Editorial

ANNALS OF MEDICINE & SURGERY

OPEN

The potential of CRISPR-Cas9 in cardiovascular medicine: a focus on hereditary cardiomyopathies

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In cardiovascular medicine, CRISPR-Cas9 technology is a game-changer, especially when it comes to treating inherited cardiomyopathies. Hypertrophic cardiomyopathy and dilated cardiomyopathy are two examples of these genetic illnesses. These conditions are frequently brought on by particular gene mutations that result in aberrant heart muscle function. Conventional therapies concentrate on symptom management rather than addressing the underlying genetic reasons. By directly targeting and editing these faulty genes, CRISPR-Cas9 may be able to provide a long-term remedy. Studies have previously shown that it is possible to successfully modify genes linked to cardiomyopathy in animal models, opening the door for potential human trials. However, as this technology advances toward clinical application, issues including off-target consequences and ethical questions about gene editing in people must be carefully addressed[1,2].

Globally, hypertrophic and dilated cardiomyopathies are two examples of hereditary cardiomyopathies that substantially increase cardiovascular morbidity and death. Heart failure, arrhythmias, and reduced cardiac function are caused by several hereditary illnesses that damage the heart muscle. Hereditary cardiomyopathies are thought to affect 1 in 500 people, which makes them a serious public health concern[3]. Instead of treating the underlying genetic reasons, current care options, such as medication, lifestyle changes, and surgical interventions, mostly concentrate on symptom control and preventing consequences. Nevertheless, these methods frequently fail to stop the spread of illness or reverse damage, placing a heavy strain on patients and healthcare systems. Gene-editing technologies such as CRISPR-Cas9 give hope for identifying and fixing the genetic abnormalities causing the clear need for fresh and precise therapy alternatives.

CRISPR-Cas9 functions by using a guide RNA (gRNA) that matches the sequence of the target gene mutation. gRNA directs the Cas9 enzyme to the specific site of the mutation in the DNA. When the Cas9 enzyme reaches the correct location, it causes a double-strand break in the DNA. The cell's natural repair processes then take over, usually utilizing a template provided by scientists to rectify the mutation or deactivate a defective gene. The mechanism of CRISPR-Cas9 is showcased in Fig. 1. This precision enables the precise editing of genes responsible for hereditary cardiomyopathies[4]. For example, hypertrophic cardiomyopathy is frequently associated with mutations in the MYH7 and MYBPC3 genes, which encode sarcomeric proteins in the heart muscle. Similarly, dilated cardiomyopathy has been linked to TTN gene mutations, which encode the protein titin, which is essential for cardiomyocyte structural integrity[5].

Recent improvements in CRISPR-Cas9 technology have allowed for precise editing of these genes in preclinical mice leading to normalized cardiac function and structure[6]. With an emphasis on inherited cardiomyopathies, recent developments have opened the door for CRISPR-Cas9 applications in human clinical trials. Trials are still in progress to assess safety, effectiveness, and delivery strategies; preliminary findings indicate that fixing genetic mutations may be possible. These studies seek to promote the application of CRISPR-Cas9 in the treatment of cardiovascular disorders by establishing feasibility, improving protocols, and addressing potential obstacles. In recent years, CRISPR-Cas9 technology has emerged as a powerful tool for precision gene editing. Within the field of cardiovascular medicine, researchers have explored various applications of CRISPR-Cas9, particularly in addressing hereditary cardiomyopathies and related conditions. Below, we summarize key studies that highlight the potential of CRISPR-Cas9 in Table 1.

Unintended genomic alterations resulting from off-target effects provide a serious obstacle to the application of CRISPR-Cas9 technology. These unintentional alterations may have unfavorable implications, including unexpected genetic disruptions and harmful cellular impacts[11]. It is still difficult to effectively transport CRISPR-Cas9 components to target tissues, particularly in cardiovascular applications. To ensure treatment efficacy and minimize off-target effects, accurate and efficient delivery mechanisms are essential[12]. Concerns about germline editing and long-term effects are among the ethical and legal issues that are brought up by the usage of CRISPR-Cas9. For CRISPR-based treatments to be advanced in clinical settings, strong regulatory frameworks and ethical issues must be addressed[11,12]. CRISPR-Cas9 has been investigated for gene

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2025) 87:1801–1803

Received: 22 September 2024; Accepted: 02 March 2025

Published online 27 March 2025

http://dx.doi.org/10.1097/MS9.0000000000003170

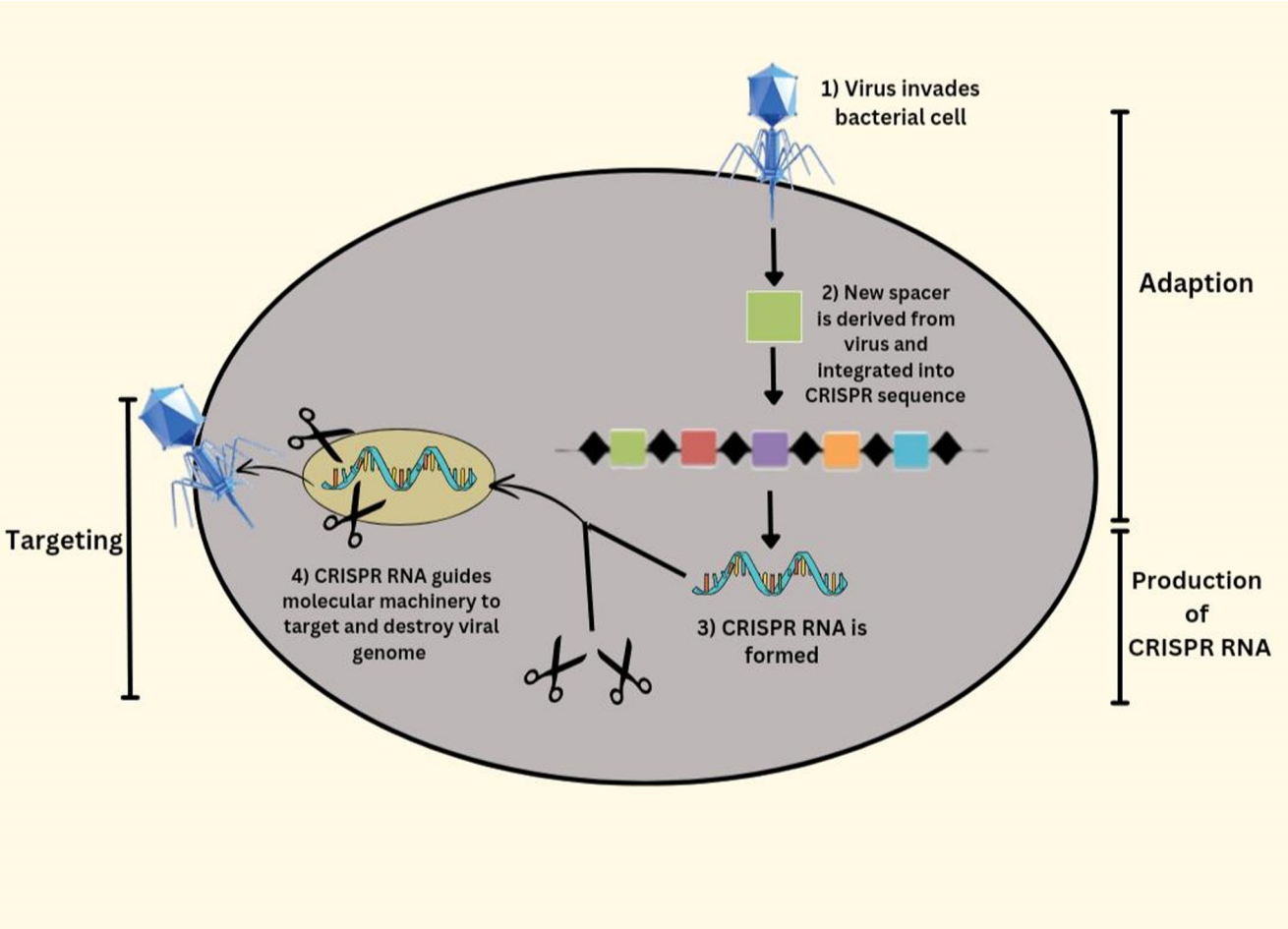

Figure 1. Mechanism of CRISPR-Cas9 gene editing. The figure illustrates the key steps involved in CRISPR-Cas9 gene editing. Cas9, guided by a single-guide RNA (sgRNA) designed to target a specific DNA sequence, binds to the target site adjacent to a protospacer adjacent motif (PAM). Cas9 introduces a double-strand break at the target DNA location. Cellular repair mechanisms are then activated, either through non-homologous end joining (NHEJ), which can result in random insertions or deletions, or homology-directed repair (HDR), which allows precise genetic modifications using a homologous DNA template.

editing in SCN5A-associated cardiac arrhythmias. SCN5A mutations affect the voltage-gated sodium channel NaV1.5, crucial for cardiac conduction. Loss-of-function mutations reduce sodium current, leading to bradyarrhythmias such as heart block and sinus node dysfunction. Conversely, gain-of-function mutations can cause hyperexcitability and tachyarrhythmias like ventricular tachycardia and long QT syndrome. CRISPR-Cas9 holds potential for correcting these mutations to restore normal cardiac rhythm[8,9,11].

With developments centered on enhancing accuracy and effectiveness to reduce off-target effects, CRISPR-Cas9 in cardiovascular therapy has a bright future. Next-generation CRISPR systems, like CRISPR-Cas12, which provide enhanced editing capabilities for cardiovascular applications, are being studied by researchers. To increase therapeutic efficacy and lower risks[13], improving delivery mechanisms – in particular, by creating safer, more focused systems – is also a top priority. Establishing precise ethical standards and legal frameworks will be essential as clinical trials progress, particularly with regard to germline editing, to guarantee the appropriate application of this technology[10].

With its unparalleled potential to provide precise genetic therapies in hereditary cardiomyopathies, CRISPR-Cas9 marks a revolutionary development in cardiovascular therapy. Even with its potential, there are still a lot of unanswered questions, especially with regard to distribution methods, ethical issues, and off-target consequences. It will be essential to address these issues through continued study and cautious regulation in order to transform CRISPR technology into secure and useful treatments. With advancements in the area, CRISPR-Cas9 holds promise for a pivotal role in personalized medicine's future, providing hope to patients with hereditary illnesses that were previously incurable.

Ethical approval

Ethics approval was not required for this editorial.

Consent

Informed consent was not required for this editorial.

Sources of funding

No funding is available.

Table 1

CRISPR/Cas9 applications in cardiovascular genetic disorders

Application	Study Title	Authors	Publication Year	Study Type	Study Insights and Implications	Reference
Gene Editing for Hereditary Cardiomyopathies	Precise Correction of a Pathogenic Mutation in the MYBPC3 Gene Using CRISPR-Cas9	Ma et al.	2017	*In Vitro* Study	Successfully corrected a MYBPC3 mutation linked to hypertrophic cardiomyopathy (HCM) in iPSCs, showcasing CRISPR-Cas9's potential for treating hereditary cardiomyopathies through precise genetic correction.	[7]
Creating Disease Models	A Mouse Model for Adult Cardiac-Specific Gene Deletion with CRISPR/Cas9	Carroll KJ, Makarewich CA, McAnally J, et al.	2016	Animal Model Development	This study successfully developed a cardiac-specific gene deletion model in adult mice using CRISPR/Cas9, offering a novel platform for studying gene functions in adult cardiac tissues and exploring potential therapeutic interventions for cardiac diseases.	[8]
Gene Therapy for Cardiac Arrhythmias	Genome Editing and Cardiac Arrhythmias	Moore OM, Ho KS, Copeland JS, Parthasarathy V, Wehrens XHT	2023	Review Study	This review used CRISPR/Cas9 to explore advancements in genome-editing technologies and their applications in treating cardiac arrhythmias by targeting key genetic mutations. It highlights CRISPR's potential in developing precision medicine strategies for heart rhythm disorders through precise gene correction and functional restoration.	[9]
Gene Editing for Marfan Syndrome	CRISPR-Cas9 Correction of FBN1 Mutations in Marfan Syndrome	He et al.	2018	In Vitro Study	Corrected FBN1 mutations associated with Marfan syndrome, offering potential therapeutic applications for this genetic disorder that often leads to cardiovascular complications.	[10]

Author's contribution

The conceptualization was done by S.R. and M.J. The literature and drafting of the manuscript were conducted by A.W. and A. B.W. The editing and supervision were done by M.H.G., U.F., A. F., I.U.H., and U.K. All authors have read and agreed to the final version of the manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Guarantor

Not applicable.

Research registration unique identifying number (UIN)

Not applicable.

Provenance and peer review

Not applicable.

Data availability statement

Not applicable.

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