

ENGINEERING THE FUTURE: CRISPR-BASED GENE EDITING IN PERSONALIZED THERAPEUTICS

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Received: 23 June 2025 | **Revised & Accepted:** 28 September 2025

Keywords: Genome editing technologies (GED), crRNA biogenesis, Neurogenetic editing, sickle cell anemia.

ABSTRACT

Genome editing technologies (GED) have revolutionized biomedical research and therapeutic development, allowing precise modifications of DNA in living cells. CRISPR-Cas9 is unique among GED tools because of its effectiveness, ease of use, and versatility. Although CRISPR-Cas9 was initially discovered to be an immune defense mechanism in bacteria, it has since evolved into a powerful gene-editing tool with numerous applications in personalized medicine. The CRISPR-Cas mechanism is examined in this review, along with adaptation, crRNA biogenesis, and interference. It also identifies important therapeutic applications in monogenic diseases, cancer immunotherapy, and infectious diseases, as well as pharmacogenetics. There is also discussion of recent developments like neurogenetic editing, programmable gene circuits, and CRISPR-based diagnostics. Enhancing therapeutic efficacy requires the use of CRISPR delivery methods, such as lipid nanoparticles, viral vectors, and non-viral substitutes. Despite its potential, CRISPR technology has drawbacks, including immunogenicity, off-target effects, and ethical issues with germline editing and equitable access.

INTRODUCTION

GED technologies enable precise DNA sequence modification in living cells to study gene function and to develop novel therapies. The most advanced GED techniques are zinc-finger nucleases, transcription activator-like effector nucleases, and CRISPR-Cas-associated nucleases (CRISPR/Cas9). Among these, CRISPR/Cas9 is the most widely used due to its flexibility, efficiency, and ease of use¹. In bacteria and archaea, naturally occurring CRISPR elements are found in the

genomes, they were first described as part of the prokaryotic immune system that defends against viral and plasmid DNA. The fundamental elements (genetic codes) of the CRISPR system include target DNA modification, CAS proteins, a protospacer adjacent motif (PAM), CRISPR arrays, and single guide RNA (sgRNA). The genomic editing tool known as CRISPR arrays consists of a cassette containing DNA repeats (21–47 base pairs) that are separated by non-repetitive sequences and a collection of CAS genes arranged in a

specific way². Clustered regularly interspaced short palindromic repeats (CRISPR)-associated systems (Cas) have changed research and biotechnology and could possibly change disease treatment in clinics. There have been numerous preclinical and clinical trials employing the CRISPR-Cas system to reverse the underlying genetic causes in order to treat a variety of refractory diseases. The CRISPR-Cas system is an exciting new avenue for preclinical and clinical research on a wide range of refractory diseases. Additionally, CRISPR-Cas may be used to improve the genetic codes of certain other diseases that involve numerous or complex genetic mutations³. For instance, the development of clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 genome editing technique, which has enabled the modification of human genomes, was only recently possible. This is similar to news from 2018 about two genetically modified babies born in China following gene editing by scientist He Jiankui⁴. While a number of experiments have been reported that use gene-editing technology to modify cells in vitro for re-infusion into the body for treatment of certain diseases, this approach does not work for most disease types and stable, efficient, safe delivery in vivo is challenging and needs the aid of delivery vectors. For example, direct pDNA (plasmid DNA), mRNA or ribonucleoproteins (RNPs) are degraded and cleared by immune clearance in vivo, so they need delivery vectors as carriers of CRISPR systems⁵. The evolution of CRISPR as a gene-editing tool is discussed in this review, along with recent tool types (Cas9, base editors, and prime editors), and therapeutic uses of this developing technology in personalized medicine, particularly for pharmacogenom

ics, infectious diseases, cancer immunotherapy, and monogenic diseases. The review also covers new applications like gene circuits, organoid modeling, neurogenetic editing, and CRISPR-based diagnostics. It also covers different CRISPR delivery methods (lipid nanoparticles, viral vectors, and exosomes) to improve the effectiveness of in vivo editing. Finally ethical implications of germline editing, accessibility.

MAIN SECTIONS

Mechanism of CRISPR-Cas Immune Defense: Adaptation, crRNA Biogenesis, and Interference

The CRISPR-Cas system identifies and cleaves foreign DNA or RNA to produce sequence-specific action. Three phases comprise the defense mechanism: (i) spacer acquisition or adaptation, (ii) crRNA biogenesis, and (iii) target interference.

(a) Adaptation

The adaptation phase involves adding new spacers (protospacers) to the CRISPR array that contain the invading genetic material. This allows the host to "remember" the invader. Spacer selection relies heavily on the Cas1 and Cas2 proteins, but some types also require other proteins like Cas4, Csn2, and even reverse transcriptases. Cas9 recognizes a sequence called a PAM (Protospacer Adjacent Motif), which is used by Type II-A systems to direct spacer selection. A procedure known as priming enhances the uptake of new spacers in certain CRISPR types without cleaving the target DNA following prior exposure.

(b) Biogenesis

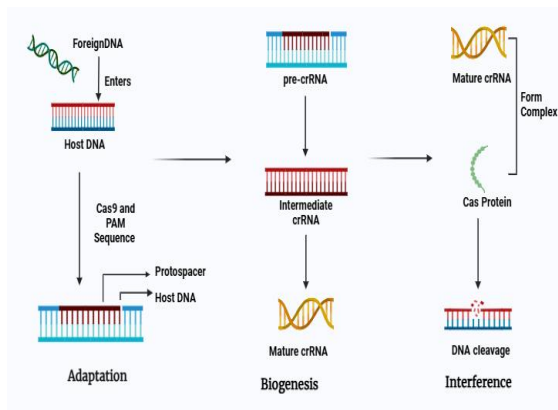


Fig (1). Three-Stage Functional Pathway of the CRISPR-Cas Defense System

During the biogenesis phase, the CRISPR array is transcribed into a long precursor crRNA (pre-crRNA), which is processed to mature crRNAs that target recognition, pre-crRNA is processed by Cas6 or Cas5d cleavage in Class 1 systems (Types I and III) to intermediates with 5' tags and hairpin-structured repeats, forms a duplex with tracrRNA, then is processed by RNase III with Cas9 in Class 2 systems (Type II), and pre-crRNA is directly processed by Cpf1 (Cas12a) in Type V-A, using the mature crRNA for DNA cleavage.

(c)Interference

The mature crRNAs direct Cas proteins to foreign nucleic acids for degradation in the interference phase. Class 1 employs multi-protein complexes (Cascade + Cas3) and class 2 uses a single effector (Cas9 or Cpf1). The target is recognized by the presence of a PAM sequence in types I, II, and V, or non-pairing 5' tag in type III. In type II systems (e.g., Cas9), a double-strand break is formed, in type I (e.g., Cas3) DNA is degraded after nicking and type III cleaves both DNA and RNA but only if the target is actively being transcribed. Type V-A relies solely on crRNA for interference,

whereas V-B requires a crRNA: tracrRNA duplex⁶.

Applications in Personalized Medicine

1. Monogenic Diseases

Monogenic diseases, which are caused by mutations in a single gene, are prime candidates for CRISPR-based gene editing therapies, offering the potential for precise correction of underlying genetic defects⁷.

A. Sickle Cell Anemia: Ex Vivo Editing of BCL11A Gene

The single gene mutation associated with SCD is severe enough to significantly impact quality of life, therefore a high level of fetal hemoglobin (HbF) can be used to alleviate the symptoms of SCD by inhibiting sickle hemoglobin polymerization and erythrocyte sickling. BCL11A is a transcriptional repressor that blocks γ -globin expression and HbF production in adult erythrocytes, and downregulation of this repressor may be a viable therapeutic approach to induce HbF⁸⁻¹⁰.

Ex vivo editing of SCD patients' hematopoietic stem and progenitor cells (HSPCs) to deactivate BCL11A has produced encouraging outcomes. This procedure entails taking bone marrow stem cells from patients, using CRISPR to render BCL11A inactive, and then reintroducing the altered stem cells into the patient. The goal is for fetal hemoglobin to be present in the new red blood cells that are created by these modified stem cells. The erythroid-specific BCL11A enhancer in HSPCs, for example, can be edited to produce fetal hemoglobin (HbF) without causing any toxicity. To break a GATA1 binding site at the BCL11A +58 erythroid enhancer, a single guide RNA (sgRNA) that is identical in human and rhesus target sequences has

been employed. In one study, rhesus monkeys' bone marrow and peripheral blood contained edited HSPCs for as long as 101 weeks. Biallelic BCL11A enhancer editing produced a strong induction of γ -globin¹¹⁻¹².

Clinical trials utilizing CRISPR-Cas9 have targeted the erythroid-specific BCL11A enhancer to increase HbF levels, leading to higher HbF and reduced disease severity¹³. The FDA has granted breakthrough approval for CASGEVY, a CRISPR/Cas9-based gene therapy for SCD.

B. Cystic Fibrosis: Correction of CFTR Gene Mutations

Cystic fibrosis (CF) is a genetic autosomal recessive disorder that occurs when mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene result in conditions such as lung injury, pancreatic insufficiency, and high levels of chloride. Although there are over 1,900 different CFTR mutations known, the most common one is F508del, a deletion of the phenylalanine residue at position 508[15]. CRISPR-Cas9 has been used to correct these mutations by genetic editing of the CFTR gene in peripheral blood mononuclear cells (PBMCs), where 33% of samples were corrected in the mutant locus; lung epithelial cells, where 23% were corrected; and organoids with the deltaF508 mutation, where 14-25% were corrected. More recently, prime editing has been utilized to correct the F508del mutation in human lung cells (which accounts for 85% of CF patients). Delivery of CRISPR components to target cells, such as lung epithelial cells in CF patients, remains a major challenge. Non-viral methods like lipid nanoparticles, or cationic liposomes delivered via a nebulizer, are being explored to overcome issues like

inflammation associated with viral vector¹⁴⁻¹⁷.

2. Cancer Immunotherapy

Chimeric antigen receptor T-cell therapy (CAR-T cell therapy) is an immunotherapy that employs engineered T cells for cancer treatment. CRISPR-Cas9 genome editing can be used to enhance the natural ability of human T cells to attack tumors, and genome engineering using CRISPR has led to new advances in CAR T cells to address logistical, technical, and immunological hurdles. For example, a clinical trial testing safety and feasibility evaluated the use of CRISPR-Cas9 gene editing to disrupt three genes (TRAC, TRBC, and PDCD1) involved with enhancing antitumor immunity and to introduce a cancer-targeting transgene called NY-ESO-1 to identify tumors. T cells were extracted from patients, CRISPR-Cas9 was used to target the genome to disrupt those three genes, and the engineered cells were successfully reinfused into the patient without serious adverse effects or rejection¹⁸⁻²¹.

3. Infectious Diseases

CRISPR-Cas technologies offer novel approaches for diagnosing and treating challenging infectious diseases due to their ability to precisely alter genome sequences²².

CRISPR Against HIV Provirus

Retroviruses such as HIV enter cells by inserting their genome into host DNA, which can remain dormant (integrated) and hidden from immune surveillance. The latent, intact proviruses of integrated HIV-1 in infected cells are a major barrier to curing HIV-1 infections. CRISPR-Cas9 systems can be targeted directly to the provirus to create double-strand breaks in viral genome sequences that might result in

permanent inactivation or excision. For example, experiments have demonstrated that dual-guide RNA-guided CRISPR/Cas9 attack of HIV-1 DNA is able to suppress both viral gene expression and replication. Researchers have been able to knockout CXCR4 and CCR5 (co-receptors for HIV-1) genes in CD4-positive T cells via CRISPR-Cas9, which confers resistance to infection by HIV-1 and CRISPR-Cas9 has been used to attack the HIV-1 DNA within both the cytoplasm and nucleus with indels in the viral genome and a reduction of viral DNA levels contributing to its inhibition²³⁻²⁵.

4. Pharmacogenomics

Pharmacogenomics investigates how genetic variation impacts an individual's body response to drugs in order to maximize therapeutic benefits and minimize toxicity. The cytochrome P450 (CYP) enzyme system, found primarily in the liver and intestine, is one of the most important drug-metabolizing enzymes. This can result in unexpectedly high or low concentrations due to variant alleles encoding drug transporters or metabolizing enzymes with altered activity, which may be influenced by genetic differences²⁶⁻²⁷.

Editing Metabolic Enzymes (e.g., CYP450 Genes) to Optimize Drug Dosing

CRISPR-Cas9 technology can also serve as a tool in the drug metabolism and disposition toolbox for the development of improved ADME models in vitro and in vivo, as well as mapping previously unexplored ADME genes. CRISPR enables us to assess drug effects on cells under different conditions by editing genes involved in drug metabolism or resistance. For instance, CYP2D6 is a polymorphic cytochrome P450 enzyme responsible for

the metabolism of approximately 20-25% of commonly prescribed drugs, although it accounts for only 2% of total CYP450 protein in the liver. Approximately 5-10% of Caucasians are poor metabolizers of CYP2D6 because of inactive variant alleles such individuals must have their doses adjusted, as poor metabolizers of codeine (which requires activation by CYP2D6 for pain relief) will not receive any analgesic effect and should be switched to another analgesic²⁸⁻³⁰.

Emerging Innovations

CRISPR-based diagnostics such as SHERLOCK and DETECTR can rapidly detect infectious diseases and cancers with ultrasensitivity at low cost. CRISPR can also be used to create programmable gene circuits that sense disease markers in real-time, resulting in smart cells for therapeutic applications (e.g., insulin secretion in response to glucose), organoids combined with CRISPR to generate patient-derived disease models of disease progression and testing therapies [35-36], and neurogenetic editing with CRISPR as a potential therapy for neurodegenerative disorders such as Huntington's, ALS, and early-onset Alzheimer's disease³¹⁻³⁷.

Delivery Strategies for CRISPR Systems

CRISPR-Cas9 systems require effective delivery to target cells for gene editing applications. Various strategies are employed, including physical methods, viral vectors, and non-viral methods³⁸.

Lipid Nanoparticles (LNPs)

One of the most common non-viral delivery platforms for CRISPR-Cas9 components is lipid nanoparticles (LNPs), which are known to be low immunogenic and effective at in vivo delivery as demonstrated by mRNA-based COVID-19 vaccines and gene-editing therapies progressing through clinical trials. LNPs

can also be engineered with tissue-specific targeting by changing the lipid composition or adding ligands. Lipid nanoparticle (LNPs) is another popular non-viral delivery platform for CRISPR-Cas9 components, including guide RNA (gRNA), messenger RNA (mRNA) encoding Cas9, and DNA knock-in templates³⁹.

Viral Vectors

CRISPR components are usually delivered by viral vectors, as they efficiently transduce cells, commonly used viral vectors include adeno-associated viruses (AAVs), lentiviruses (LVs), and adenoviruses (AdVs). AAVs may be preferable for in vivo applications because of their lower immunogenicity and reduced risk of insertional mutagenesis compared to LV, which can integrate genetic material into the host genome, allowing for long-term gene expression but at an increased risk of off-target editing⁴⁰.

Non-Viral Methods

Non-viral delivery methods offer alternatives to viral vectors, often with fewer safety concerns. These include physical methods like electroporation and microinjection, which directly introduce CRISPR components into cells or tissues. Electroporation is suitable for ex vivo and in vitro applications allowing for large cargo delivery, though it can be stressful to cells. Other non-viral approaches involve nanoparticles, such as liposomes and cell-penetrating peptides. Emerging non-viral strategies also include DNA origami and exosome-based delivery systems, which aim for more targeted and safer editing⁴¹⁻⁴⁴.

Ethical and Societal Considerations **Germline Editing Debate**

Because heritable changes in genes are passed on to future generations, germline gene editing is controversial and highly

regulated, it remains forbidden by many countries for a number of scientific, ethical, and safety reasons such as the uncertainty of long-term effects and risk of off-target mutations. The case in China where human embryos were gene-edited also known as "CRISPR babies," garnered widespread condemnation from the scientific community and was considered unethical for many reasons including its potentially irreversible and multigenerational effects. A key difference is that somatic cell editing is not heritable because it affects non-reproductive cells. However, germline editing has permanent implications and consequences on multiple generations and may be ethically problematic. For these reasons and many more, clinical germline gene editing remains banned in most countries because of the potential risks and uncertainties⁴⁵⁻⁴⁹.

Equity in Access

Ethically, it will be important that gene-editing treatments remain affordable, if they remain costly, they could widen existing health disparities and disproportionately benefit wealthier individuals and countries, marginalizing vulnerable populations. They will need policies and frameworks to ensure equitable access for all, not just the wealthiest nations or people, and to prevent the development of new forms of inequality or discrimination, a topic that is particularly relevant in discussions regarding health equity⁵⁰⁻⁵³.

Consent and Regulation

One ethical consideration is that patients should always give truly informed consent to any gene therapy intervention, including inheritable ones, and in the case of gene-editing treatments, this can prove difficult

given their complexity and unpredictable outcomes⁵⁴⁻⁵⁵.

CONCLUSION

CRISPR-Cas9 has rapidly emerged as a groundbreaking technology in genome editing, offering new avenues for treating genetic disorders, cancers, and infectious diseases. Its versatility, coupled with continuous advancements in delivery strategies and precision tools, underscores its potential in personalized medicine. However, technical limitations and profound ethical concerns, particularly related to germline editing and equitable access, must be addressed. With responsible governance, informed consent, and commitment to health equity, CRISPR has the capacity to redefine therapeutic paradigms and improve global health outcomes. Its future success will depend on balancing innovation with safety, accessibility, and ethical integrity.

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