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Article

CRISPR-CAS9 IN THE TREATMENT OF INHERITED DISEASES: FROM LABORATORY TOOL TO CLINICAL PRACTICE

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Abstract: Over the past decade, CRISPR-Cas9 genome editing has undergone a remarkable transformation — from a foundational research tool to a tangible therapeutic strategy. This article reviews the core mechanisms of the CRISPR-Cas9 system and its derivatives — including base editing and prime editing — and examines clinical outcomes in the treatment of hereditary hemoglobinopathies, hereditary transthyretin amyloidosis, hereditary angioedema, and genetically driven cardiovascular disease. Particular attention is given to exagamglogene autotemcel (Casgevy), the first FDA-approved CRISPR-based therapy, alongside pressing challenges such as off-target editing, immune responses, and the delivery of therapeutic components to target tissues.

Keyword: CRISPR-Cas9, Genome Editing, Gene Therapy, Base Editing, Prime Editing, Casgevy, Hereditary Hemoglobinopathies, Transthyretin Amyloidosis, Hereditary Angioedema, Cardiovascular Disease

Introduction

Genomic — or hereditary — diseases arise from mutations in DNA and affect millions of people worldwide. Until recently, most of these conditions were considered incurable, with treatment limited to symptom management and supportive care. The discovery of CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats associated protein 9) as a universal genome editing platform fundamentally altered this landscape [1].

Originally characterized as an adaptive immune mechanism in bacteria, CRISPR-Cas9 was repurposed for precise DNA editing in human cells in 2012–2013. In 2020, Jennifer Doudna and Emmanuelle Charpentier received the Nobel Prize in Chemistry for this discovery, widely regarded as one of the most consequential advances in modern biology. The technology is now being evaluated in clinical trials for conditions affecting the blood, cardiovascular system, liver, immune function, and cancer [2].

The aim of this article is to synthesize current evidence on the application of CRISPR-based therapies in inherited disease, encompassing both approved treatments and the most promising investigational programs.

Materials and Methods

Mechanism of Action of the CRISPR-Cas9 System

The CRISPR-Cas9 system functions as a set of molecular scissors: a single guide RNA (sgRNA) directs the Cas9 endonuclease to a defined genomic target sequence, where it introduces a double-strand break at a precise location. The cell responds to this break through two primary repair pathways:

Non-homologous end joining (NHEJ) — a rapid but error-prone mechanism that frequently introduces small insertions or deletions (indels), effectively disrupting the target gene.
Homology-directed repair (HDR) — a high-fidelity pathway that uses a donor template to correct a mutation or insert a functional gene copy.

Results

Advances in CRISPR Technology

Beyond the classical CRISPR-Cas9 system, several refined variants have emerged. Base editing, pioneered in David Liu's laboratory at Harvard, enables the conversion of individual nucleotides without generating double-strand DNA breaks. Adenine base editors (ABEs) mediate A→G transitions, while cytosine base editors (CBEs) catalyze C→T changes. This approach substantially reduces the risk of chromosomal rearrangements and unintended mutations, improving the overall safety profile [3].

Prime editing, introduced in 2019, represents an even more versatile platform: it can execute all 12 types of point mutations as well as small insertions and deletions, without requiring a donor DNA template. The Cas12a (Cpf1) system offers additional advantages over Cas9, including higher specificity and the capacity to process multiple guide RNAs simultaneously [4].

Sickle Cell Disease and Beta-Thalassemia

The most clinically advanced application of CRISPR therapy is in the treatment of hereditary hemoglobinopathies — specifically sickle cell disease (SCD) and transfusion-dependent beta-thalassemia (TDT). Both conditions result from mutations in the HBB gene, which encodes the beta-globin subunit of hemoglobin.

The central therapeutic strategy involves reactivating fetal hemoglobin (HbF) by disrupting or editing regulatory elements within the BCL11A gene, a transcriptional repressor of gamma-globin expression. Under normal physiological conditions, fetal hemoglobin is silenced after birth; restoring its expression can compensate for defective beta-globin [5].

Exagamglogene autotemcel (Casgevy, co-developed by CRISPR Therapeutics and Vertex Pharmaceuticals) became the first CRISPR-based medicine to receive regulatory approval. It was authorized by the UK's MHRA in November 2023, by the U.S. FDA in December 2023 for SCD, and in January 2024 for TDT. Subsequent approvals followed in Saudi Arabia, the European Union (EMA), and Canada [6].

Clinical data demonstrate compelling efficacy. Results published in The New England Journal of Medicine showed that 94% of patients with SCD were free of vaso-occlusive crises for at least twelve months following treatment. Among patients with TDT, the majority achieved transfusion independence. The procedure is performed ex vivo: hematopoietic stem cells (CD34+) are harvested from the patient, edited in the laboratory, and reinfused after myeloablative conditioning [7].

Beam Therapeutics is pursuing a parallel clinical program, BEACON, with BEAM-101 — a base editing–based therapy in which the first patient received treatment in January 2024. Data presented at the 2024 American Society of Hematology (ASH) annual meeting confirmed durable efficacy and a favorable safety profile. Because base editing does not generate double-strand DNA breaks, it is theoretically associated with lower genotoxic risk than conventional CRISPR-Cas9 [8].

Hereditary Transthyretin Amyloidosis

Hereditary transthyretin amyloidosis (hATTR) is a rare but life-threatening disease caused by mutations in the TTR gene, leading to the production of misfolded transthyretin protein that forms toxic aggregates in peripheral nerves and the myocardium. The liver is the primary source of TTR and thus a natural therapeutic target.

Intellia Therapeutics developed NTLA-2001, the first systemic (intravenous) CRISPR therapy to be administered in humans, using lipid nanoparticles (LNPs) as the delivery vehicle. This platform also represents the first example of delivering genome editing components throughout the body rather than

to a single cell type.

Results published in The New England Journal of Medicine in November 2024 showed rapid, deep, and sustained reductions in pathological TTR levels in the blood — approximately 90% on average — maintained throughout the observation period. Based on these findings, Intellia initiated a global Phase 3 trial, with the first patient enrolled in January 2025. The company is targeting market authorization by 2027, pending positive outcomes [9].

Hereditary Angioedema

Hereditary angioedema (HAE) is a rare, potentially life-threatening condition caused by deficiency or dysfunction of C1-esterase inhibitor, characterized by recurrent episodes of swelling in the skin, subcutaneous tissues, and mucous membranes.

Intellia's NTLA-2002 targets the KLKB1 gene in hepatocytes, reducing the production of kallikrein — the enzyme that drives bradykinin synthesis, which is responsible for the edema. As of October 2024, Intellia reported that NTLA-2002 had successfully completed Phase 2 clinical trials and was advancing toward Phase 3. The therapy is administered as a single intravenous infusion. This approach — permanently silencing a disease-driving gene rather than correcting it — illustrates a conceptually novel strategy for disrupting pathological signaling cascades.

Genetically Driven Cardiovascular Disease

Hypercholesterolemia is among the leading risk factors for cardiovascular disease. Mutations in the PCSK9 gene underlie familial hypercholesterolemia, a condition associated with markedly elevated LDL levels. Verve Therapeutics developed VERVE-102, a single-dose base editing therapy designed to permanently inactivate PCSK9 in hepatocytes. Preliminary results published in late 2024 indicated good tolerability in the first two patient cohorts with no serious adverse events.

In November 2025, the Cleveland Clinic presented results from the first Phase 1 clinical trial of CTX310 (CRISPR Therapeutics), a single intravenous infusion targeting ANGPTL3 — a regulator of lipid metabolism. The results were simultaneously published in The New England Journal of Medicine. The trial enrolled 15 patients aged 31 to 68 with uncontrolled hyperlipidemia. Within two weeks of infusion, significant reductions in LDL cholesterol and triglycerides were observed, sustained for at least 60 days, with no serious adverse effects. This study provided an important proof of concept for the safety of in vivo genome editing in cardiovascular disease [10].

CRISPR Applications in Oncology

CRISPR technologies are being actively investigated in the development of next-generation CAR-T cell therapies. Allogeneic (donor-derived) CAR-T cells incorporating multiple CRISPR edits offer a potential route around the key limitations of autologous CAR-T: high individualized manufacturing costs, lengthy production timelines, and the risk of T-cell exhaustion. CRISPR Therapeutics is advancing several programs — CTX112 and CTX131 — targeting both hematologic malignancies and solid tumors.

Promising results have emerged from Caribou Biosciences' CB-010 program. In the Phase 1 ANTLER trial involving 16 patients with relapsed B-cell lymphoma, the overall response rate was 94%, with a complete response documented in 69% of participants. Seven of the 16 patients achieved a complete response lasting more than six months, and the longest response exceeded 24 months.

Researchers at the University of Minnesota completed the first clinical trial of a CRISPR-based tumor-infiltrating lymphocyte (TIL) therapy incorporating CISH gene knockout for advanced colorectal cancer. Results published in Lancet Oncology in 2025 demonstrated good tolerability among 12 patients with metastatic Stage IV disease. One patient experienced complete regression of metastases, which was sustained for more than two years.

Discussion

Challenges and Limitations

Off-Target Effects

Despite the high specificity of CRISPR-Cas9, unintended edits at off-target genomic sites remain a concern. Their frequency depends on guide RNA design, the editor variant used, and the characteristics of the target genome. Next-generation tools — including high-fidelity Cas9 variants (eSpCas9, HiFi Cas9), base editing, and prime editing — have substantially reduced this risk [11].

Delivery of Therapeutic Components

Efficient and safe delivery of CRISPR components to target tissues remains one of the primary technical challenges. Three main approaches are currently employed: viral vectors (adeno-associated viruses, lentiviruses), non-viral systems (lipid nanoparticles), and physical methods (electroporation). Each carries a distinct profile with respect to efficiency, tissue tropism, and immunogenicity.

A tragic case involving an AAV6 vector used within Cure Rare Disease's program for Duchenne muscular dystrophy — in which a patient died from acute respiratory distress syndrome due to an immune reaction to the viral vector — underscored the urgency of developing safer alternative delivery platforms [12].

Immune Responses and Long-Term Safety

The Cas9 protein is recognized as foreign by the human immune system, potentially triggering both humoral and cellular immune responses. The long-term safety of genome editing — including potential oncogenic risk — requires sustained clinical follow-up over many years. As of 2025, long-term outcome data remain limited, given the relative recency of these therapies.

Ethical Considerations and Access

The high cost of CRISPR therapies poses a significant barrier to equitable access. Casgevy, for example, is priced at approximately $2.2 million per treatment course. The development of outcomes-based pricing models tied to clinical benefit is an active area of debate at the health systems level. Germline editing — the introduction of heritable changes into the genome — remains subject to an international moratorium due to serious ethical concerns [13].

Future Directions

According to the CRISPR Medicine News clinical trials registry, as of February 2025, more than 239 clinical trials involving genome editing–based therapies were underway worldwide. The largest proportion involves Phase 3 studies in blood disorders, hereditary amyloidosis, and immunodeficiencies [14].

Key priorities for future development include: the creation of in vivo platforms targeting a broader range of tissues (including the brain, muscle, and lung); advances in tissue-specific non-viral delivery systems (LNPs with targeted tropism); the integration of epigenome editing to regulate gene expression without altering the underlying nucleotide sequence; and the manufacture of "off-the-shelf" allogeneic cell therapies to reduce production costs.

The integration of CRISPR into personalized medicine — including the design of individualized therapies for patients with rare mutations — marks a fundamentally new chapter in treating conditions that were once considered beyond the reach of medicine [15].

Conclusion

CRISPR-Cas9 and its derivatives have achieved an unprecedented transition from scientific concept to real-world clinical practice in under fifteen years. The approval of Casgevy in 2023–2024 marked a historic milestone, establishing the viability of CRISPR-based therapy for serious inherited disease. Clinical outcomes in sickle cell disease, transthyretin amyloidosis, hereditary angioedema, and familial hypercholesterolemia demonstrate meaningful efficacy and an acceptable safety profile.

At the same time, several foundational challenges — including off-target effects, immunogenicity, treatment costs, and the limited depth of long-term safety data — require continued investigation. Taken together, the pace of scientific progress, the growing body of evidence, and accumulating international regulatory experience provide a sound basis for cautious optimism: CRISPR-based therapies are poised to become a defining pillar of future medicine.

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