main advantages of small nucleic acid drugs is their ability to target many disease proteins that are untargetable by traditional small molecules, providing a powerful new tool in the fight against rare genetic disorders (Stockton et al., 2020).

The development of small molecule and small nucleic acid drugs has transformed the landscape of rare disease treatment. Advances in AI-assisted drug discovery, improved drug screening technologies, and the development of novel therapeutic approaches have all contributed to the successful treatment of rare diseases. Small molecule drugs are increasingly used to treat conditions such as Gaucher disease and cystic fibrosis, while small nucleic acid drugs like ASOs and siRNAs offer new therapeutic possibilities for genetic disorders like SMA and DMD. Together, these innovations represent the future of rare disease therapeutics, offering hope for patients with conditions that were once considered untreatable.

3.3 Hematopoietic Stem Cell Drugs in Rare Disease Treatment

Hematopoietic stem cells (HSCs) have emerged as a powerful therapeutic tool, particularly in treating rare diseases. These cells, which give rise to all blood cell types, have the unique ability to regenerate and repair damaged tissues. Over the years, stem cell therapies have been at the forefront of treating conditions that were previously untreatable, providing patients with new hope. Some of these treatments have gained regulatory approval and are being used globally to address rare diseases.

A major milestone in stem cell therapy occurred in 2011 when the FDA authorized the distribution of Prochymal, a stem cell-based treatment developed by Osiris Therapeutics. Prochymal became the first stem cell therapy approved for the treatment of Crohn's disease and pediatric graft-versus-host disease (GVHD) (Patel and Genovese, 2011). Following this success, other stem cell therapies have been developed and approved for use in treating rare conditions. For instance, in 2012, Athersys, a U.S.-based company, received FDA approval for MultiStem, a stem cell therapy for treating Type I mucopolysaccharide storage disorder (Tambuyzer et al., 2020).

In Europe, hematopoietic stem cell gene therapies have been approved for the treatment of several rare diseases. Strimvelis®, a gene therapy approved in 2016, was developed to treat severe combined immunodeficiency (SCID) caused by adenosine deaminase deficiency. This groundbreaking therapy has demonstrated significant success in restoring immune function in patients with this life-threatening genetic condition (Tang et al., 2015). Additionally, Orchard Therapeutics received approval for Libmeldy in 2020, a gene therapy for treating early-onset cerebral leukodystrophy, a rare genetic disorder that leads to severe neurodegeneration. Similarly, Skysona, another gene therapy developed by Bluebird Bio and approved in 2021, is used to treat adrenal cerebral leukodystrophy (Thiesing et al., 2000).

In Japan, the introduction of Temcell, a bone marrow mesenchymal stem cell product for treating GVHD, marked a significant step forward. Temcell, approved in 2016, has since been expanded into studies for the treatment of Epidermolysis bullosa, a rare skin disorder. This expansion demonstrates the growing scope of stem cell therapies in treating rare diseases and underscores the importance of ongoing research into the potential of these therapies (Tosolini & Sleigh, 2017). Furthermore, stem cell therapies for diseases such as acromegaly and Parkinson's disease are nearing the

Table 1. Marketed genetic drugs in rare diseases.

Disease	Therapy Name	Name of the Company	Target mechanism	Approval authority	Approval Time
Lipoprotein deficiency hereditary disease	Glybera	UniQure	AAV-based gene therapy	EC	2017/10
Spinal muscular atrophy	Zolgensma Spinraza	AveXis (Novartis) Ionis Pharmaceuticals	Gene therapy for expressing SMN protein Gene therapy for expressing SMN protein	FAD FAD	2019/5/24 2016/12/23
Severe immunodeficiency	Strimvelis	Orchard Therapeutics	Gene therapy for expression of adenosine deaminase	EC	2016/5
Porphyria	Givlaari	Alnylam	Targeted ALAS1 gene therapy	FDA	2019/11
B-mediterranean anemia	LentiGlobin	Bluebird bio	Autologous stem cell therapy based on lentiviru	EC	2019/5
Familial hypercholesterolemia	Leqvio	Novartis	Gene therapy targeting PCSK9	EC	2020/12/23
Adrenoleukodystrophy	Skysona Libmeldy	Bluebird bio Orchard Therapeutics	Gene therapy of ALD protein expression Gene therapy for expression of functional enzyme ARSA	EC EC	2021/7/21 2022/1/10
Retinal nutritional atrophy	Luxturan	Spark Therapeutics	Retinal dystrophy associated with RPE65 mutation	FDA	2022/1/10

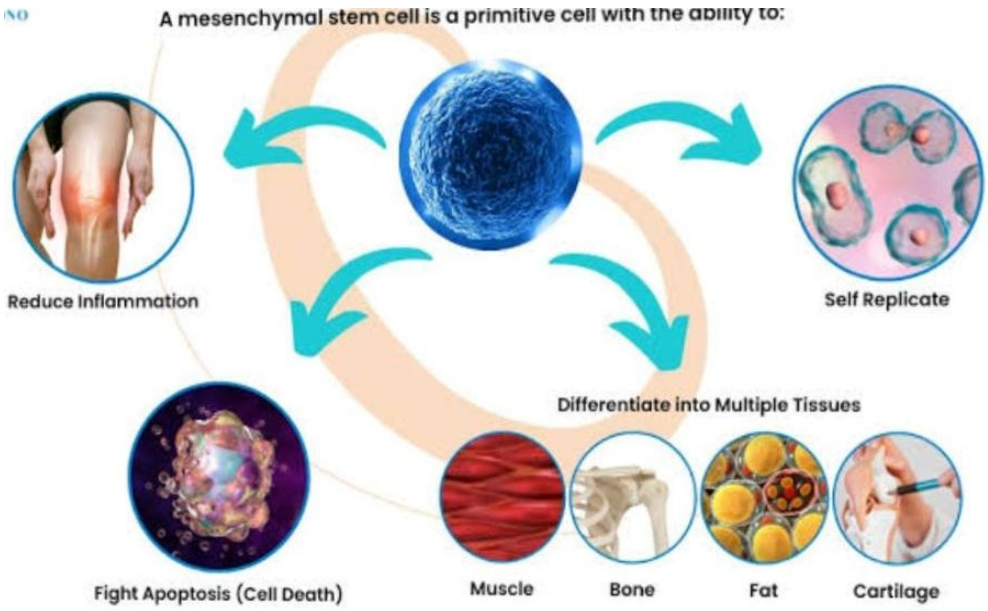

Figure 1. Stem Cell Therapy

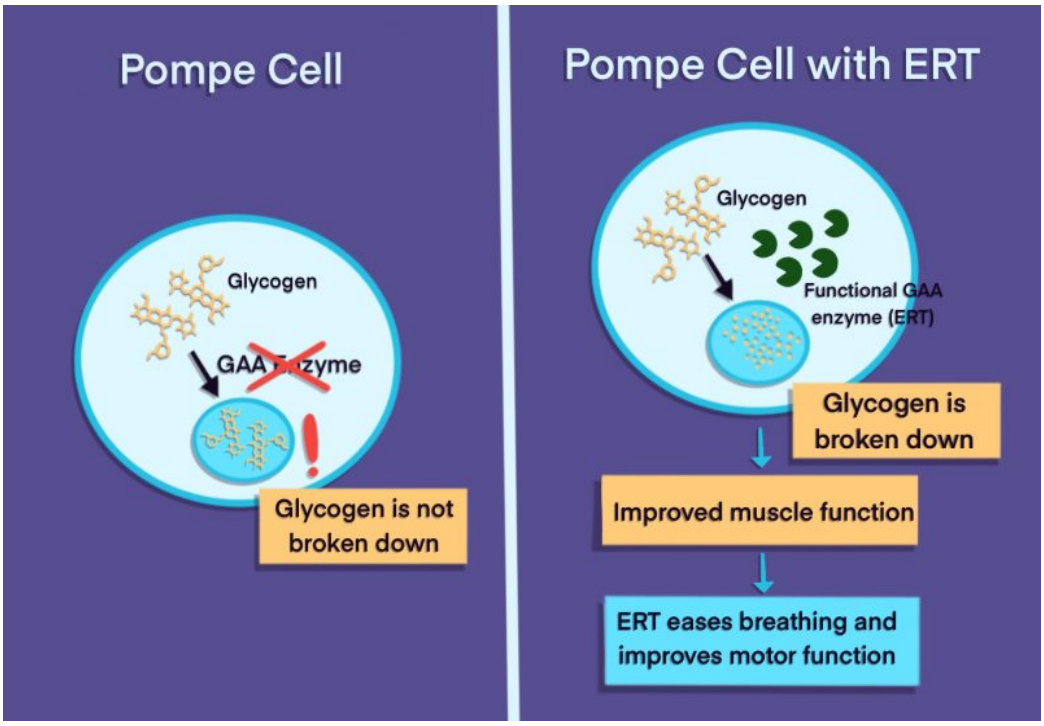

Figure 2. Enzyme replacement therapy

Table 2. List of global marketed small nucleic acid drugs.

Category	Pharmaceuticals	Enterprise	Indications	Market Time
siRNA	Onpattro	Alynlam	Familial amyloid polyneuropathy	2018
siRNA	Givlaari	Alynlam	Acute hepatic porphyria	2019
siRN	OXLUMO	Alynlam	Primary hyperoxaluria type1	2020
siRN	Inclisiran	Alynlam Novartis	Adult hypercholesterolemia and mixed dyslipidemia	2020
ASO	Vitravene	Lonis, Novartis	Cytomegalovirus retinitis	1998
ASO	Kynamro	Lonis, Sanofi	Familial hypercholesterolemia of the pure type	2013
ASO	Exondys51	Sarepta Therapeutics	Duchenne muscular dystrophy	2016
ASO	Spinraza	Lonis, Biogen	Spinal muscular atrophy	2016
ASO	Tegsedi	lonis	Hereditary amyloidosis of transthyretin protein	2018
ASO	Waylivra	Lonis	Familial celiac disease syndrome	2019

completion of clinical trials, and these treatments may soon be available to the public.

4. Case Studies: Triumphs of Precision Medicine in Rare Disease Treatment

The success of stem cell therapies is part of a broader movement in precision medicine, where treatments are tailored to the genetic makeup of patients. Precision medicine has led to significant advances in the treatment of rare diseases, with targeted therapies offering tangible benefits to patients.

One remarkable case is Trikafta, a drug developed by Vertex Pharmaceuticals for cystic fibrosis (CF), a hereditary disease that causes severe lung damage. Trikafta is a triple-combination therapy that specifically targets the defective CFTR protein responsible for CF's progression. This treatment has brought significant improvements in lung function and overall health for patients with certain CF mutations. Clinical trials have shown reductions in hospitalizations, respiratory symptoms, and exacerbations, representing a paradigm shift in CF management (Tripathi et al., 2021).

Another success story comes from the treatment of Spinal Muscular Atrophy (SMA), a rare neuromuscular disease caused by a deficiency in survival motor neuron (SMN) protein. Zolgensma, a gene therapy developed by Novartis, has shown transformative effects in infants diagnosed with SMA. Clinical trials have demonstrated higher survival rates, improved motor function, and the achievement of developmental milestones previously thought impossible. Zolgensma offers groundbreaking hope for SMA patients and highlights the power of gene therapy in addressing the underlying causes of rare diseases (Wirth et al., 2013).

In the realm of cancer treatment, imatinib (Gleevec) has revolutionized the management of chronic myeloid leukemia (CML), a rare and often fatal cancer of the blood. By specifically targeting the BCR-ABL gene fusion, which causes CML, Gleevec has turned what was once a fatal disease into a chronic, manageable condition. Clinical research has shown that patients treated with Gleevec experience longer survival rates, a lower rate of disease progression, and an improved quality of life. Gleevec is a prime example of how targeted therapies can transform the treatment of rare diseases and provide patients with a renewed sense of hope (Yamada, 2021).

These case studies underscore the triumphs of precision medicine and highlight the profound impact of targeted therapies on patients with rare diseases. The continued development of stem cell therapies and gene treatments, alongside the expansion of precision medicine approaches, promises to offer even more life-changing treatments in the future. By specifically targeting the genetic and molecular causes of rare diseases, these therapies hold the potential to revolutionize the way we treat and manage these challenging conditions.

5. Prospects of Treatments for Rare Diseases

The treatment of rare diseases has advanced significantly in recent years, with gene therapy, combined therapies, and stem cell treatments emerging as promising avenues for tackling conditions that were once considered untreatable. These therapies are making substantial strides, particularly in ophthalmology and neuromuscular disorders, offering new hope for patients suffering from rare conditions.

5.1 Application of Gene Therapy in Ophthalmology

Gene therapy has shown considerable promise in treating rare eye diseases, particularly those related to retinal disorders. One of the most significant advancements in the field is the use of adeno-associated virus (AAV) gene therapy. In 2022, AAV gene therapy became a key player in the treatment of neuromuscular rare illnesses, and its application in ophthalmology has also shown remarkable potential. Age-related macular degeneration (AMD), a common cause of vision loss, is one such disorder benefiting from gene therapy. AMD can lead to retinal lesions and central vision loss, making it a prime target for therapeutic intervention (Zaher et al., 2021; Yuan et al., 2018).

In January 2022, Molecular Therapeutics reported the initiation of a mid-term clinical trial for its AAV gene therapy, 4D-150, which involves intravitreal injection to target retinal conditions. Similarly, in February 2022, REGENXBIO released preliminary results from its Phase 2 ALTITUDE trial, which tested RGX-314, an ocular AAV gene therapy product designed to treat wet age-related macular degeneration (wAMD). These trials are part of a broader effort to harness the power of AAV gene therapy to treat retinal diseases effectively.

In addition to AMD, gene therapy has become a promising treatment for Leber's hereditary optic neuropathy (LHON), a rare condition with no clinically viable treatment. GenSight Biologics released long-term clinical data in January 2022 for LUMEVOQ, an AAV-based gene therapy that showed substantial improvements in patients' vision up to four years after a single injection. Another notable development in this field is Ocugen's AAV gene therapy, OCU400, which began dosing its first patient in April 2022 for pigmentary retinitis caused by mutations in the NR2E3 and RHO genes.

5.2 Application of Combined Therapy in Rare Diseases

While gene therapy is a breakthrough treatment for many rare diseases, its use is often limited by immune responses to the viral vectors (like AAV) used to deliver the therapeutic genes. Over time, patients can develop immunity to these viral vectors, which renders further treatments ineffective. To overcome this challenge, the emerging field of exosome-based therapy has garnered significant

interest. Exosomes, small vesicles secreted by cells, have been shown to deliver gene therapies without triggering adaptive immune responses. This makes exosome-mediated gene delivery a promising alternative for patients who might otherwise be immune to viral-based gene therapy.

Companies such as Sarepta and Codiak are leading the charge in developing exosome-based therapies. Sarepta is known for its precision gene therapy in rare diseases, while Codiak focuses on advancing exosome engineering technologies. Their collaboration is paving the way for more effective gene therapies that do not rely on viral vectors, offering a solution to one of the major challenges in gene therapy for rare diseases. The growing interest in exosome technology has attracted significant investment, further propelling advancements in the field.

5.3 Stem Cell Therapy in Rare Diseases

Alongside gene therapy, stem cell treatments are gaining attention as a potential solution for rare diseases. Stem cells have the ability to regenerate and repair damaged tissues, making them an ideal candidate for treating conditions that lack effective therapies. Stem cell-based treatments have already been developed for several rare disorders, providing patients with new therapeutic options.

Stem cell research holds significant promise for the future treatment of rare diseases. As technology improves, stem cells may play an even more central role in the treatment of conditions that currently have no viable treatment options. Furthermore, combining gene therapy with stem cell technologies could offer a more comprehensive solution. For example, epidermolysis bullosa (EB), a rare skin disorder, could potentially be treated using genetically engineered stem cells, offering a dual benefit of gene correction and tissue regeneration.

The application of gene therapy, exosome-based therapies, and stem cell treatments are reshaping the landscape of rare disease treatment. These advancements provide new hope for patients who were previously left without effective treatment options. As research and development continue, the fusion of these technologies promises to bring even more breakthroughs, offering the potential to treat and possibly cure rare diseases in the near future. These innovative therapies are not only advancing the treatment of rare diseases but also opening new doors for personalized medicine and precision treatments.

6. Conclusion

In conclusion, innovations in targeted therapy have emerged as a transformative force for individuals affected by rare and often overlooked medical conditions. The precision and specificity of these therapies mark a paradigm shift in healthcare, moving from generalized approaches to more personalized, effective treatments. By leveraging advances in genetics, molecular biology, and diagnostic technologies, researchers are developing therapies that target the root causes of rare diseases, offering hope for more effective and sustainable solutions.

Nevertheless, the journey from research to real-world application demands continued collaboration among scientists, clinicians, pharmaceutical companies, and regulatory bodies. This cooperative effort is essential to navigate the complexities of rare diseases and accelerate the development and approval of new therapies. Additionally, ensuring equitable access to these cutting-edge treatments is crucial to address existing healthcare disparities and provide all patients with the opportunity to benefit from these breakthroughs.

Overall, the progress in targeted therapy for rare diseases paints a hopeful picture for the future of medicine. These advancements embody the core principles of precision medicine, reflecting a collective commitment to improving the quality of life for those living with rare conditions and ensuring that no patient is left behind.

Author contributions

A.Y. contributed to data analysis, visualization, and interpretation. J.A.C. was responsible for supervision, critical revision of the manuscript, and project administration. Both authors read and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

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