Healing hearts: unlocking the potential of gene therapy in revolutionizing cardiovascular disease treatment

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In medical science, few areas hold as much promise and excitement as gene therapy. It is a cutting-edge field that aims to harness the body's own genetic machinery to combat diseases at their root cause. While gene therapy has shown potential across various diseases (notably in rare monogenetic disease areas), here we dive into the latest advancements specifically focused on the heart. With cardiovascular diseases remaining a leading cause of global morbidity and mortality, researchers are tirelessly exploring innovative ways to tackle rare and common heart-related ailments. In this article, we discuss the fascinating world of gene therapy, exploring recent breakthroughs as well as remaining challenges and their implications for cardiovascular health.

The complexity of heart diseases

Cardiovascular diseases, such as coronary artery disease, heart failure and arrhythmias, affect millions worldwide and often lead to devastating consequences. Traditional treatments, while effective to some extent, often address symptoms rather than tackling the underlying genetic and non-genetic abnormalities. The complexity of heart disease extends beyond the anatomical structures and encompasses the intricate interplay between various cell types and disease processes within the cardiovascular system. The heart is composed of many different cell types, including cardiomyocytes (heart muscle cells), endothelial cells (lining the blood vessels), smooth muscle cells and pericytes (found in the walls of large and small blood vessels), fibroblasts (responsible for tissue repair) and cells of the immune system. Each cell type can cause and/or respond to disease progression and can contribute to the overall pathophysiology of heart disease, thereby underpinning the complexity. For example, in conditions like coronary artery disease, the endothelial cells lining the blood vessels may undergo a change leading to their dysfunction, culminating in the development of plaque and narrowing of the arteries. Cardiomyocytes, the contractile cells of the heart, can become damaged due to insufficient blood supply, high blood pressure or other factors such as direct loss due to a heart attack. Smooth muscle cells may proliferate in response to vessel injury, contributing to the formation of scar tissue and arterial narrowing. Additionally, fibroblasts play a role in tissue remodelling and scarring; some of this is important to stabilize the heart after a heart attack but can also contribute to tissue fibrosis and loss of heart function in heart failure.

Effective gene therapy should aim to restore normal function and coordination among these various cell types to promote overall cardiovascular health by preventing, stabilizing or reversing injury but repair and/or regeneration. By developing strategies to target and modulate the gene expression of specific cell types, researchers aim to restore balance and alleviate the disease burden on the heart and blood vessels (Figure 1). However, there remains a need for innovative approaches to address the underlying genetic factors that contribute to heart diseases. Gene therapy offers a glimmer of hope by targeting these anomalies directly, offering long-term solutions and potential cures.

The marvels of gene therapy

To truly appreciate the significance of gene therapy, we must first grasp the concept of genes as the intricate blueprints that dictate the functioning of our bodies. These genetic instructions are carried by DNA, the molecular building blocks of life. First, gene therapy can seek to address genetic disorders by modifying or

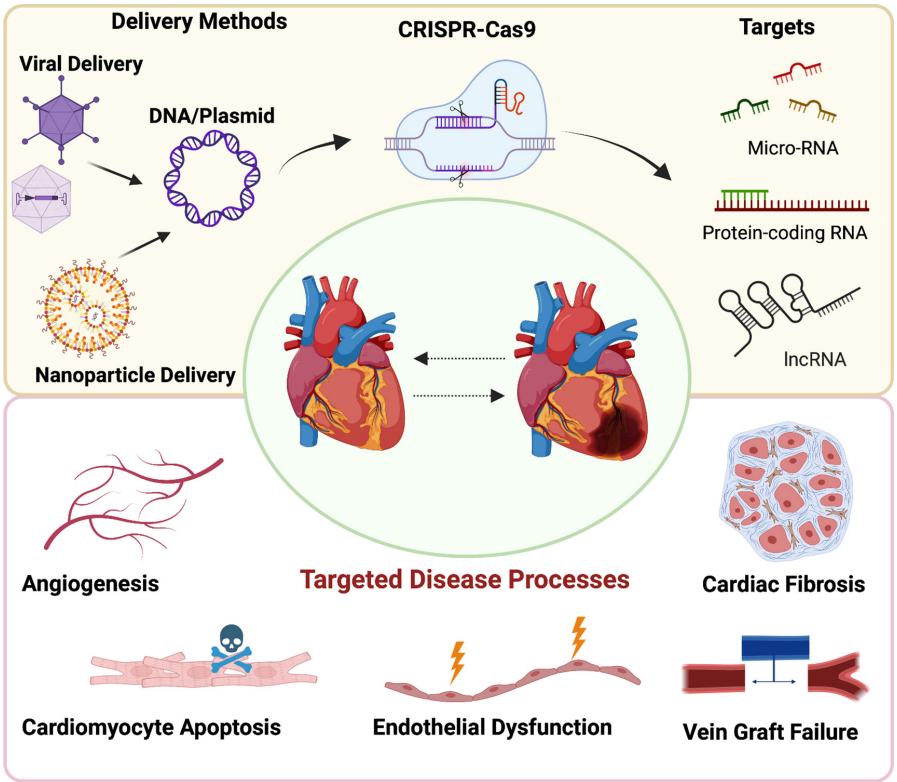

Figure 1. Advances in gene therapy for cardiovascular disease: delivery methods, targets and disease processes (created with Biorender.com by Dr Georgios Krilis).

replacing faulty genes, offering hope for conditions that were once considered incurable. Second, apart from correcting faulty genes, gene therapy also aims to fine-tune gene expression in specific tissues like the heart, through eliciting a beneficial effect by gene manipulation. Researchers are also exploring the use of small RNA molecules called microRNAs or long non-coding RNAs (lncRNAs), which can regulate the activity of specific genes. By manipulating the levels of microRNAs, scientists can modulate gene expression patterns associated with various heart diseases.

Revolutionary strategies for cardiovascular repair

Gene therapies are gaining significant attention for their potential in treating vascular diseases, such as *ex vivo* gene therapy for bypass grafts. They also hold promise for boosting the growth of new blood vessels in the heart and other body parts, known as angiogenesis. Additionally, gene therapy could aid in regenerating and strengthening heart muscle cells after a heart attack, particularly in patients with heart failure. Furthermore, researchers are exploring gene editing techniques to address genetic abnormalities that affect the heart. These areas of focus highlight the wide-ranging possibilities of gene therapies in improving cardiovascular health and combating cardiac conditions.

Coronary bypass surgery improves blood supply to the heart muscle in people with coronary heart disease. However, vein grafts used in the procedure often fail over time due to the narrowing caused by a complex pathological remodelling of the graft. Research from our lab has led to the development of a gene therapy technique to reduce graft failure. This approach involves delivering a protective gene called TIMP-3 into the graft wall cells using an adenoviral vector. TIMP-3 prevents adverse remodelling. After successful animal and lab tests, our team is now ready to conduct the first human trials of this gene therapy.

Unleashing the power of CRISPR–Cas9

In the field of (cardiovascular) gene therapy, a ground breaking tool has emerged that holds immense promise for revolutionizing treatment approaches: CRISPR–Cas9. CRISPR, short for clustered regularly interspaced short palindromic repeats, combined with Cas9, an enzyme, offers unprecedented precision and efficiency in editing genes, providing a powerful tool to address genetic abnormalities and promote cardiovascular health.

The beauty of CRISPR–Cas9 lies in its ability to precisely target specific genes and make highly accurate modifications within the genome. By leveraging the natural defence mechanism of bacteria against viral invaders, scientists have harnessed the CRISPR–Cas9 system to manipulate genes in a controlled manner. This revolutionary technology allows researchers to edit, repair or replace faulty genes associated with cardiovascular diseases, offering a potential path to treat previously untreatable conditions.

One of the most exciting applications of CRISPR–Cas9 in cardiovascular gene therapy is the potential to correct genetic mutations that underlie inherited cardiac disorders. By precisely targeting and modifying the affected genes, scientists can potentially reverse or mitigate the effects of these genetic abnormalities. A proof of principle was demonstrated in the lab of professor Eric Olson at UT Southwestern Medical Center (TX, USA) for a disease called Duchenne muscular dystrophy in small animal models. Duchenne muscular dystrophy is a type of illness caused by mutations in a single gene (*DMD*). This condition mainly affects boys and men, with about 1 in 3500 being affected. It leads to progressive muscle weakness over time, with an average life expectancy of 26. Mice suffering from Duchenne muscular dystrophy were treated by deleting a defective portion of the *Dmd* gene using a CRISPR–Cas9 system delivered by a viral vector. Although not in the context of cardiovascular disease, this approach holds tremendous promise for patients suffering from conditions such as hypertrophic cardiomyopathy, familial hypercholesterolemia, and various arrhythmias.

Moreover, CRISPR–Cas9 opens new avenues for promoting cardiac regeneration and repair. Following a heart attack, the heart muscle often sustains significant damage, leading to heart failure. By utilizing CRISPR–Cas9, researchers can potentially reprogram or activate specific genes involved in cardiomyocyte regeneration. This could stimulate the growth of new, healthy heart muscle cells, promoting recovery and restoring cardiac function.

In a recent research, also led by professor Eric Olson at UT Southwestern Medical Center, CRISPR–Cas9 gene editing has shown that it could be employed as a cardioprotective strategy for patients with heart disease. They modified calcium calmodulin-dependent protein kinase IIδ (*CaMKIIδ*), a key gene involved in cardiac disease, to prevent the overactivation of the CaMKIIδ protein and mitigate damage following a heart attack.

While the potential of CRISPR–Cas9 in cardiovascular gene therapy is immense, it is crucial to approach its implementation with caution. Researchers are actively working to address challenges related to off-target effects, delivery methods and ethical considerations. The technology is rapidly evolving, and on-going studies are focused on refining the precision and safety of CRISPR–Cas9 applications.

Navigating challenges and future directions

While gene therapy presents immense potential for transforming cardiovascular healthcare, several challenges remain to be overcome. The long-term safety of gene therapy, off-target effects and immune responses are areas of active research.

Among the major hurdles faced by researchers in this field, the lack of efficient delivery strategies stands out as a critical obstacle that must be overcome to unlock the full therapeutic potential of gene-based interventions. The heart, blood vessels and other affected tissues present a complex anatomical and physiological environment that necessitates precise and targeted gene delivery. However, existing delivery methods often fall short in terms of achieving efficient and specific transfection rates.

Viral vectors, which have been extensively used in gene therapy, exhibit high transduction efficiency but are not without limitations. They may trigger immune responses and have limited cargo capacity, restricting the size and number of genes that can be delivered. Additionally, concerns regarding their potential long-term presence in a damaged tissue necessitate thorough safety assessments. Overcoming these limitations and optimizing viral vectors for cardiovascular gene therapy remains a significant research focus.

Non-viral vectors, including liposomes, nanoparticles and plasmid DNA, offer advantages such as reduced immunogenicity and increased safety. However, achieving efficient gene delivery with non-viral vectors remains a challenge. They often face hurdles in overcoming biological barriers, such as cellular uptake and intracellular trafficking, which limit their ability to reach the target cells and achieve sustained gene expression.

Another hurdle is the need for site-specific delivery within the cardiovascular system. For effective treatment, therapeutic genes must reach the precise location of interest, such as damaged heart tissue or diseased blood vessels. Achieving this level of spatial and temporal control poses a significant challenge. Developing delivery strategies that can precisely target and localize therapeutic genes to the desired sites while minimizing off-target effects is a critical area of on-going research.

Conclusion

As we delve deeper into the world of gene therapy for the heart, the possibilities for treating cardiovascular diseases seem boundless. The recent advancements in

targeted gene delivery, cardiac repair strategies and the unprecedented precision of CRISPR–Cas9 open up a new era in personalized medicine. While we are still on the path to fully unravel the mysteries of the human heart, gene therapy shines as a beacon of hope, offering the potential to rewrite the genetic code of cardiovascular health. With each breakthrough, we inch closer to a future where heart diseases may no longer be the leading cause of global mortality, bringing us closer to a healthier world. ■

Further reading

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Andrew Baker graduated from the University of London in 1990 with a First Class BSc (Joint Honours) in pharmacology and toxicology and then studied for his PhD with the Leukaemia Research Fund at the University of Wales College of Medicine, graduating in 1994. He joined the group led by Professor Andrew Newby for his post-doctoral work in Cardiff and developed adenoviral vectors for gene delivery studies in the cardiovascular system. He then transferred to a lectureship at the University of Bristol (Bristol Heart Institute) to continue studies on adenovirus-mediated gene transfer to assess vascular function and gene therapy. In 1999, Dr Baker joined the University of Glasgow as a Senior Lecturer in Molecular Medicine, then as Reader and in 2005 as Professor of Molecular Medicine. In 2011 he was awarded a British Heart Foundation Chair of Translational Cardiovascular Medicine. In 2015 he was awarded a Fellowship of the Academy of Medical Sciences before relocating his BHF Chair to the Centre for Cardiovascular Science at the Queen's Medical Research Institute, University of Edinburgh. He became Head of the Centre for Cardiovascular Science in 2017. Prof Baker's research tackles vascular injury. His lab is interested in understanding the events that occur in the aftermath of both acute and chronic injuries to the vessel wall at the molecular, cellular, and whole organism level. Emphasis has been on the role of matrix metalloproteinases and non-coding RNA. Once mechanisms are established, he uses their in-depth expertise in interventional strategies to form potential new opportunities for therapeutic intervention. These are tested in cell culture models, in small and large animal models, and in human tissues (where available and relevant). If successful, his lab then moves to first-in-human trials. Email: andy.baker@ed.ac.uk