

Review

CRISPR in Action: Unlocking New Cures for Human Diseases

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Abstract: The groundbreaking discovery of CRISPR -Cas9 technology has fundamentally opened new avenues for modern medicine, enabling the highly precise editing of the human genome to effectively treat a wide array of genetic and chronic diseases. This comprehensive review paper first introduces the fascinating natural origins of the CRISPR -Cas system within bacterial adaptive immunity. It subsequently details its sophisticated mechanism as a revolutionary gene-editing tool, specifically examining the structural features and endonuclease activity of the Cas9 protein, the precise targeting function of single guide RNA (sgRNA), and the subsequent cellular DNA repair mechanisms, namely non-homologous end joining (NHEJ) and homology-directed repair (HDR). Furthermore, the research highlights key clinical applications that have recently transitioned from the laboratory to patient care. This ranges from Casgevy, the landmark first FDA-approved CRISPR therapy for sickle cell disease in 2023, to highly promising emerging strategies aimed at complete HIV eradication and the development of enhanced CAR-T cell therapies for refractory cancers. While CRISPR technology demonstrates significant long-term potential for cost-effectiveness by offering unprecedented "one-time cures," several critical challenges persist. Its current exorbitant clinical price, the persistent risk of unintended off-target genomic effects, and complex ethical boundaries—particularly concerning heritable germline editing—remain major hurdles to global implementation. This paper concludes that while CRISPR is undeniably poised to transform the landscape of genomic medicine, further scientific breakthroughs, robust regulatory frameworks, and substantial cost reduction strategies are absolutely essential to ensure its widespread clinical accessibility and safety.

Keywords: CRISPR -cas9; gene editing; sickle cell disease; car-t therapy; bioethics; off-target effects

1. Introduction

CRISPR technology represents a revolutionary advancement in the field of genetic engineering, utilizing naturally occurring CRISPR -associated proteins derived from bacterial immune systems to precisely edit the genomes of various organisms [1]. This innovative tool has opened new avenues for scientific exploration and practical applications, particularly in the realm of medicine. By enabling targeted modifications to DNA sequences, CRISPR holds immense potential for addressing genetic disorders, improving therapeutic interventions, and advancing personalized medicine. The discovery of CRISPR technology marked a significant milestone in biotechnology, offering unprecedented precision and efficiency compared to earlier genome-editing methods. This research paper aims to delve into the diverse applications of CRISPR in medical science, including its role in gene therapy, the development of novel treatments for hereditary diseases, and its potential in combating infectious diseases. Furthermore, emerging research suggests that CRISPR could play a pivotal role in cancer treatment by targeting specific genetic mutations. As the technology continues to evolve, its implications for medicine are expected to expand, paving the way for groundbreaking advancements in healthcare and disease management.

1.1. Introduction to CRISPR Therapy

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CRISPR therapy represents a groundbreaking application of genetic engineering, utilizing the CRISPR system originally identified in the immune mechanisms of bacteria to edit human genomes with the aim of treating various diseases. This innovative approach enables precise modifications to DNA sequences, offering potential cures for genetic disorders and other medical conditions. For instance, in the case of sickle cell disease, CRISPR technology can be employed to edit hematopoietic stem cells, effectively preventing the red blood cells from adopting the characteristic sickle shape that leads to numerous health complications. Similarly, in oncology, CRISPR can be used to modify T cells, a critical component of the immune system, to enhance their ability to recognize and attack cancer cells [2, 3]. By reprogramming these immune cells, CRISPR therapy holds promise for improving the efficacy of cancer immunotherapy. The versatility and precision of this technology underscore its transformative potential in modern medicine, paving the way for personalized treatments that target the root causes of diseases at the genetic level.

1.2. CRISPR in Nature

CRISPR plays a crucial role in the immune defense mechanisms of many bacterial species. It functions by targeting and cleaving phage DNA sequences, thereby preventing bacterial infection by these viruses. Phages, or bacteriophages, are viruses that specifically infect bacteria, and the CRISPR system acts as a molecular defense tool to neutralize this threat. The CRISPR system comprises two main components: the Cas9 protein and the guide RNA (gRNA). The Cas9 protein serves as a molecular "scissor" that performs the cutting action, while the gRNA acts as the "eye," guiding the system to the specific DNA sequence that needs to be cleaved. This precise targeting mechanism ensures that only the intended DNA sequence is disrupted, leaving other genetic material intact.

The Cas9 protein is a complex, two-lobed structure consisting of the recognition lobe (REC) and the nuclease lobe (NUC). The REC lobe is responsible for carrying the gRNA, while the NUC lobe contains two critical nuclease domains, HNH and RuvC, which execute the DNA cleavage. During the immune response, the gRNA first identifies the target DNA sequence by recognizing a protospacer adjacent motif (PAM) through the PAM-interacting domain (PID). Once the gRNA binds to a PAM, the nearby double-stranded DNA is unwound, allowing the gRNA to form complementary base pairs with the target DNA [4]. This RNA-DNA hybrid is stabilized within the cleft between the REC and NUC lobes, ensuring precise alignment. Meanwhile, the non-target DNA strand is displaced and held in a groove along the Cas9 protein's surface to maintain separation of the two strands. When the gRNA achieves near-complete or complete base pairing with the target DNA, the HNH domain cleaves the target DNA strand, followed by the RuvC domain cleaving the non-target strand. This dual-strand cleavage effectively disrupts the phage DNA, rendering it non-functional and neutralizing the threat. The entire process is a highly coordinated molecular mechanism that underscores the efficiency and specificity of the CRISPR system in bacterial immunity. The reaction mechanism is visually represented in Figure 1, which illustrates the step-by-step process of DNA recognition and cleavage by the CRISPR -Cas9 system.

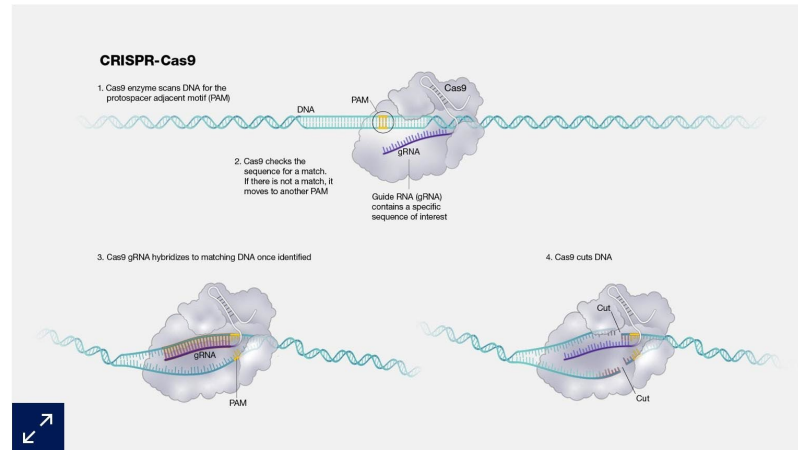


Figure 1. CRISPR Reaction Mechanism. Source: CRISPR. (N.d.). Genome.gov. [https://www.genome.gov/genetics-glossary/CRISPR]

1.3. CRISPR as a Technology

The mechanism by which CRISPR edits the genomes of organisms mirrors the natural CRISPR immune system [2]. In this process, the guide RNA plays a crucial role by identifying specific target DNA sequences. The Cas9 protein then acts as molecular scissors, making precise cuts in the DNA. These cuts can render the DNA sequence non-functional, particularly if it contains errors, or researchers can introduce a template DNA sequence to guide the cell in repairing the broken DNA with a specific, desired edit. This approach allows for highly targeted genetic modifications, which are invaluable in both research and therapeutic applications.

In gene editing, the guide RNA is typically engineered into a single-guide RNA (sgRNA), which combines two natural RNA components. The CRISPR RNA (crRNA) provides the sequence that directs the Cas9 protein to a specific DNA target, while the trans-activating crRNA (tracrRNA) forms the structural scaffold necessary for Cas9 binding. Once the Cas9 protein cleaves the target DNA, the cell employs one of two repair mechanisms: non-homologous end joining (NHEJ) or homology-directed repair (HDR). NHEJ is the more common repair pathway, wherein cellular proteins rejoin the broken DNA ends directly. However, this process is inherently error-prone and often introduces small insertions or deletions (indels), which can disrupt the function of the targeted gene, as illustrated in Figure 2 on the left. HDR, on the other hand, is a less frequent but more precise repair mechanism [5, 6]. Researchers can exploit HDR to introduce specific DNA sequences by providing a template DNA segment. This template must include homologous sequences that match the broken DNA ends, enabling the repair process to incorporate the desired genetic changes with high accuracy, as shown in Figure 2 on the right. These two repair pathways are fundamental to the versatility and precision of CRISPR -based gene editing.

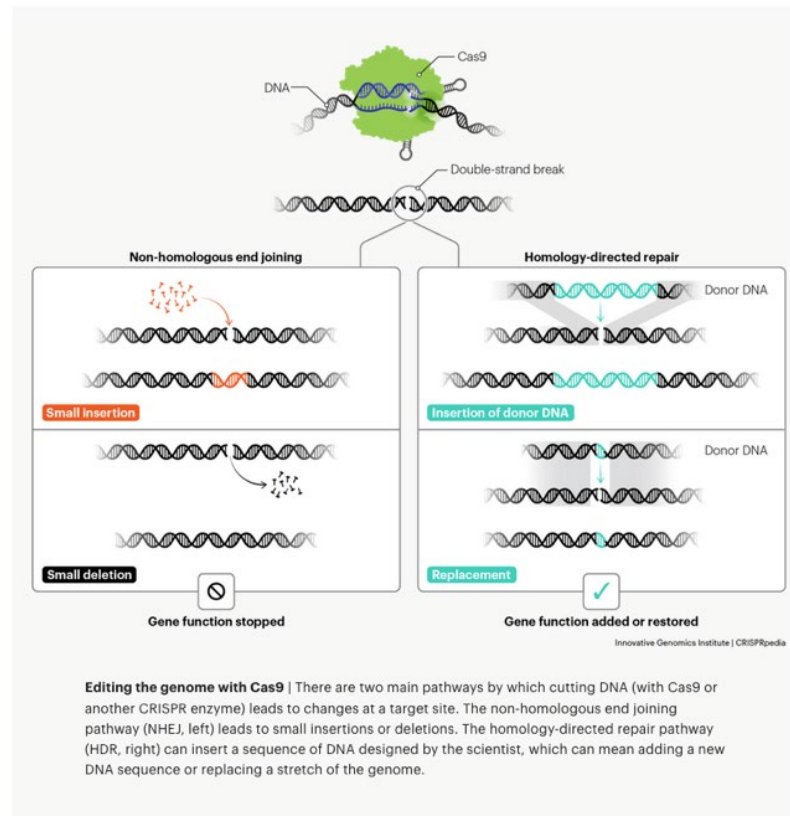


Figure. 2, The Two Main Ways for Cells to Repair a DNA Break, NHEJ and HDR. Source: CRISPR Technology - Innovative Genomics Institute (IGI). (2025, January 17). Innovative Genomics Institute (IGI). <https://innovativegenomics.org/CRISPRpedia/CRISPR-technology/#Expanding-the-CRISPR-toolkit>

The Cas9 protein, while highly effective at cutting DNA sequences, does not always yield the desired outcomes. To address this limitation, researchers have developed modified versions of Cas proteins tailored for specific purposes [7]. One such modification involves substituting critical amino acids in Cas9 with alanine, rendering the enzyme inactive and creating what is known as "dead" Cas9 (dCas9). Although dCas9 cannot cut DNA, it retains its ability to recognize and bind to specific DNA targets. This property allows researchers to attach functional proteins to dCas9 for various applications. For instance, attaching adenine deaminase to dCas9 enables the conversion of adenine into inosine, while cytosine deaminase facilitates the conversion of cytosine into uracil. Additionally, regulatory proteins can be linked to dCas9 to modulate gene expression. When an activator protein is attached, it enhances transcription, whereas a repressor protein decreases transcription. These advancements in modifying Cas proteins have significantly expanded the toolkit available for precise genetic and epigenetic modifications, offering new possibilities for research and therapeutic interventions.

2. CRISPR Therapies Now Exist

In December 2023, the U.S. Food and Drug Administration approved Casgevy, marking a significant milestone as the first CRISPR-based therapy authorized for human use. This approval represents a groundbreaking advancement in the field of genetic medicine, showcasing the potential of CRISPR technology to address complex genetic disorders. The development of Casgevy highlights the culmination of years of research and innovation aimed at translating genetic editing tools into viable therapeutic solutions [8].

Casgevy is specifically designed to treat sickle cell disease, a severe and inherited blood disorder that affects approximately 100,000 individuals in the United States [9]. This condition arises from mutations in the hemoglobin gene, which plays a critical role in transporting oxygen throughout the body. The mutation leads to the production of abnormal hemoglobin, causing red blood cells to adopt a rigid, crescent-like "sickle" shape. These misshapen cells are less efficient in oxygen delivery and are prone to clumping together, which can obstruct blood flow and result in significant health complications.

The sickling of red blood cells has profound consequences for individuals with this condition. The restricted blood flow caused by these cells can lead to severe pain episodes, commonly referred to as sickle cell crises. Over time, the lack of adequate oxygen delivery to tissues and organs can result in chronic organ damage, debilitating disabilities, and, in many cases, a shortened lifespan. The disease imposes a substantial burden on patients, both in terms of physical suffering and the need for ongoing medical care [10].

Casgevy employs CRISPR -Cas9 gene-editing technology to address the underlying genetic cause of sickle cell disease. This therapy involves extracting blood stem cells from the patient, editing the DNA sequences within these cells to correct the genetic mutation, and then transplanting the modified cells back into the patient's bone marrow. The edited cells are designed to produce increased levels of fetal hemoglobin, a form of hemoglobin that is highly effective in oxygen transport and does not cause red blood cells to sickle [11]. By enhancing the production of fetal hemoglobin, Casgevy helps to prevent the formation of sickled cells, thereby improving oxygen delivery and alleviating the symptoms of the disease. This innovative approach offers a promising therapeutic option for individuals suffering from this debilitating condition.

3. Future and Emerging Therapies

3.1. CRISPR for HIV

Human immunodeficiency virus (HIV) remains one of the most challenging diseases faced by humanity. The virus possesses the ability to convert its RNA into DNA through reverse transcription, subsequently integrating the viral DNA into the host genome. This integration makes it currently impossible to completely eradicate the virus from infected individuals. The primary method for controlling HIV replication is through combination antiretroviral therapy (cART), which effectively suppresses viral activity. However, patients are required to adhere to cART for their entire lives, as discontinuation of the therapy can lead to a resurgence of viral replication. Despite its efficacy, cART is associated with significant side effects, including metabolic disturbances and organ toxicity, which can impact the quality of life for patients. Furthermore, access to cART remains a challenge for many individuals, particularly in regions with limited healthcare infrastructure or economic constraints.

CRISPR -based tools offer a promising avenue for addressing HIV infections [9]. By utilizing CRISPR technology, scientists can precisely target and excise integrated proviral DNA from the host genome, effectively removing the viral genetic material. Additionally, CRISPR can be employed to modify host genes, such as CCR5, which serves as a receptor facilitating HIV entry into cells. By knocking out CCR5, the virus encounters greater difficulty in infecting modified cells. Furthermore, CRISPR can be used to enhance the expression of cellular factors like APOBEC3G and Tetherin, which are known to inhibit viral replication and prevent the release of new viral particles from infected cells (Figure 3). These multifaceted approaches demonstrate the versatility of CRISPR technology in combating HIV, offering hope for a potential cure that goes beyond the limitations of current therapies.

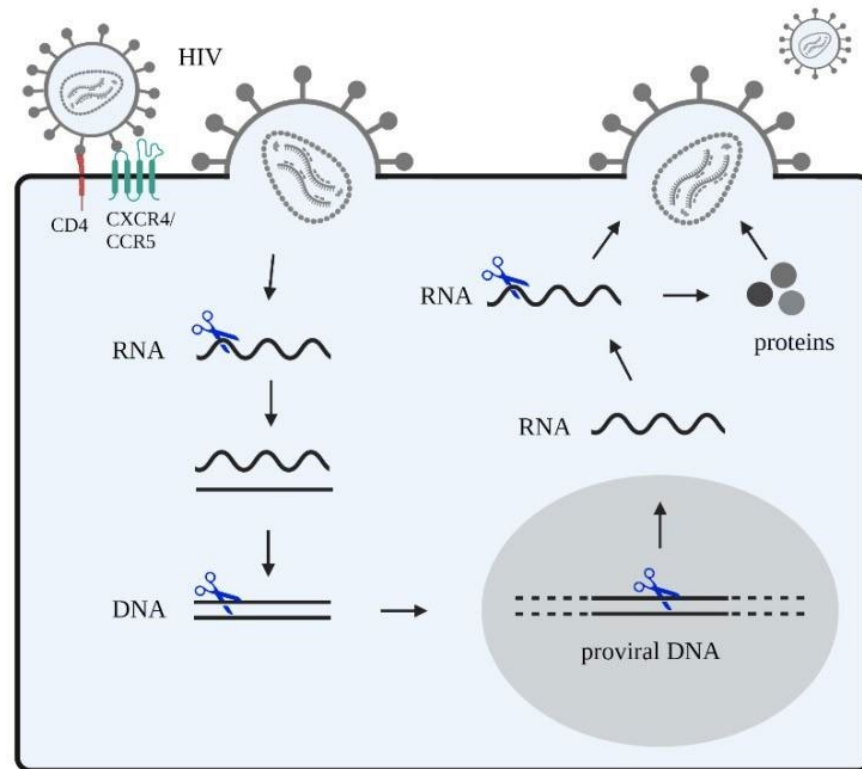


Figure 3. CRISPR Preventing HIV Infection and Replication. Source: Hussein, M., Molina, M. A., Berkhout, B., & Herrera-Carrillo, E. (2023). A CRISPR -Cas Cure for Hiv/aids. *International Journal of Molecular Sciences*, 24(2), 1563. [<https://doi.org/10.3390/ijms24021563>]

In summary, CRISPR -Cas gene editing techniques represent a groundbreaking strategy for combating HIV infections and potentially achieving a cure. The ability to precisely target and modify both viral and host genetic material provides a unique advantage over traditional therapies. However, extensive long-term studies, including both *in vitro* and *in vivo* infection experiments, are essential to evaluate the efficacy and safety of these technologies. Challenges such as off-target effects, immune responses, and scalability must be addressed to ensure the clinical viability of CRISPR -based interventions. Despite these hurdles, the potential of CRISPR to revolutionize HIV treatment underscores the importance of continued research and development in this field, paving the way for transformative advancements in global healthcare.

3.2. CRISPR for Cancer

Cancer is a disease characterized by mutations in an organism's DNA, which lead to uncontrolled cell growth. These mutations enable cancer cells to invade nearby tissues and spread to distant parts of the body, forming new tumors. Additionally, cancer cells can manipulate blood vessels to grow toward tumors, ensuring a steady supply of oxygen and nutrients while removing waste products [12]. They can disrupt the normal growth of surrounding cells and evade detection by the immune system. In some cases, cancer cells even exploit the immune system to shield themselves from destruction. These complex mechanisms present significant challenges in effectively targeting and eliminating cancer cells.

Researchers have developed innovative methods to enhance the ability of T cells to locate and attack cancer cells by editing their genomes. This process involves extracting T cells from the patient's blood and introducing a gene that encodes a specialized receptor known as a chimeric antigen receptor (CAR). This receptor is designed to bind to specific proteins found on the surface of the patient's cancer cells. The modified CAR-T cells are then cultivated in the laboratory to increase their numbers before being reintroduced into the patient's body. Once inside the body, these engineered cells actively seek out and

destroy cancer cells. CAR-T cell therapy is currently being explored for its potential in treating various types of cancer, offering a promising avenue for personalized medicine and targeted treatment strategies.

CRISPR, as a cutting-edge gene-editing tool, has revolutionized the modification of T cells by introducing a technique known as the ribonucleoprotein (RNP) delivery strategy. In this approach, CRISPR components, including the Cas9 protein and guide RNA, are pre-assembled into an RNP complex before being directly delivered into the target T cells. This method offers several advantages over traditional techniques that rely on DNA or mRNA delivery. By using RNP delivery, researchers can significantly reduce the risk of off-target effects, thereby enhancing the precision of gene editing. Furthermore, this strategy improves editing efficiency and minimizes the likelihood of triggering adverse immune responses, which are common concerns in gene therapy. These benefits make CRISPR an invaluable tool for advancing CAR-T cell therapy, enabling more effective and safer treatments for cancer patients [1]. As research progresses, the integration of CRISPR technology into immunotherapy holds great promise for overcoming some of the most challenging aspects of cancer treatment.

4. Potential Controversy

4.1. Ethical Considerations

In contemporary discussions surrounding bioethics, the Oviedo Convention has emerged as a significant international agreement. This convention, adopted by many European Union member states, explicitly prohibits the practice of heritable gene editing in humans. The rationale behind this prohibition lies in the ethical concerns associated with altering the human germline, which could have far-reaching implications for future generations [13]. By preventing modifications that can be passed down to offspring, the convention aims to safeguard human genetic integrity and avoid potential societal and biological risks. The debate surrounding this issue continues to evolve as advancements in genetic technologies challenge existing ethical frameworks.

In 2018, a Chinese researcher, He Jiankui, conducted a controversial experiment involving the genetic modification of human embryos. His work aimed to introduce a genetic alteration that would confer resistance to HIV, a significant global health challenge. The modification, however, was heritable, meaning it could be passed on to future generations. This experiment sparked widespread ethical and scientific debate, as it raised concerns about the potential misuse of gene-editing technologies and the lack of comprehensive regulatory oversight. Following public and governmental scrutiny, He Jiankui was sentenced to three years in prison for "illegally practicing medicine" and fined 3 million RMB (approximately \$429,000). This case highlighted the urgent need for robust ethical guidelines and international cooperation to regulate the application of gene-editing technologies, ensuring they are used responsibly and for the benefit of humanity. The incident also underscored the importance of balancing scientific innovation with ethical considerations to prevent unintended consequences in the field of genetics.

4.2. High Cost

The cost of CRISPR -based therapies remains a significant barrier to widespread adoption, despite their potential to revolutionize the field of gene therapy. For instance, Casgevy, a CRISPR -based treatment designed to address sickle cell disease, has been priced at \$2.2 million per patient. This exorbitant cost places it far beyond the financial reach of most families, particularly in regions where healthcare systems may not provide sufficient subsidies or insurance coverage for such advanced treatments. The high price is largely attributed to the complexity of the technology, the rigorous research and development processes involved, and the specialized infrastructure required for its production and delivery. Additionally, the limited scale of manufacturing and the personalized nature of these therapies further contribute to their elevated costs. While CRISPR therapies hold immense promise for addressing genetic disorders, their current pricing structure risks creating disparities in access, potentially limiting their

transformative impact to only the wealthiest segments of the population. Efforts to reduce production costs, streamline delivery mechanisms, and expand manufacturing capabilities will be critical to ensuring that these groundbreaking treatments can benefit a broader demographic in the future.

4.3. Off-Target Effects

CRISPR tools, while revolutionary in their ability to edit genetic material with precision, are not without limitations. One significant challenge is the occurrence of off-target effects. These effects arise when the CRISPR-associated enzymes, guided by the gRNA, bind to and cut DNA sequences that are not the intended target [2]. This can happen even when there is only a partial match between the gRNA and the DNA sequence. Such unintended cuts can lead to undesirable genetic modifications, potentially causing irreversible harm to the organism. These unintended changes may also be heritable, meaning they could persist across multiple generations, raising concerns about long-term genetic stability and safety. To address these challenges, researchers are actively exploring various strategies to enhance the specificity of CRISPR tools. For instance, modifications to the structure of the CRISPR-associated enzymes are being investigated to reduce their likelihood of binding to non-target sequences. Additionally, advancements in computational algorithms are aiding in the design of more precise gRNAs, further minimizing the risk of off-target activity. These efforts are critical for ensuring the safe application of CRISPR technology, particularly in sensitive fields such as human gene therapy and agricultural biotechnology. By improving the accuracy of CRISPR systems, scientists aim to unlock their full potential while mitigating associated risks.

5. Conclusion

CRISPR, as an innovative gene-editing technology, holds transformative potential for addressing genetic disorders and advancing therapeutic interventions. Its ability to precisely modify DNA sequences offers a promising avenue for treating diseases that were previously considered untreatable. Despite these advantages, the current cost of CRISPR-based therapies remains prohibitively high compared to conventional treatment methods, posing a significant barrier to widespread adoption. Furthermore, ethical concerns surrounding gene editing, such as the potential misuse of the technology for non-therapeutic purposes or unintended genetic consequences, necessitate robust discussions and policy frameworks. To fully realize the benefits of CRISPR, substantial efforts are required to enhance its accessibility, reduce costs through technological advancements, and establish comprehensive regulatory guidelines that ensure its safe and equitable application. Future research should focus on improving the efficiency and specificity of CRISPR systems, minimizing off-target effects, and exploring scalable manufacturing processes. Additionally, interdisciplinary collaboration among scientists, ethicists, and policymakers will be crucial in addressing societal concerns and fostering public trust in gene-editing technologies. By overcoming these challenges, CRISPR could revolutionize medicine and pave the way for a new era of personalized and precision healthcare.

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