

Chapter 4

CRISPR–Cas9

Technology for Precision Cardiovascular Medicine


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ABSTRACT

CRISPR/Cas9 technology emerged as a critical tool in cardiovascular medicine to enable genome editing and engineer novel therapies. Use of CRISPR for correcting mutations has transformed the research on dyslipidemia, atherosclerosis, and cardiomyopathies. The synergism between CRISPR and artificial intelligence (AI) enhance accuracy by optimizing guide RNA design, minimizing off-target effects, and maximizing delivery strategies. Additionally, CRISPR editing systems like CRISPRoff/CRISPRon enable modulation of gene expression without genome changes, hence offer therapeutic intervention. Its uses in cardiovascular systems biology have also solved precise disease modeling, enabled high-resolution decomposition of mechanisms, and drug discovery. Although its potential is great, its clinical

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translation is foiled by safety, long-term efficacy, ethical, and equal accessibility issues. Expanding the CRISPR platform with base and prime editing has potential to circumvent these limitations, positioning CRISPR as a keystone technology in driving cardiovascular medicine.

1. INTRODUCTION: TRANSFORMING CARDIOVASCULAR MEDICINE THROUGH CRISPR

Cardiovascular diseases (CVDs) still dominate morbidity and mortality burdens worldwide, and their treatment requires much more than the conventional risk factor-based approach. Accelerating this transition from the conventional treatment model to precision cardiovascular medicine are major breakthroughs in genome engineering, especially the CRISPR/Cas9 system (Velayuthaprabhu & Archunan, 2005; Velayuthaprabhu et al., 2007; Alagendran et al., 2010; Velayuthaprabhu et al., 2011; Velayuthaprabhu et al., 2013; Velayuthaprabhu et al., 2016; Kuchi Bhotla et al., 2020; Meyyazhagan et al., 2020; Arumugam et al., 2020; Mohd et al., 2021; Bhotla et al., 2021; Mohd et al., 2021; Lee et al., 2021; Pushparaj et al., 2022; Sangeetha et al., 2022; Gundappa et al., 2022; Sangeetha et al., 2022; Meyyazhagan et al., 2022; Ramya et al., 2023; Paranitharan et al., 2025). Using genome editing technologies, one can interrogate and modify disease-associated loci with unprecedented accuracy. These provide insight into the mechanisms of dyslipidemias, atherosclerosis, cardiomyopathies, arrhythmias, and hypertensive disorders. Such innovations will bridge the gap between fundamental cardiovascular genetics and individualized therapeutic design beyond the classical risk factors of hypertension and diabetes toward genotype-driven prediction and intervention (Chen et al., 2022).

Epigenetic modulation, the analysis of rare variants, and polygenic risk scores (PRS) all further stratify cardiovascular risk in a granular manner and provide important additional insights into heritable and regulatory mechanisms in disease inception and progression (Costantino et al., 2018; Tada et al., 2021). Clinical translation will require responsible consideration of safety, off-target mutagenesis, delivery efficiency, and long-term efficacy, with multiple bioethical considerations (Dzilic et al., 2018).

Among genome editing systems, CRISPR/Cas9 represents the most transformative technology capable of correcting pathogenic variants implicated in both monogenic and polygenic CVDs (Figure 1). The majority of preclinical research using atherosclerosis, inherited arrhythmias, hypertrophic and dilated cardiomyopathies, and Duchenne muscular dystrophy (DMD) models has indeed documented that mutation-specific repair improved cardiac function (Bonowicz et al., 2025; Wilton-Clark & Yokota, 2023). Moreover, functional non-coding RNAs, includ-

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