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CRISPR–Cas9: A comprehensive review of gene editing for inherited blood disorders

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ABSTRACT

The CRISPR–Cas9 system is a highly promising and versatile platform for genome editing with significant potential for gene therapy. It employs locus-specific nucleases, guided by programmable RNAs, to cleave target DNA sites and introduce double-strand breaks, thereby enabling precise genome modification through endogenous DNA repair mechanisms. This review aims to elucidate the relationship between CRISPR–Cas9 technology and inherited blood disorders, and to highlight the most important evidence-based recommendations for the diagnosis and effective management of these conditions. The review synthesises recent literature—including clinical trials, systematic reviews, and meta-analyses published between 2019 and 2022—identified through comprehensive searches of Web of Science, PubMed, PMC, ScienceDirect, Frontiers in Genome Editing, OJRD, AMJ Med, and Google Books using terms such as *CRISPR–Cas9 system* and *inherited blood disorders*. Studies involving gene modification of haematopoietic cells form the foundation for discussing contemporary models of blood diseases. We also summarise the applications of gene modification in experimental, preclinical, and clinical haematology, including gene-function interference, target identification, drug discovery, and chimeric antigen receptor or T-cell receptor engineering. Future research should prioritise the optimisation of delivery systems, improvement of target specificity, and evaluation of long-term safety. We hope that this review will support haematology practitioners and genetic research specialists in deepening their understanding of the impact of CRISPR–Cas9 on human biology and promote greater awareness across the healthcare system. Finally, we discuss the rapidly evolving landscape of haematology and the ongoing advancements in CRISPR–Cas9 technology that are poised to further transform the field.

INTRODUCTION

Inherited blood disorders encompass conditions affecting hemoglobin synthesis and structure, deficiencies in enzymes that provide energy to red blood cells or protect them from oxidative damage, as well as abnormalities of erythrocyte membrane proteins. The most common inherited blood diseases include coagulation factor deficiencies, hemophilia, platelet disorders, sickle cell

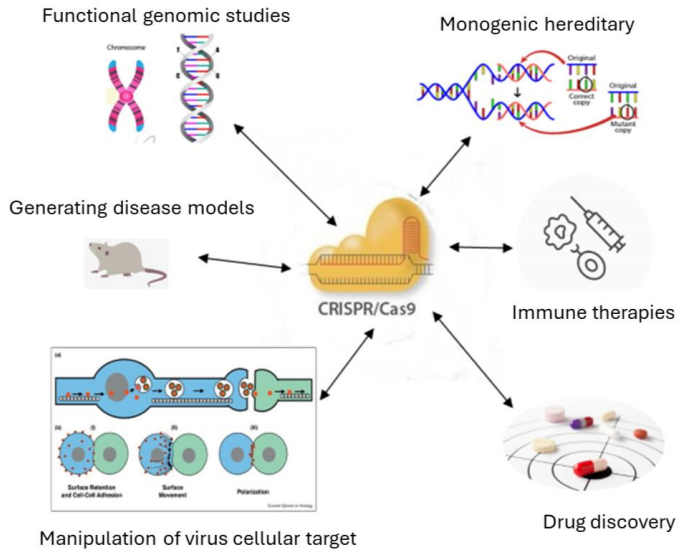
anemia, thalassemia, thrombophilia, and von Willebrand disease. According to the World Health Organization (2006), hemolytic anemias and hemoglobinopathies continue to create major challenges for health systems, particularly due to viral infections and limited access to specialized care.

Recent epidemiological data indicate that inherited red blood cell diseases remain widespread worldwide, with stable or increasing prevalence driven by population migration, growth, and socio-economic factors (Mattiuzzi & Lippi, 2020; Wendt et al., 2023). Despite improvements in diagnostics, effective therapy remains a challenge (Shi et al., 2025).

Inherited hemoglobin disorders are a significant component of the global burden of rare diseases. Hemoglobin mutation variants affect approximately 7% of the global population, with around 300,000–500,000 babies born annually with severe hemoglobinopathies (De Sanctis et al., 2023). Management options vary considerably across countries, highlighting the urgent need for effective and accessible disease-modifying therapies.

Current treatments, including chronic transfusions, iron chelation, allogeneic hematopoietic stem cell transplantation (HSCT), and hydroxyurea, provide temporary disease control but are limited by donor availability, immune complications, and financial constraints (Khan et al., 2025). While genome editing of hematopoietic stem and progenitor cells (HSPCs) offers therapeutic potential, challenges remain in applying this therapy safely. CRISPR-Cas9/AAV6-mediated editing has been associated with side effects such as cellular senescence and genotoxic inflammation, raising questions about long-term safety (Conti et al., 2025).

Figure 1:
Applications of CRISPR/Cas9 technology in hematology research and human therapy



Source: Gonzalez-Romero et al., 2019

The CRISPR-Cas9 system shows promise as an ideal therapeutic strategy for congenital hematological diseases. This system allows precise reconstruction, disruption, or introduction of genes in HSPCs for therapeutic purposes without disrupting normal cell function. This review discusses the introduction, challenges, and future prospects of CRISPR-Cas9 in treating congenital hematological disorders, including sickle cell disease (SCD), β-thalassemia, and hemophilia (Chehelgerdi et al., 2024; Schiroli et al., 2019; Xiao et al., 2024).

METHODS

This review synthesises current literature on genome editing using the CRISPR-Cas9 system for the treatment of hereditary blood disorders. Searches covered publications between 2019 and 2025 in PubMed, PMC, ScienceDirect, Frontiers in Genome Editing, OJRD, AMJ Medicine, and Google Books.

Inclusion criteria

Validated scientific studies (clinical or preclinical), systematic reviews, and narrative literature describing CRISPR or genome editing for hereditary haematological disorders.

Exclusion criteria

Studies not published in English and those lacking relevance to haematological diseases.

Evidence base

Peer-reviewed literature, open-access journal articles, clinical trial reports, and publicly accessible scientific studies.

Data synthesis

A narrative thematic approach was employed, organised around epidemiology, current therapies, CRISPR-Cas9 applications, delivery technologies, and future directions.

OVERVIEW AND MECHANISM OF CRISPR-Cas9

CRISPR was first identified as a bacterial adaptive immune system. The Cas9 nuclease, guided by mature guide RNA (gRNA) and trans-activating crRNA sequences, introduces precise double-strand breaks (DSBs) at targeted genomic sites (Lu et al., 2022). CRISPR-Cas9 has since been adapted for genome modification in mammalian cells by engineering sequence-specific crRNAs and complementary palindromic repeats (Lu et al., 2022). The system has been successfully applied to modify diverse cell types ex vivo and across multiple in vivo models, including mice, fish, monkeys, and pigs (Chehelgerdi et al., 2024).

A modified CRISPR-dCas9 platform blocks transcriptional elongation or releases transcriptional repression without inducing DSBs (Qi et al., 2013). Repressor or activator domains, such as KRAB or VP64, can be fused to dCas9, enabling gene silencing or activation. These tools have facilitated up to ~1000-fold increases in endogenous gene expression, offering insights into gene-function relationships (Gilbert et al., 2014).

Earlier genome-editing platforms—including zinc-finger nucleases (ZFNs), transcription-activator-like effector nucleases (TALENs), and meganucleases—represented significant technological progress but were limited by low specificity, design complexity, and reduced targeting efficiency (Lu et al., 2022; Lu, Happi Mbakam, Song, & Tremblay, 2022). CRISPR-Cas9 has therefore emerged as a more flexible and efficient alternative.

DELIVERY SYSTEMS

Types of CRISPR-Cas9 delivery formats

CRISPR-Cas9 may be delivered as plasmid DNA encoding Cas9 and sgRNA, as mRNA with sgRNA, or as ribonucleoprotein (RNP) complexes. Plasmid formats offer stability but face challenges such as nuclear entry, slower expression kinetics, and increased off-target activity. (Behrouzian Fard et al., 2025). Chemically modified mRNA enhances stability and translation efficiency. RNP delivery, which introduces Cas9 protein and sgRNA directly, is considered the most precise and transient option (Sioson et al., 2021; Iqbal et al, 2023).

CONSIDERATIONS IN LOADING AND DISTRIBUTION

The large molecular size of plasmids, RNA molecules, and Cas9 protein requires efficient loading strategies. Physical delivery methods allow direct membrane penetration but can compromise cell viability. Viral vectors—particularly AAV—have limited cargo capacity (<4 kb), which restricts the delivery of larger plasmids (Front Med, 2021; J Nanobiotech, 2024). Delivery modes include physical, viral, and non-viral strategies, each with advantages and limitations (Front Chem, 2022, 2023; J Nanobiotech, 2022).

Table 1:

Some of the common strategies for administering CRISPR/Cas9, their advantages, and limitations

Types of delivery	Delivery Strategies	Delivery formats	Advantages	Limitations	Applications
Physical delivery methods	Microinjection Electroportation HTV1	DNA; MRNA Protein DNA; mRNA; Protein DNA; Protein	Dosage controllable; Direct Easy to operate; No cargo size restriction Easy to operate; Low price	Technical limitation; *In vitro* only; Time-consuming *In vitro* only; Affects cell viability Traumatic to tissue; Low specificity	*In vitro*; *In vivo* *In vitro* *In vitro;* *In vivo*
Viral vector delivery methods	AAV AV LV	DNA DNA DNA	Minimal immunogenicity Large capacity; High deliver efficiency Large packaging capacity; Persistent gene transfer	Limited capacity High immunogenicity; Difficult scale production Insertional mutation; Long-lasting expression of Cas9	*In vivo* *In vivo* *In vitro*
Non-viral vector delivery methods	LNPs Polymeric nanoparticles Inorganic nanocarries DNA nanostructure	mRNA; Protein Protein Protein Protein	Easy to operate; Low cost; Easy to operate Excellent chemical stability Well histocompatibility	Specific cell tropism; Variable efficiency; Cytotoxicity; Variable efficiency; Modification of template DNA	*In vitro;* *In vivo* *In vivo* *In vitro;* *In vivo* *In vivo*

Source: (Liang et al., 2023)

APPLICATIONS IN SPECIFIC DISEASES

β-Thalassaemia

β-Thalassaemia arises from mutations in the HBB gene, leading to reduced β-globin synthesis, excess α-globin chains, ineffective erythropoiesis, and severe anaemia (Finotti et al., 2015; Ribeil et al., 2013). Although allogeneic HSCT is curative for some patients, donor limitations necessitate alternatives. CRISPR-Cas9 can correct HBB mutations or reactivate fetal haemoglobin (HbF) by disrupting regulatory regions such as BCL11A (Cavazzana-Calvo et al., 2010; Finotti et al., 2015).

Sickle Cell Disease (SCD)

SCD is caused by a single-nucleotide mutation in HBB, producing haemoglobin S (HbS). Under hypoxia, HbS polymerises, deforming RBCs and causing vaso-occlusion, haemolysis, anaemia, and multi-organ damage (Gewin, 2015; Hoban et al., 2016; Weatherall, 2010). CRISPR-Cas9 has demonstrated high efficiency in correcting HBB mutations in patient-derived iPSCs (Huang et al., 2015; Ugalde et al., 2023). Another promising approach targets BCL11A to reactivate HbF, though concerns remain regarding immune reactions to Cas9 and off-target mutations (Fontana et al., 2025; Adashi et al., 2023).

Fanconi Anaemia

Fanconi anaemia (FA) results from mutations in genes involved in the FA/BRCA DNA repair pathway, including FANCA, FANCC, and FANCG. It is characterised by genomic instability, congenital abnormalities, bone marrow failure, and elevated cancer risk (Auerbach, 2009; Soulier, 2011; Taniguchi & D'Andrea, 2006). Correcting FA mutations using iPSC technology has shown promise, but efficacy is limited by low homology-directed repair (HDR) rates and uncertain long-term safety (Rio et al., 2014; Raya et al., 2009).

Thrombocytopenia

Thrombocytopenia refers to a decrease in platelet count caused by inherited or acquired conditions (Drachman, 2004). Although research remains limited, CRISPR-Cas9 has successfully converted HPA-1b to HPA-1a in iPSCs, improving megakaryocyte viability. Nonetheless, challenges persist due to poor differentiation efficiency and off-target risks (Zhang et al., 2016).

Haemophilia

Haemophilia A and B result from deficiencies in coagulation factors VIII and IX, respectively (Ratnoff & Bennett, 1973). Earlier AAV-based gene therapies showed promise (High, 2012; McIntosh et al., 2013; Nathwani et al., 2011). CRISPR-Cas9 has been used to correct chromosomal inversions in iPSCs derived from patients with haemophilia A, enabling the production of functional endothelial cells capable of secreting FVIII (Park et al., 2015). Limitations include the complexity of F8 gene structure and potential immune responses to Cas9.

Diamond-Blackfan Anaemia (DBA)

DBA is a rare congenital erythroid aplasia caused by mutations in ribosomal protein genes, resulting in ribosomal stress and TP53 activation (Dutt et al., 2011; Jaako et al., 2011). Current treatments—including glucocorticoids and HSCT—carry significant adverse effects (Ball, 2011; Vlachos et al., 2001, 2008). CRISPR-Cas9 has demonstrated potential in zebrafish models, although editing ribosomal genes poses safety risks due to their essential functions (Ablain et al., 2015).

CHALLENGES AND LIMITATIONS

Despite substantial progress, CRISPR-Cas9 faces major challenges before routine clinical application. Off-target DNA cleavage threatens genomic stability (Schiroli et al., 2019; Xiao et al., 2024). Delivery challenges persist, especially with viral vectors that may provoke immune responses (Lu et al., 2022). Ethical concerns related to germline editing and equitable access further complicate clinical translation (De Sanctis et al., 2023). Additionally, the long-term stability of edited HSPCs remains uncertain (Chehelgerdi et al., 2024).

Future Prospects

CRISPR-Cas9 technology offers a highly precise method for targeting inherited blood disorders and reactivating fetal haemoglobin, holding promise for both ex vivo and in vivo therapies (Chehelgerdi et al., 2024; Lu et al., 2022). Enhancing delivery systems, reducing off-target activity, and establishing robust long-term safety data are essential for successful clinical translation (Schiroli et al., 2019; Xiao et al., 2024). Ethical considerations, regulatory oversight, and equitable access will shape the future of gene therapy (De Sanctis et al., 2023; Zheng, 2025; Kolanu, 2024).

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CONCLUSION

CRISPR-Cas9 shows strong potential for precise genome modification and correction of mutations responsible for inherited blood disorders such as β-thalassemia and SCD (Chehelgerdi et al., 2024; Lu et al., 2022). Promising results have been observed in the restoration of gene function in HSPCs and in patient-derived iPSCs (Schiroli et al., 2019; Xiao et al., 2024). Significant challenges remain—particularly off-target effects, delivery barriers, and uncertainties surrounding long-term cell stability (De Sanctis et al., 2023; Zheng, 2025). Current research focuses on improving vectors, expanding clinical trials, and developing strategies to minimise adverse effects (Lu et al., 2022; Xiao et al., 2024).

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