

Stem Cell Gene Editing: A Comprehensive Review of Innovations, Clinical Applications, and Ethical Horizons

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ABSTRACT

The days since humanity has had mortality bought by old age and disease, discussion of extending life with inventions in biology and health sciences, have always had a major place in scientific and medical fields. Although a novel idea, in the past few decades, there has been an upsurge of Stem Cell therapies and Gene Editing talks in the developmental stages, and many have already been employed with success. Stem cells have shown promising aspects in cell regeneration and tissue repair, however, the generation of complete and complex internal organs and organ systems, outside the body is still in the works. Gene editing is another highly effective scientific resource which has shown the possibilities of modifying and altering the gene at the molecular level. The CRISPR- Cas systems, along with many others, are of significance due to their ability of targeted gene modification in the Genomic DNA of a variety of organisms, amongst which, it has proved especially useful in the disease therapy and treatment. Gene Editing and Stem Cell Technologies together have provided us with a much stronger chance of disease treatment and gene targeting, than we have ever had before, therefore creating new possibilities for studying genetic diseases and developing potential cell-based therapies. This review highlights recent advances in stem cell and gene-editing technologies, emphasizing their integration, therapeutic potential, current challenges, and future prospects in personalized and regenerative medicine.

Keywords: Gene editing, CRISPR-Cas, Stem cell, Gene therapy, iPSCs

1. Introduction

Stem cells are undifferentiated cells characterized by their capacity for self-renewal and differentiation into specialized cell types [1]. They are present in both embryonic and adult tissues and are classified according to their developmental potency, which refers to their ability to generate different cell lineages. Unipotent stem cells can produce only a single cell type while retaining self-renewal capability. In contrast, totipotent stem cells possess the highest developmental potential, giving rise to all embryonic and extraembryonic tissues. The zygote, formed following fertilization, is a classic example of a totipotent cell capable of generating all three germ layers as well as the placenta [2]. Between these extremes lie other stem cell categories, including pluripotent stem cells (PSCs), which are particularly valuable for

regenerative medicine and gene-editing applications. PSCs can differentiate into cell types derived from all three germ layers but cannot form extraembryonic tissues. Embryonic stem cells (ESCs), derived from the inner cell mass of preimplantation embryos, represent a natural source of pluripotent cells. Similarly, induced pluripotent stem cells (iPSCs), generated through the reprogramming of somatic cells, exhibit pluripotency and functional characteristics comparable to ESCs (Figure 1) [2].

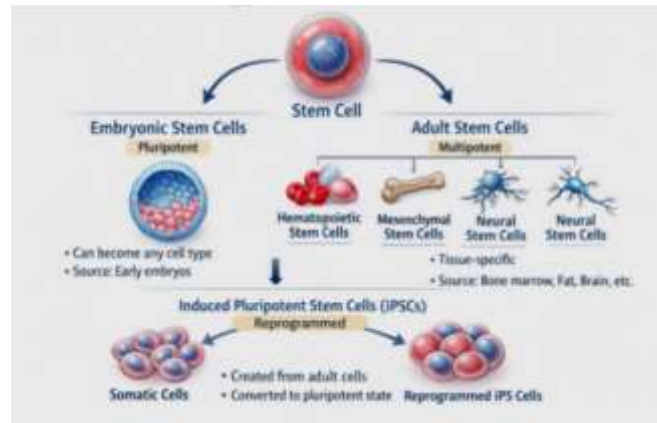


Fig.1. Stem Cell and its types

Embryonic stem cells (ESCs) are pluripotent cells derived from the inner cell mass (ICM) of the blastocyst, an early embryonic stage formed during normal development following fertilization. Cells isolated from the ICM can be cultured in vitro and possess the ability to differentiate into cell types of all three germ layers, making them valuable for regenerative medicine and gene-editing applications. Despite their therapeutic potential, the use of ESCs remains associated with ethical concerns related to embryo-derived cell isolation. In contrast, adult or somatic stem cells reside within developed tissues and are generally multipotent, with the capacity to generate a limited range of lineage-specific cell types. Their primary physiological function is the maintenance, repair, and regeneration of damaged tissues [2]. Notable examples include hematopoietic stem cells (HSCs), which give rise to all blood cell lineages, and mesenchymal stem cells (MSCs), which differentiate into osteogenic, chondrogenic, and adipogenic cell types. Stem cell editing involves the precise modification of genetic material within stem cells through advanced genome-engineering technologies. By combining stem cell biology with gene-editing approaches, researchers can investigate disease mechanisms, model genetic disorders, screen therapeutic compounds, and develop personalized regenerative therapies. The advent of genome-editing tools, particularly CRISPR-Cas systems, has further enhanced the potential of stem cells in disease correction and translational medicine.

Gene therapy was initially conceived as the introduction of functional genes into cells to compensate for defective or missing genetic material. The emergence of genome-editing technologies has transformed this concept by enabling precise modification of genomic DNA to achieve therapeutic outcomes. These technologies facilitate the correction of disease-causing mutations, targeted insertion of therapeutic genes, and removal or inactivation of harmful genetic sequences, thereby offering unprecedented opportunities for the treatment of inherited and acquired disorders [3]. Advances in molecular genetics have significantly improved our understanding of the genetic basis of human diseases, leading to the development of strategies aimed at directly addressing their underlying causes. Early gene therapy approaches relied primarily on the delivery of exogenous DNA to replace defective genes; however, decades of research have revealed substantial challenges associated with the safe, efficient, and controlled introduction of genetic material into target cells. Major limitations included variable gene expression,

insertional mutagenesis, and low targeting specificity. Despite these obstacles, remarkable progress has been achieved in the development of gene-delivery systems and genome-engineering platforms, resulting in improved precision, efficiency, and safety. Technologies such as CRISPR-Cas, TALENs, and zinc-finger nucleases have enabled targeted manipulation of specific genomic loci, expanding the therapeutic potential of gene-based interventions. Nevertheless, challenges related to off-target effects, delivery efficiency, long-term safety, and ethical considerations remain. This review focuses on stem cell editing, highlighting its underlying principles, major methodologies, therapeutic applications, and the ethical and societal implications associated with its clinical translation and future development.

2. Gene Editing In Stem Cells

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) is a powerful genome-editing technology that enables precise and targeted modification of DNA sequences. Originally identified as part of the adaptive immune system of bacteria and archaea, CRISPR functions through CRISPR-associated (Cas) proteins that recognize and cleave invading nucleic acids, providing defense against viral infections. Its simplicity, specificity, and versatility have made CRISPR a transformative tool in biomedical research and therapeutic development. Numerous inherited disorders, including cystic fibrosis, Huntington's disease, Duchenne muscular dystrophy, and sickle cell disease, arise from mutations in single genes. Advances in genomic research have highlighted the potential of correcting such genetic defects through targeted genome modification. CRISPR facilitates gene disruption, correction, or insertion at specific genomic loci, offering promising strategies for the treatment of genetic diseases. Beyond genome editing, CRISPR-based technologies are widely applied in transcriptional regulation, epigenome engineering, functional genomics, chromosome imaging, and high-throughput genetic screening, expanding their impact across diverse areas of biological and medical research [4].

CRISPR-Cas9 has emerged as a versatile genome-editing platform with significant applications in stem cell research and regenerative medicine. The technology enables precise correction of disease-causing mutations in induced pluripotent stem cells (iPSCs), followed by their differentiation into specific cell types for disease modeling and therapeutic applications (Figure 2) [5]. Gene-edited iPSCs also provide valuable in vitro models for investigating disease mechanisms and evaluating potential treatments. Furthermore, CRISPR-mediated engineering of stem cells has facilitated the development of organoids and advanced cellular models that closely mimic human physiology and pathology. Hematopoietic stem cells (HSCs) are another important target for CRISPR-based modification, offering promising avenues for the treatment of inherited and acquired genetic disorders [5]. The self-renewal capacity and differentiation potential of stem cells make them ideal candidates for genome editing. In particular, iPSCs generated through somatic cell reprogramming can be maintained in vitro and subjected to targeted gene correction, disruption, or insertion, enabling the development of patient-specific disease models and personalized regenerative therapies[2].

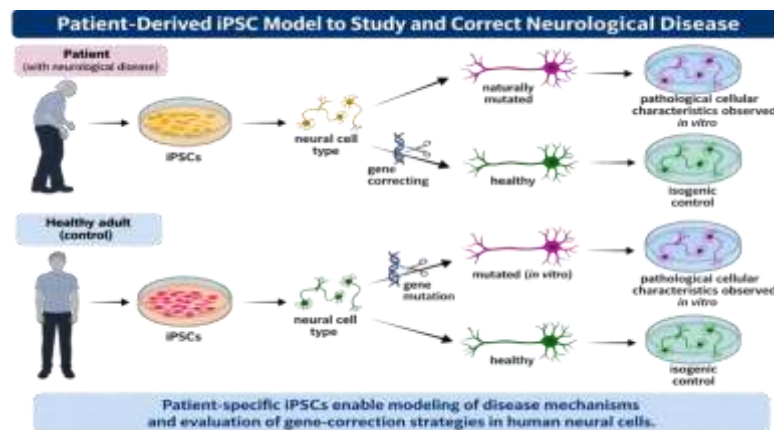


Fig 2. iPSCs from a patient or a healthy adult and different cell types (Beghini, *et al.*, 2024).

Gene editing strategies typically rely on the induction of targeted double-strand breaks (DSBs) in DNA, which are subsequently repaired through two major cellular pathways: non-homologous end joining (NHEJ) and homology-directed repair (HDR) [6]. NHEJ is the predominant repair mechanism in mammalian cells and functions without the need for a homologous DNA template. Following a DSB, the broken DNA ends are recognized by the Ku70/Ku80 heterodimer, which recruits DNA-dependent protein kinase (DNA-PK) and other repair factors to form a synaptic complex. The DNA ends are then processed and ultimately sealed by DNA ligase IV (LIG4) [7]. During this repair process, small insertions or deletions (indels) may be introduced at the break site, often disrupting gene function and resulting in gene knockout. In protein-coding regions, indels that are not multiples of three nucleotides can produce frameshift mutations, leading to altered or truncated proteins [7]. In contrast, HDR utilizes a homologous DNA template to accurately repair the break, enabling precise sequence modification, gene correction, or targeted gene insertion. Owing to its simplicity and efficiency, NHEJ is widely employed for gene disruption studies, whereas HDR is preferred for precise genome engineering applications.

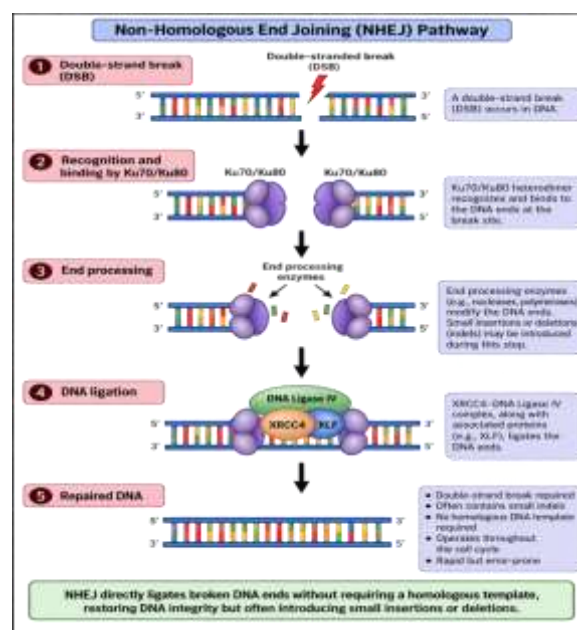


Fig 3. NHEJ route of repair of double strand break, causing introduction of indels, without need of homologous DNA template.

HDR, is a higher precision process of DSB repairing, where a DNA sequence template (in CRISPR, this template contains the edited sequence which alters the DNA to induce modification or inactivation) is provided and the cell uses this template to synthesize the complementary sequence [8]. However, HDR is not as effective as NHEJ, especially in stem cells, as its effects depends strongly on the stage of cell cycle and the availability of a suitable donor template. Another way is through in vivo editing of Hematopoietic stem cells (HSCs) through mRNA delivery. HSCs are found in the bone marrow, and they are multipotent, being able to produce multiple kinds of blood cells and immune cells (myeloid and Lymphoid lineages). HSCs produce blood and immune cells throughout life, this paves way for defect correction in the many cells formed from HSCs. HSCs from host are taken and gene modification is done and reintroducing them back into host does not warrant worry of Graft-versus-host disease (GVHD). However, conditioning is required where the old, affected HSCs must be removed to make space for the new modified HSCs. Gene editing applied in HSCs are facilitated through lipid nanoparticles like CD117-targeted lipid nanoparticles (CD117/LNPs). This greatly reduces the risk of unintended damage from chemotherapy and radiation used for HSC conditioning. This lipid nanoparticle carries mRNA which encodes for different proteins as intended [9]

3. Applications of Gene Editing In Stem Cells

3.1 Genetic disease modelling:

Induced pluripotent stem cells (iPSCs) have emerged as powerful tools for modeling human genetic diseases due to their capacity for unlimited self-renewal and differentiation into disease-relevant cell types. Because patient-derived iPSCs retain the genetic variants responsible for disease, they provide physiologically relevant platforms for investigating disease mechanisms and cellular pathologies [11]. The integration of genome-editing technologies, particularly CRISPR-Cas9, has significantly enhanced the utility of iPSC-based disease models. Precise introduction of pathogenic mutations into healthy iPSCs or correction of disease-causing variants in patient-derived iPSCs enables the generation of isogenic cell lines that differ only at specific genetic loci, allowing direct assessment of mutation-specific effects [10]. Such approaches facilitate the identification of causal relationships between genetic alterations and disease phenotypes under controlled experimental conditions. A notable example is Leber congenital amaurosis (LCA), an inherited retinal disorder, in which CRISPR-Cas9-mediated correction of an pathogenic LCA5 variant in patient-derived iPSCs restored lebercilin expression and localization following differentiation into retinal organoids. This study highlights the potential of combining genome editing with iPSC-derived organoid systems to investigate disease pathogenesis and evaluate therapeutic interventions at the cellular level [12].

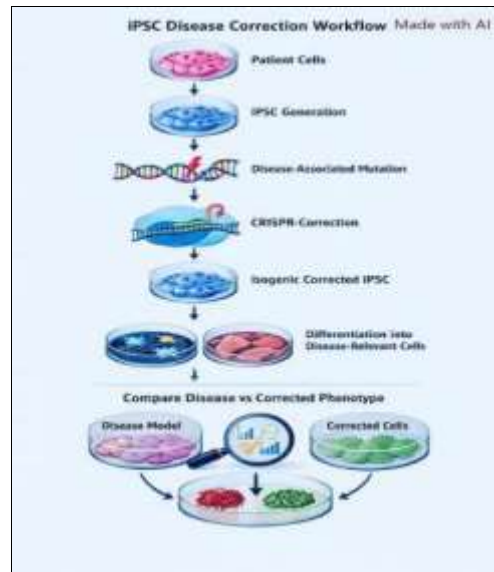


Fig. 4. Schematic representation of the application of gene editing in stem-cell-based genetic disease modelling (AI generated)

The utility of iPSC-based disease models has been further demonstrated in focal segmental glomerulosclerosis, where CRISPR-Cas9-mediated correction of a pathogenic PAX2 mutation in patient-derived iPSCs resulted in improved podocyte function following differentiation, confirming the causal role of the mutation in disease manifestation [13]. Together, these studies highlight the power of combining stem cell technology with genome editing to generate isogenic disease models, establish genotype-phenotype relationships, and investigate underlying disease mechanisms. Such platforms provide valuable tools for target identification, drug screening, and the development of precision therapies, thereby advancing translational and regenerative medicine (Figure 4) [10].

3.2 Gene correction and treatment of genetic disorders:

Unlike conventional therapies that primarily alleviate symptoms, genome editing aims to correct the underlying genetic defect or modify disease-associated pathways at the cellular level. Stem cells are particularly suitable for this approach because genetically modified cells can self-renew and generate functional progeny after transplantation [17]. Among stem-cell populations, hematopoietic stem and progenitor cells (HSPCs) have been extensively investigated for therapeutic gene editing. HSPCs can be isolated from patients, genetically modified *ex vivo*, and reinfused following appropriate conditioning. Because these cells give rise to multiple blood-cell lineages, successful modification of long-term repopulating HSPCs can provide a sustained source of therapeutically corrected blood cells [17].

Sickle cell disease (SCD) and transfusion-dependent β -thalassemia are prominent examples of successful HSPC-based gene-editing therapies. Rather than directly correcting mutations in the HBB gene, a widely adopted strategy targets the erythroid-specific enhancer of BCL11A, a repressor of fetal hemoglobin (HbF) expression. Disruption of this enhancer reactivates HbF production, compensating for defective adult hemoglobin [17]. In a clinical study by Frangoul *et al.*, CRISPR-Cas9-edited CD34⁺ HSPCs targeting the BCL11A enhancer resulted in sustained HbF production, transfusion independence in a β -thalassemia patient, and elimination of vaso-occlusive crises in an SCD patient during follow-up [17]. Similarly, CRISPR-mediated disruption of regulatory regions in HBG1 and HBG2 promoted persistent HbF expression and clinical improvement following transplantation of edited autologous HSPCs [15].

These studies demonstrate that therapeutic benefit can be achieved by modifying regulatory pathways rather than directly correcting disease-causing mutations. However, comprehensive assessment of editing efficiency, genomic stability, off-target effects, and long-term safety remains essential for the development of effective stem-cell-based gene therapies [14,16]. The clinical success of edited HSPCs highlights the promise of combining stem-cell transplantation with precise genome engineering for inherited disorders [17].

3.3. Regenerative medicine and tissue repair

Regenerative medicine aims to restore the structure and function of tissues damaged by injury, disease, or degeneration. Owing to their capacity for self-renewal and differentiation into specialized cell types, stem cells are central to tissue repair and regenerative therapies. However, their therapeutic efficacy is often limited by poor survival, suboptimal differentiation, and unfavorable microenvironments following transplantation. Genome-editing technologies, particularly CRISPR-based systems, have emerged as powerful tools to enhance stem cell function by enabling precise modification of genes involved in cell survival, proliferation, differentiation, and tissue regeneration. Genetic engineering can improve stem cell resistance to hypoxia, oxidative stress, and inflammatory conditions encountered after transplantation, thereby increasing therapeutic effectiveness [17]. In addition, CRISPR/dCas9-mediated transcriptional activation allows controlled regulation of endogenous genes without introducing permanent DNA double-strand breaks, facilitating directed differentiation into cardiac, neural, osteogenic, and chondrogenic lineages. Studies have demonstrated that activation of cardiac lineage-specific factors in stem cells enhances myocardial repair, improves cardiac function, and reduces scar formation following transplantation in experimental models. Similarly, targeted genetic modification of mesenchymal stem cells has been shown to promote cell survival, proliferation, and tissue regeneration under ischemic conditions. Beyond cardiac applications, gene-edited stem cells are being investigated for neural, retinal, bone, cartilage, skin, and liver regeneration. Furthermore, combining genetically modified stem cells with biomaterial scaffolds and tissue-engineering approaches may provide supportive microenvironments for enhanced tissue repair (Figure 5). Despite promising advances, challenges related to editing accuracy, off-target effects, maintenance of stem cell identity, and long-term safety must be addressed before widespread clinical translation can be achieved [18].

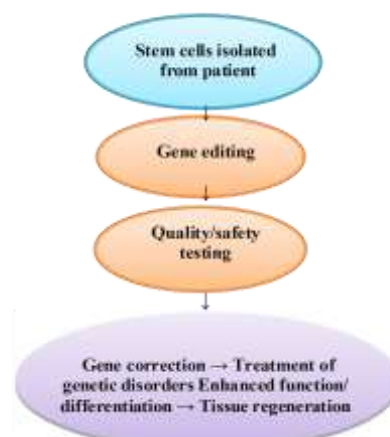


Fig 3. Generation of disease-specific and gene-corrected stem-cell models for genetic disease research.

3.4 Cancer research and cancer therapy

Cancer is a genetically complex disease characterized by the accumulation of mutations and dysregulation

of signaling pathways that promote uncontrolled cell proliferation, survival, and progression. Gene-editing technologies, particularly CRISPR-Cas systems, have emerged as powerful tools for investigating cancer biology and identifying novel therapeutic targets [22]. Stem cell models, including hematopoietic stem and progenitor cells (HSPCs) and induced pluripotent stem cells (iPSCs), can be genetically engineered to study the early events of malignant transformation. Introducing specific mutations into these cells enables researchers to evaluate their effects on cellular proliferation, differentiation, and disease progression, particularly in cancers driven by aberrant stem or progenitor cell populations [21]. HSPCs have proven especially valuable for modeling hematological malignancies. CRISPR-Cas9-mediated editing allows the introduction or disruption of leukemia-associated genes, facilitating the investigation of their roles in disease development. For example, an *in vivo* CRISPR screening study identified *Pbrm1* as a regulator of myeloid leukemia progression, demonstrating the utility of genome editing in uncovering genes involved in leukemogenesis [24]. Genome-wide CRISPR knockout, CRISPR interference (CRISPRi), and CRISPR activation (CRISPRa) screens further enable the systematic identification of genes influencing cancer-cell survival, proliferation, therapeutic response, and interactions with the tumor microenvironment, thereby revealing previously unrecognized molecular pathways and therapeutic targets [21].

Beyond disease modeling, CRISPR-based approaches are being explored for direct therapeutic intervention. In acute myeloid leukemia, disruption of the oncogenic *RUNX1-RUNX1T1* fusion gene reduced leukemic-cell proliferation and tumor burden in experimental models [24]. Gene editing has also advanced cancer immunotherapy by enhancing the tumor-targeting capabilities of immune cells and identifying regulators of anti-tumor immune responses in T cells and natural killer cells [25]. Furthermore, genetically modified HSPCs can serve as a renewable source of engineered blood cells for next-generation cellular therapies. Notably, CRISPR-mediated deletion of *CD33* in healthy donor HSPCs has been proposed to improve the safety and selectivity of anti-*CD33* therapies for acute myeloid leukemia [23]. Despite these advances, challenges including tumor heterogeneity, off-target effects, and efficient delivery remain significant obstacles [22]. Nevertheless, the integration of stem-cell biology with CRISPR-based genome editing holds considerable promise for understanding cancer mechanisms and developing targeted, personalized therapies [21,25].

3.5. Drug discovery and screening

The development of effective therapeutics requires reliable disease models that accurately recapitulate disease pathology and predict treatment responses. Induced pluripotent stem cells (iPSCs) have emerged as valuable tools for drug discovery because of their unlimited self-renewal capacity and their ability to differentiate into disease-relevant cell types that are often inaccessible from primary tissues [15]. Their utility is further enhanced by gene-editing technologies, which enable the introduction, correction, or modification of specific genetic variants, allowing researchers to establish direct links between genotype and phenotype [10]. Gene editing can be employed to validate the functional significance of disease-associated mutations by comparing genetically corrected cells with their mutant counterparts. Correction of a pathogenic variant and subsequent restoration of normal cellular function provides strong evidence for its causal role in disease development [10]. This strategy can be integrated with compound screening approaches to identify small molecules capable of reversing disease phenotypes or compensating for the effects of defective genes. Similarly, stem cell-derived disease models can be used to screen large chemical libraries for compounds that alleviate pathological features or prevent cell death, particularly in cell types that are difficult to isolate or maintain under conventional culture conditions [15]. A major

advantage of iPSC-derived systems is their scalability, which facilitates high-throughput drug screening. In addition, CRISPR-based genetic screening technologies, including CRISPR knockout, CRISPR interference (CRISPRi), and CRISPR activation (CRISPRa), can be combined with chemical screening to identify genes and pathways that drive disease processes [10,21]. Once critical molecular targets have been identified, small-molecule libraries can be screened to discover compounds that modulate the same pathways and possess therapeutic potential [10,21].

A notable example is the study by Zhang et al. (2024), which combined CRISPRi/a screening with human iPSC-derived cardiomyocytes to investigate doxorubicin (DOX)-induced cardiomyopathy. DOX is an effective chemotherapeutic agent whose clinical use is limited by cardiotoxicity. CRISPR-based screening identified genes involved in DOX-induced cellular damage, and subsequent small-molecule screening revealed carbonic anhydrase 12 (CA12) as a promising therapeutic target. Inhibition of CA12 reduced cellular injury and improved cardiomyocyte function following DOX exposure, demonstrating the value of integrating genome editing with drug-discovery pipelines [21]. Beyond target identification, gene-editing technologies facilitate the characterization of drug mechanisms of action and the assessment of potential off-target effects. Genetic screens can reveal the pathways affected by specific compounds, thereby accelerating therapeutic development and improving target validation [21]. Furthermore, stem cell-derived models have become increasingly important for drug toxicity testing. iPSC-derived cardiomyocytes, hepatocytes, neurons, and other specialized cell types can be used to evaluate compound safety in human-relevant systems, addressing limitations associated with animal models and immortalized cell lines that often fail to accurately predict human responses [15].

The combination of gene editing and stem cell technologies also supports personalized medicine. Patient-specific iPSCs can be generated from individuals with distinct genetic backgrounds and differentiated into disease-relevant cell types. These models enable researchers to investigate patient-specific disease mechanisms and evaluate therapeutic responses in vitro. For monogenic disorders in particular, correcting disease-causing variants and assessing changes in cellular function or drug response can establish the clinical relevance of specific genetic alterations [10,15]. Despite these advantages, stem cell-based drug discovery platforms face several challenges. iPSC-derived cells may not fully replicate the complexity, maturation state, and tissue architecture of adult human organs. Moreover, genetic and phenotypic variability among patients can complicate data interpretation. High-throughput CRISPR screening approaches also require careful optimization to ensure efficient editing, reproducibility, and accurate analysis of screening outcomes [10,21].

Nevertheless, the integration of stem cell biology with genome-editing technologies represents a transformative approach for modern drug discovery. By enabling disease modeling, target identification, high-throughput compound screening, toxicity assessment, mechanism-of-action studies, and personalized medicine applications, these technologies provide powerful platforms for accelerating therapeutic development. Continued advances in stem cell engineering and genome-editing methodologies are expected to further enhance their impact on future drug discovery and precision medicine efforts [10,15,21].

4. Future Developments in Stem cells gene editing

4.1. Improving Homology-Directed Repair (HDR) Efficiency

Homology-directed repair (HDR) remains an essential genome-editing pathway because it enables precise genetic modifications, including targeted gene correction, sequence replacement, and insertion of large

DNA fragments that cannot be readily achieved through base editing. Despite its advantages, HDR efficiency in stem and progenitor cells remains relatively low, limiting its therapeutic application. A major challenge is that genome editing-induced DNA double-strand breaks (DSBs) activate cellular DNA damage responses, including the p53 pathway, which can impair stem cell proliferation, survival, and engraftment potential. Consequently, current research focuses on enhancing HDR efficiency while minimizing cellular stress, genomic instability, and unintended mutations. Improved delivery systems, optimized repair templates, and transient modulation of DNA repair pathways may increase the safety and effectiveness of HDR-based stem cell therapies [32].

4.2. *In Vivo* Gene Editing of Stem Cells

In vivo stem cell editing represents a promising advancement in regenerative medicine, wherein genome-editing components are delivered directly to stem cells within the body. This approach eliminates the need for cell isolation, ex vivo manipulation, and reinfusion, thereby simplifying therapeutic procedures. Recent studies have demonstrated the potential of targeted delivery systems, particularly nanoparticles, for editing hematopoietic stem cells (HSCs) directly in vivo. Such strategies may reduce the requirement for preconditioning treatments such as chemotherapy or radiation, which are often necessary for conventional stem cell transplantation. As a result, in vivo editing could enhance treatment accessibility, safety, and clinical applicability [33].

4.3. Gene-Edited Organoids and Disease Modelling

Gene-edited organoids are emerging as powerful platforms for studying human diseases. These three-dimensional structures closely mimic the cellular composition and architecture of native tissues, bridging the gap between conventional cell cultures and animal models. When generated from stem cells and combined with genome-editing technologies, organoids enable precise investigation of disease-associated genetic alterations within physiologically relevant tissue environments. Such models facilitate the study of disease mechanisms, drug responses, and therapeutic interventions with greater accuracy than traditional systems. Collectively, continued advances in stem cell biology, genome editing, and organoid technology are expected to accelerate the development of novel therapies and improve the management of a wide range of genetic and acquired disorders [34].

5. Future Horizons in Stem cell gene editing

The future of stem cell editing is being shaped by the development of next-generation genome-editing technologies that offer greater precision and safety than conventional CRISPR-Cas9 systems. Emerging approaches such as base editing and prime editing enable targeted genetic modifications without introducing double-strand DNA breaks, thereby reducing the risk of unintended genomic alterations. Base editors directly convert one nucleotide into another, whereas prime editors function as a programmable “search-and-replace” system capable of introducing precise genetic changes. These advances hold significant promise for correcting disease-causing mutations in stem cells with improved efficiency and accuracy [35]. As genome-editing technologies continue to mature, their application is expanding beyond monogenic disorders to complex diseases influenced by multiple genetic and environmental factors. This progression will require sophisticated strategies involving multiplex gene editing and modulation of entire gene regulatory networks. In parallel, considerable efforts are focused on developing in vivo editing approaches, where genome-editing components are delivered directly to target tissues within the body. Unlike current ex vivo methods, which require cell isolation, laboratory modification, and re-infusion, in vivo editing has the potential to simplify treatment and improve accessibility, particularly for tissues that

are difficult to target, such as the brain [35]. Together, these innovations are expected to accelerate the clinical translation of stem cell-based therapies and advance precision medicine.

6. Ethical consideration of stem cells and gene editing

As stem cell therapies and gene-editing technologies advance toward clinical application, ethical concerns extend beyond the source of stem cells to issues of informed consent, patient awareness, treatment expectations, and long-term safety. Patients must be provided with clear information regarding the potential benefits, limitations, risks, and uncertainties associated with gene-edited stem cell therapies. Although significant progress has improved the safety and efficacy of these interventions, unexpected outcomes remain possible due to biological variability, procedural limitations, or non-compliance with clinical guidelines. The importance of patient adherence was highlighted in a clinical study on autologous cartilage repair using allogeneic mesenchymal stem cells and autologous chondrons, where unfavorable outcomes in some patients were attributed to failure to follow rehabilitation protocols rather than the therapy itself [36]. These findings underscore the necessity of comprehensive patient education, informed consent, and strict adherence to treatment protocols to maximize therapeutic success.

Public engagement is equally important in addressing the societal implications of stem cell research. The widely adopted "14-day rule," which limits the in vitro culture of human embryos beyond 14 days after fertilization or the appearance of the primitive streak, has served as an ethical framework for embryonic research for several decades. However, recent advances in stem cell-derived embryo models and developmental biology have renewed discussions regarding its reassessment. These models can replicate key features of early human embryogenesis, providing valuable insights into implantation, organogenesis, placental development, and the origins of developmental disorders. Extending research within carefully regulated ethical frameworks may enhance understanding of early disease mechanisms and improve therapeutic strategies. Consequently, transparent communication and public participation are essential to ensure informed societal dialogue, maintain public trust, and support responsible scientific advancement [37].

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