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# CRISPR Technology in the Treatment of Leber Congenital Amaurosis (LCA)

**Bowen Zhang**[1, *]

[1]The Branch Campus of Qingdao No.2 Middle School, Qingdao, China
*Corresponding author: sweetscones@outlook.com

**Abstract:**

Leber congenital amaurosis (LCA) is a severe inherited retinal disease and one of the leading causes of childhood blindness. With the rise of gene therapy, CRISPR-Cas9 gene editing technology has brought new hope for the treatment of LCA. This article reviews the research progress of CRISPR in LCA treatment. This article focuses on key experiments in LCA treatment, particularly animal models and clinical studies targeting core pathogenic genes such as CEP290, RPE65, and GUCY2D. Among them, the EDIT-101 clinical trial targeting CEP290 mutations achieved the first-ever CRISPR gene editing in humans and preliminarily validated its safety and efficacy in selected patients, confirming the feasibility of the nonhomologous end joining (NHEJ) strategy in non-dividing retinal cells. Although animal studies have shown that CRISPR can effectively repair mutations and restore some visual function, it still faces many challenges, including the low efficiency of HDR strategies in non-dividing cells, the need to optimize vector delivery efficiency for clinical applications, and the commercialization challenges posed by rare diseases. This article aims to provide reference and insights for future research directions in the field of LCA treatment using CRISPR.

**Keywords:** CRISPR, gene therapy, retinal degeneration, Leber congenital amaurosis (LCA).

## 1. Introduction

Among inherited retinal diseases, Leber's congenital amaurosis (LCA) is one of the earliest and most severe diseases. Severe visual impairment usually occurs in infancy and is one of the main causes of childhood blindness. It is caused by abnormal visual cycles, degeneration or death of visual cells, and accounts for 5% of all inherited retinal diseases. Due to its early onset, approximately 20% of blind school-age children are caused by this disease. Common LCA mutation genes include GUCY2D (LCA1), RPE65 (LCA2), CEP290 (LCA10), etc [1]. With the advancement of precision medicine, genetic diagnosis and targeted therapy have brought new hope to LCA patients, significantly improving the accuracy of diagnosis and the effectiveness of treatment. CRISPR/Cas is an acquired immune system present

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in bacteria and archaea. CRISPR RNA (crRNA) forms a crRNA-ribonucleoprotein (crRNP) effector complex with single or multiple Cas proteins with nuclease activity, which plays a vital role in preventing the invasion and integration of foreign DNA such as viruses or plasmids [2]. With the discovery of Cas proteins and the application of recombinant DNA technology, researchers have integrated and modified the CRISPR/Cas system and used it as a tool for genome editing. Currently, the most widely used is the CRISPR/Cas9 system, which includes crRNA, trans-activating crRNA (tracrRNA) and Cas9 protein [3]. As of 2025, CRISPR-Cas9 has achieved the first in vivo editing and preliminary efficacy verification in the treatment of LCA, opening up a new avenue for the treatment of inherited retinal diseases. However, it is still in its early stages and has obvious shortcomings: low editing efficiency, few patients with indications, high development costs and long-term safety evaluation. To achieve widespread clinical application, technical optimization, expanded research scale, and studies in a wider range of patient types are necessary. This article comprehensively analyzes and summarizes representative studies on CRISPR for the treatment of LCA, in order to assess the potential application value of this treatment approach.

## 2. The Composition of CRISPR and Its Editing Principle

### 2.1 Structure of the CRISPR System

Taking CRISPRCas9 as an example, the system structure includes gRNA, PAM sequence, and Cas9 protein. gRNA, also known as guide RNA, consists of crRNA and tracrRNA (or combined into a single sgRNA), which is responsible for guiding the Cas9 protein to recognize the target DNA sequence. The PAM sequence is a short conserved sequence (usually NGG) that the target DNA must contain for Cas9 to recognize and bind. The Cas9 protein is guided to the target DNA by the gRNA. After recognizing and binding to the PAM, it creates a double-strand break (DSB), as shown in Figure 1. The current mainstream vector for delivering gRNA and Cas9 is adeno-associated virus (AAV).

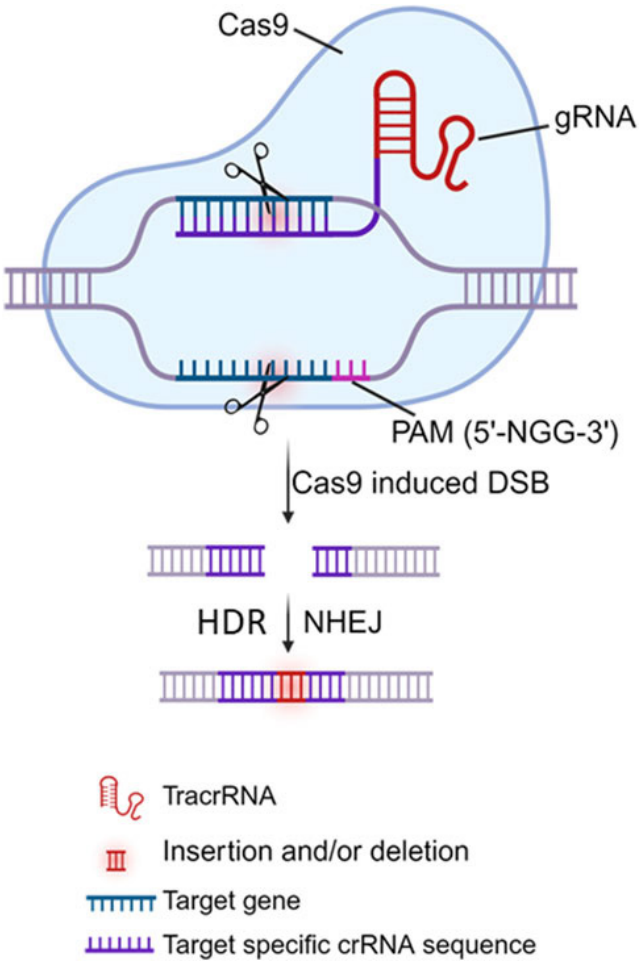


**Fig. 1 The working mechanism of CRISPR/Cas9 gene editing [4].**

### 2.2 CRISPR Editing Principle

After the Cas9 protein scans for conserved protospacer adjacent motif (PAM) sequences, the crRNA specifically recognizes and binds to the target site, activating Cas9's nuclease activity and causing DSBs. By varying the 20 nucleotides in the crRNA that complement the target sequence, the CRISPR/Cas9 system can target different DNA sequences with PAM characteristics genome-wide. Once the target DNA is cut, the cell recruits proteins involved in the endogenous repair machinery to initiate DNA repair at the double-strand break site. Repair results can include insertions, deletions, or base substitutions. The DSB repair mechanisms involved in this process primarily include two pathways: nonhomologous end joining (NHEJ) and homology-directed recombination (HDR). Among them, NHEJ completes repair by directly connecting the broken DNA ends, but the accuracy of this mechanism is low, often causing random insertion or deletion of nucleotides (insertion and deletion, indel), which may

cause frameshift mutations or premature termination of the original sequence, achieving the purpose of knocking out protein-coding genes, silencing gene expression, or targeted destruction of gene regulatory elements to inhibit or activate downstream gene expression. In addition, by designing two sgRNAs to simultaneously guide Cas9 to generate DSBs at two different target sites on the same chromosome arm and induce NHEJ-mediated repair, the DNA sequence of a specific gene or regulatory element can be deleted or reversed. NHEJ repair based on single DSB or double DSB is one of the main development strategies for clinical genome editing to treat genetic diseases [5].

### 2.3 Two Pathways of DSB Repair Mechanism

Two pathways of DSB repair include HDR (Homology-Directed Repair) and NHEJ (Non-Homologous End Joining). HDR uses an externally provided "donor DNA" as a reference for repair, allowing cells to precisely repair DNA breaks. This allows for precise insertions (knock-in, KI) or gene replacement. NHEJ directly splices broken DNA ends together without the need for a template. This often results in random insertions or deletions (indels), causing frameshift mutations and leading to gene silencing or inactivation (knock-out, KO). Homology-directed repair (HDR) utilizes exogenous DNA as a donor template, precisely inserting it into a specific location in the genome, thereby accurately replacing the target gene or inserting and expressing a new gene. In contrast to HDR, NHEJ remains active throughout the cell cycle and can occur in both dividing and non-dividing cells, enabling the knockout or targeted modification of specific DNA sequences in target cell populations. However, compared to NHEJ, HDR is only active in the late S/G2 phase of the cell cycle and occurs at a very low frequency in animal embryos and in vivo tissues. The efficiency of HDR-based insertional mutagenesis strategies is generally only 0.5%–20%, which significantly limits the widespread application of this technology in clinical therapeutic research [6].

For example, in the EDIT-101 experiment, the CEP290 c.2991+1655A>G mutation is located in intron 26 (a non-coding region), creating a pseudo-splicing site and resulting in aberrant mRNA. Disruption of this site through the NHEJ mechanism prevents aberrant splicing and restores normal protein expression. NHEJ disrupts the mutation site by introducing indels, which is sufficient to eliminate the pseudo-splicing signal without requiring the insertion of specific sequences. HDR aims to precisely replace the mutated sequence, but it is not advantageous for intronic mutations because normal splicing does not depend on precise sequence. Random indels (1-20 bp insertions/deletions) introduced by NHEJ efficiently block aberrant splicing, functionally equivalent to the precise repair achieved by HDR. This simplifies therapeutic design and avoids the complex templates required for HDR. Retinal pigment epithelium (RPE) and photoreceptor cells are non-dividing (post-mitotic) cells that lack the S/G2 phase, making HDR nearly impossible (efficiency <1%). NHEJ is active throughout the cell cycle (including G0/G1) and predominates in non-dividing cells, achieving editing efficiencies of 20-50%. NHEJ is well-suited to the biological characteristics of retinal cells, ensuring high editing efficiency. HDR requires inducing cell division (e.g., through drugs or gene manipulation), which is not feasible in the retina and may impair cellular function. EDIT-101 uses dual AAV vectors to deliver Cas9 (approximately 4.2 kb) and gRNA, respectively, approaching the AAV capacity limit of 4.7 kb. HDR requires the delivery of an additional DNA repair template (hundreds to thousands of base pairs), exceeding the capacity of existing AAV systems. Dual AAV systems require simultaneous infection of the same cell with two vectors, which is already less efficient than single AAV systems (e.g., Luxturna). Adding an HDR template would further reduce delivery efficiency and increase manufacturing and quality control challenges. NHEJ eliminates the need for a template, requiring only Cas9 and gRNA, simplifying delivery and clinical translation. NHEJ reduces AAV design complexity, minimizing immune responses and production costs. The dual AAV NHEJ strategy has been validated in preclinical trials and demonstrated its feasibility. NHEJ boasts significantly higher editing efficiencies (20-50%) than HDR (<1%), shortening clinical trial cycles and accelerating patient treatment. HDR requires optimization of template sequence, delivery method, and cell cycle regulation, which increases R&D time and cost and delays clinical translation. The Phase I/II trial of EDIT-101 (initiated in 2019, NCT03872479) is designed for NHEJ, and preliminary results (as of 2024) show improved vision in some patients, validating the practicality of NHEJ. The NHEJ strategy has been validated in preclinical and early clinical trials and has been shown to be effective for LCA10. The low efficiency and high complexity of HDR make it uncompetitive in the current LCA treatment [7,8].

## 3. Pathological Mechanisms of LCA

Leber congenital amaurosis (LCA) is a rare, inherited retinal dystrophy that causes severe visual impairment at birth or in early infancy. Its pathological mechanism primarily involves degeneration of retinal photoreceptors (rods and cones) and the retinal pigment epithelium (RPE), disrupting phototransduction and the visual cycle, ulti-

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mately leading to visual loss. Genetically, LCA is caused by mutations in over 20 genes, accounting for approximately 70% of cases. These mutations disrupt processes such as photoreceptor development, ciliary function, and protein trafficking. Key genes include RPE65 (visual cycle), CEP290 (ciliary transport), GUCY2D (phototransduction), and AIPL1 (chaperone protein function). LCA is often inherited as an autosomal recessive trait, and the phenotype varies from individual to individual. Among them, RPE65 (Retinal pigment epithelium–specific 65 kDa protein), located in retinal pigment epithelial cells, is a key enzyme in the visual cycle, responsible for converting all-trans retinyl esters to 11-cis retinol, providing 11-cis retinal, the light-sensing molecule required for photoreceptors. Mutations in RPE65 often result in protein deficiency or enzyme inactivity, preventing the production of 11-cis retinal. This prevents the regeneration of rhodopsin and cone pigments, leading to loss of photoreceptor function and premature, severe visual impairment. CEP290 (Centrosomal protein 290 kDa) is located in the transition zone of primary cilia. In photoreceptor cells, it regulates transciliary transport of outer segment proteins, maintaining the normal structure and function of photoreceptor outer segments. Mutations in CEP290 often result in loss of function, impairing ciliary protein transport, resulting in structural abnormalities and gradual degeneration of photoreceptor outer segments. Among them, the common deep intronic mutation c.2991+1655A>G results in aberrant splicing (pseudo-exon insertion), leading to premature protein termination and the most typical pathogenic mechanism of LCA10. GUCY2D (Guanylate cyclase 2D, retinal) is a guanylate cyclase in the photoreceptor outer segment membrane. It is responsible for converting GTP to cGMP, maintaining the dark current and resetting phototransduction, and is crucial for shutting down and recovering from light signaling. Recessive mutations that lead to complete loss of GUCY2D protein function (null mutations) prevent cGMP synthesis, preventing photoreceptors from returning to the dark state, leading to a near-complete cessation of phototransduction and causing LCA1. Dominant mutations, often located in the dimerization domain (such as the p.R838 variant), alter the calcium sensitivity of GC-E and GCAPs, leading to preferential cone cell degeneration and the initiation of CORD6. AIPL1 (Aryl hydrocarbon receptor-interacting protein-like 1) is a photoreceptor-specific HSP90 co-chaperone protein primarily responsible for the correct folding and assembly of the phosphodiesterase PDE6, an essential factor in the phototransduction signaling cascade. Mutations in AIPL1 disable its function, preventing the proper assembly of PDE6 and leading to its degradation. This leads to excessive accumulation of cGMP, disrupted $Ca_2^+$ homeostasis, and rapid photoreceptor degeneration, resulting in LCA4.

# 4. CRISPR Intervention Strategies for LCA Treatment

## 4.1 EDIT-101

### 4.1.1 EDIT-101 experiment principles

In LCA10, a deep intronic mutation (c.2991+1655A>G) in the CEP290 gene introduces a pseudointron outside of a codon, leading to aberrant mRNA splicing. This results in a truncated CEP290 protein with impaired or complete loss of function. This dysfunction affects the CEP290 protein, which is crucial for maintaining the connecting cilia of photoreceptor cells and the RPE. This abnormality leads to impaired light signal transduction, triggering retinal degeneration and vision loss, the pathological hallmarks of LCA10. The goal of CRISPR therapy (such as EDIT-101) is to knock out this aberrant splice site, disrupting the pseudointron and restoring normal mRNA splicing and functional CEP290 protein expression, thereby alleviating this dysfunction.

### 4.1.2 EDIT-101 experimental preclinical data (in vitro and animal models):

The goal was to repair the CEP290 gene mutation (c.2991+1655A>G) by introducing indels through NHEJ, disrupting the aberrant splice site and restoring normal mRNA and protein expression. The model used patient-derived induced pluripotent stem cells (iPSCs) differentiated into retinal organoids. Humanized mice (HuCEP290) harboring the c.2991+1655A>G mutation were injected subretina with dual AAV (AAV5) vectors to deliver Cas9 and gRNA, respectively. Key results demonstrated editing efficiency: in iPSCs, 40-50% of cells generated indels, and normal CEP290 mRNA expression increased to 50-70%. In mouse retinal cells, editing efficiency was 30-40%, with the proportion of normal mRNA increasing to 60%. CEP290 protein localization and ciliary function were restored in iPSC-derived retinal organoids, demonstrating effective mutation repair. Mouse electroretinograms (ERGs) showed enhanced rod responses and improved low-light vision after editing. High safety, in vitro off-target analysis: Highly specific gRNA design, off-target rate <0.1% (whole genome sequencing). No significant inflammation or retinal toxicity in mice, and no abnormal genomic rearrangements were detected [7].

### 4.1.3 EDIT-101 clinical trial data (Phase I/II, NCT03872479)

The first patient was dosed in March 2019. The goal was to evaluate the safety, efficacy, and tolerability of EDIT-101. Eighteen patients (aged 3 years and older) with LCA10, a confirmed c.2991+1655A>G mutation, and residual retinal function were enrolled. The trial was divided into three dose groups (low, medium, and high) and administered via a single subretinal injection. As of the 2024 pause, there were no serious adverse events (SAEs). Common side effects were mild intraocular inflammation (controllable with steroids) and transient blurred vision. No systemic immune responses or off-target genomic abnormalities were detected (whole genome sequencing).

Efficacy demonstrated by improved vision in 6 of 18 patients (33%): Best-corrected visual acuity (BCVA) improved by >0.3 logMAR (approximately 3 lines on the eye chart) in 2 patients. Multiphoton maze navigation: 4 patients showed significant improvement in low-light navigation ($p<0.05$). Visual field (Goldmann) improved by 10-20% in 3 patients. The mid- and high-dose groups showed superior efficacy compared to the low-dose group, but individual variability was significant. A limitation was that 12 patients (67%) did not experience significant visual improvement, possibly due to advanced retinal degeneration or insufficient editing efficiency. Editing efficiency (retinal biopsy): 10-20%, lower than preclinical models (30-50%). In October 2024, Editas Medicine paused the trial due to the limited number of LCA10 patients (approximately 300 in the US) and limited commercial prospects, and data did not advance to Phase III. The achievement was the successful completion of precise gene editing, successfully targeting the CEP290 mutation and restoring normal splicing, demonstrating the applicability of CRISPR in human ophthalmic diseases. Preclinical studies have shown functional protein restoration in iPSC and animal models, and improved retinal electrophysiology. Clinically, 33% of patients showed improved vision, verifying the translational potential of CRISPR from laboratory to human. Low off-target rate (<0.1%) and highly specific gRNA design, no serious adverse events in clinical trials, established the safety of ophthalmic CRISPR. Eye immune privilege reduces AAV immune response, and local injection reduces systemic risks. The EDIT-101 experiment was the first human ophthalmic CRISPR trial (2019), laying the foundation for other retinal diseases. Dual AAV delivery overcomes the limitation of the large CEP290 gene (7.5kb) and demonstrates the high efficiency of NHEJ in non-dividing cells [2,3].

The shortcomings are reflected in inconsistent efficacy, with 67% of patients having no significant visual improvement, and late-stage retinal degeneration limiting efficacy. Clinical editing efficacy (10-20%) is lower than preclinical efficacy (30-50%), which may be due to uneven dual AAV delivery efficiency. The dual AAV system requires simultaneous infection of two vectors, which reduces editing efficiency and increases production complexity. The AAV capacity limit (4.7kb) cannot accommodate HDR templates, limiting the application of precise repair. LCA10 patients only account for 20-30% of LCA, making recruitment difficult and commercial prospects insufficient, leading to the suspension of the trial. The follow-up time is short (1-5 years), and long-term safety (such as late-onset genomic rearrangements) is unknown. Further monitoring of potential off-target effects and progression of retinal degeneration is needed [7,8].

### 4.2 Rpe65 Mutant Mice (LCA2 Model)

The goal is to repair the Rpe65 gene mutation and simulate LCA2. CRISPR-Cas9 is delivered via AAV8, targeting the Rpe65 point mutation (R44Q), and attempting HDR repair. The model is Rpe65 R44Q/R44Q mice. The experimental results showed that the HDR repair rate was 5-10%, and NHEJ indels accounted for 30%. The ERG of the HDR repair group recovered to 50% of the wild type, and visual acuity improved. The limitation is that the HDR efficiency is low, and NHEJ causes partial gene inactivation, reducing the efficacy. The conclusion is that CRISPR can partially restore visual function in LCA2 mice, but the HDR efficiency limits clinical translation. In this experiment, NHEJ dominated the repair, similar to EDIT-101, but LCA2 is more suitable for gene supplementation (such as Luxturna). Compared with the NHEJ strategy of EDIT-101, the Rpe65 experiment attempted HDR, but the efficiency was low, which strengthened the rationality of EDIT-101's choice of NHEJ [9].

### 4.3 4.3 Cep290 rd16 Mice (LCA10 Model)

The goal is to repair the Cep290 intronic mutation (similar to c.2991+1655A>G). CRISPR-Cas9 is delivered via AAV5, and NHEJ destroys the abnormal splicing site. The model is Cep290 rd16 mouse (intronic mutation). The experimental results show that 25-35% of retinal cells produce indels. Normal Cep290 mRNA increased by 40%, rod cell survival increased by 30%, and ERG response was enhanced. The off-target rate was <0.5%, and there was no significant retinal inflammation. The experimental conclusion is that NHEJ effectively repairs Cep290 mutations and improves visual function, supporting the EDIT-101 strategy. The editing efficiency of the animal model is higher than that of EDIT-101 clinical (10-20%), suggesting the need for optimized human delivery [10].

### 4.4 4.4 Gucy2d Mutant Mice (LCA1 Model)

The goal was to repair the Gucy2d point mutation (mim-

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icking LCA1). CRISPR-Cas9 was combined with an HDR template and delivered with AAV8. The model was a Gucy2d knock-in mouse (point mutation). The experimental results showed that the HDR repair rate was 3-8%, and NHEJ accounted for 20%. In the HDR group, the retinal guanylate cyclase activity recovered by 30%, and night vision improved. HDR efficiency was low, and NHEJ resulted in some ineffective editing. The experimental conclusion was that HDR showed potential in LCA1 mice, but its low efficiency limited its application. NHEJ was dominant, suggesting that EDIT-101 selected NHEJ for its universal applicability. This reinforced the rationality of EDIT-101 avoiding HDR, as NHEJ is more suitable for non-dividing retinal cells [11].

## 5. Summary of Existing Experimental Results

### 5.1 Advantages and Prospects of CRISPR in LCA Treatment

Animal studies have shown that NHEJ editing efficiencies of 20-50% are highly efficient, demonstrating its ophthalmic applicability. LCA models (Cep290, Rpe65, and Gucy2d) have validated CRISPR's potential in retinal therapy. NHEJ is particularly well-suited to non-dividing cells, further confirmed by the 33% visual improvement seen in EDIT-101 patients. CRISPR also boasts broad-spectrum potential, with gRNAs designed to target multiple genes, demonstrating promising cross-disease applications. Animal studies and EDIT-101 clinical data support CRISPR's clinical feasibility, with a high safety profile, low off-target rates (<0.5%), and no significant toxicity.

### 5.2 Current Shortcomings

HDR is limited. Studies in Gucy2d and Rpe65 mutant mice have shown low HDR efficiency (3-10%), making it unsuitable for non-dividing cells. Therefore, EDIT-101 opts for NHEJ. Delivery efficiency is insufficient, with animal models (30-50%) outperforming EDIT-101 clinical trials (10-20%). Dual AAV or AAV9 delivery requires optimization. Late-stage degenerative changes (such as late-stage LCA10) limit efficacy. Animal studies have primarily focused on early intervention, suggesting a need for earlier clinical treatment. Commercialization challenges exist, with EDIT-101 suspended due to a limited patient population. Animal studies do not directly address recruitment and cost issues for rare diseases.

## 6. Conclusion

CRISPR-Cas9 technology has shown great potential in the treatment of LCA, and its feasibility for clinical application has been demonstrated in preliminary studies. In particular, the EDIT-101 clinical trial targeting a CEP290 gene mutation, as the first in vivo CRISPR gene editing project conducted in humans, achieved milestone results. This trial successfully demonstrated the safety and efficacy of CRISPR in human ophthalmological diseases. Specifically, in non-dividing retinal cells, the NHEJ-based repair strategy was able to efficiently repair the pathogenic mutation and restore partial visual function. This breakthrough not only offers hope for LCA patients but also lays the foundation for the treatment of other inherited ophthalmic diseases. However, current research is still in its early stages, and this technology still faces many challenges before it can be widely used in the clinic. First, while NHEJ strategies have performed well for some mutation types, HDR strategies are limited by their extremely low efficiency in non-dividing cells for mutations requiring precise gene replacement. Future research is needed to develop technologies with higher HDR efficiency or explore other precise editing tools. Secondly, the editing efficiency observed in clinical trials (10-20%) is significantly lower than that in animal models (30-50%), indicating that optimizing the AAV vector delivery system and injection technique is crucial. Finally, as a rare disease, LCA has a small patient population, which poses significant challenges to clinical trial recruitment and commercial development. Although the EDIT-101 trial was suspended for commercial reasons, its scientific value cannot be ignored. In summary, CRISPR has opened up a new avenue for LCA treatment. Future research should focus on improving the efficiency of precise gene editing, optimizing delivery systems to enhance clinical efficacy, and exploring new editing strategies to address a wider range of mutation types. At the same time, through international collaboration and interdisciplinary research, it may be possible to overcome the commercial bottlenecks presented by rare diseases and ultimately translate this revolutionary technology into clinical therapies that benefit more patients.

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