SYNCARDIA: Mechanogated Cardiac Regeneration

Present Technology

Currently, the most advanced cardiac fibroblast regeneration therapy involves the use of human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs).[1] In laboratories, scientists can help these stem cells become heart muscle cells by exposing them to chemical signals that mimic early heart development.[2] These signals push the cells through stages where they first become early heart precursors and eventually become cardiomyocytes capable of integrating with the tissue surrounding the scar.

The goal of these cells is to replace stiff scar tissue with new muscle that can contract and restore pumping function in the damaged heart.[3] For the heart to beat in a coordinated way, electrical signals must pass smoothly from cell to cell. This conduction process uses gap junctions, tiny channels that directly connect neighboring cells.[4]

Rather than integrating into the heart's electrical network, hPSC-CMs often generate their own electrical impulses instead of waiting for the heart's main pacemaker.[5] Because of this, clusters of transplanted cells can begin firing independently. When this happens, the graft acts as an ectopic pacemaker, meaning a new, abnormal source of electrical signals that cause ventricular tachycardia, a condition where the heart beats dangerously fast and out of sync.[6] This risk of arrhythmia is the largest obstacle preventing stem-cell heart therapy from being safely used in patients.

Another approach to heart regeneration is through direct reprogramming. After a heart attack, the damaged area fills with fibroblasts, cells whose normal role is to produce connective tissue, such as collagen, to stabilize injured tissue.[5] Rather than removing these fibroblasts, scientists aim to genetically convert them into cardiomyocytes using transcription factors.[5]

Gata4, Mef2c, and Tbx5, also known as GMT, are key regulators of heart development and are the main transcription factors used.[7] These proteins bind to specific regions of DNA that control cardiac genes, including genes responsible for producing contractile proteins such as cardiac troponin T and myosin, and proteins involved in electrical signaling such as connexin-43. When these genes are activated by GMT, the fibroblasts gradually stop behaving like scar cells and begin developing characteristics of heart muscle cells.

However, fibroblast DNA is tightly packed and chemically locked in a way that blocks access to many heart-related genes.[8] Because of this, GMT often cannot fully activate the cardiac complex. Many fibroblasts only partially convert, producing cells that express some heart proteins but lack proper structure and electrical coordination.[9] These unstable cells interfere with electrical conduction in the heart and increase arrhythmia risk.[7] Another challenge is the delivery of GMT. Modified viruses are often used to insert the transcription factor genes into fibroblasts, but these viruses can unintentionally activate genes in healthy cells or disrupt important DNA regions. This heightens the risk of irregular cell behavior and abnormal growth. Additionally, current reprogramming methods do not take advantage of the heart's mechanical environment after injury. The border around the scar becomes much stiffer and experiences strong stretching forces with each heartbeat.[4] These physical forces influence how genes are activated inside cells and can make fibroblasts more flexible in their identity. Existing technologies do not coordinate reprogramming with these physical cues.

History

Myocardial Infarction (MI) was first clinically diagnosed in the late nineteenth and early twentieth centuries when physicians began linking chest pain, coronary artery occlusion, and sudden cardiac death.[10] By the mid-1900s, electrocardiography established that MI is caused by

prolonged ischemia (reduction in blood flow to organs) caused by blockage of the coronary arteries, leading to irreversible cardiomyocyte death. Early treatment focused on symptom management through bed rest and later through pharmaceutical drugs such as beta blockers.[10]

By 1958, cardiovascular treatment shifted to targeting root causes instead of solely symptoms.[11] Mason Sones's development of coronary angiography in 1958 at the Cleveland Clinic enabled the first moving imaging of coronary arteries in living patients, allowing precise identification of obstructions.[12] Using the visualization, René Favaloro performed the first successful bypass graft in 1967, allowing blood to bypass coronary obstructions.[12] Another therapy, thrombolytics, emerged by using fibrinolytic medication to dissolve dangerous blood clots and restore blood flow during acute myocardial infarctions, saving heart muscle.[13] While these interventions significantly reduced mortality rates, researchers recognized the loss of cardiomyocytes and their replacement with fibroblast scar tissue, but did not address it.

Early regenerative efforts to replace fibroblast scar tissue began in the late 1990s through bone marrow-derived stem cells.[13] In 1998, biologist James Thomson isolated the first human embryonic stem cell lines from embryos, showing that human cells could be cultured while still maintaining the ability to differentiate into any cell type in the body.[14] Winning the Nobel Prize in 2012, Shinya Yamanaka discovered that mature cells can be reprogrammed into pluripotency, which provides the theoretical foundation for SYNCARDIA's reprogramming architecture.[15]

While cardiac biology advances, a separate field, lipid nanoparticle engineering, was transforming therapeutic molecule delivery. Liposomes, artificially made spherical bilayer structures, were first observed to be able to hold biological material by Alec Bangham in the 1960s.[16] In the 1970s, researchers such as Gregory Gregoriadis showed that liposomes could function as drug carriers.[17] This led many researchers to begin experimenting with how to

enhance LNP efficiency. Specifically, cationic lipids such as DOTMA and DOPE allowed for the LNPs to deliver material without viral vectors.[18] In the 2010s, the first FDA-approved LNP-based siRNA therapeutic, patisiran, confirmed that LNPs could safely deliver genetic therapies in humans.[19] In fact, LNPs, along with breakthrough mRNA technologies, were developed and used in vaccines against COVID-19, securing LNPs as a realistic platform for nucleic acid delivery.[19]

Future Technology

By 2045, SYNCARDIA will revolutionize post-MI recovery by moving beyond passive stenting toward active, mechanically-intelligent biological regeneration.

SYNCARDIA uses non-viral lipid nanoparticles (LNPs) as its delivery platform. LNPs protect nucleic acids from degradation and enable intracellular delivery and expression without permanent genome integration, making them a realistic approach for cardiac gene delivery.[20]

To maximize safety and spatial precision, SYNCARDIA combines a standard intravenous (IV) delivery with localized ultrasound (FUS) activation. The SYNC-LNPs are engineered with a "stealth" shell that prevents them from being absorbed by the liver or spleen. After systemic circulation, a FUS transducer is placed over the patient's chest, increasing vascular permeability in the targeted region to allow SYNC-LNPs to enter the heart tissue selectively at the ultrasound focus. This allows for surgical precision through a simple IV drip, removing the risks and costs associated with invasive heart surgery.

Importantly, SYNCARDIA does not assume that delivery alone creates specificity. Instead, it is a biological AND-gate system, meaning gene expression occurs only when all conditions are met simultaneously.

Layer 1: Microenvironmental Uptake Bias

The infarct scar and border-zone region are mechanically distinct from healthy myocardium. Because substrate stiffness can regulate internalization pathways, SYNCARDIA's LNP formulation would be tuned to increase uptake probability in stiff, scar-associated fibroblast environments[21].

Layer 2: Mechanogated Program Initiation

SYNCARDIA's second targeting layer uses mechanotransduction as a biological permission signal. After MI, the infarct border zone experiences abnormal cyclic strain because viable myocardium continues contracting while scar tissue does not. Fibroblasts sense these forces through integrins and focal adhesion complexes that transmit extracellular matrix tension into actin cytoskeletal tension[22]. Under high mechanical tension, the transcriptional co-activators YAP and TAZ accumulate in the nucleus and activate TEAD-dependent transcription[22,23].

SYNCARDIA uses this pathway as a mechanogated switch. The earliest stage of its genetic program is encoded under TEAD-responsive regulatory control within the delivered expression cassette. This increases the probability that the program initiates only in cells actively experiencing high cytoskeletal tension and nuclear YAP/TAZ activity, which is expected to be enriched in infarct border-zone fibroblasts.

Layer 3: Fibroblast and Injury-State Gating

Mechanogating alone cannot guarantee cell-type specificity. SYNCARDIA therefore includes fibroblast and injury-state gating so that early program initiation is strongly enriched in activated cardiac fibroblasts involved in infarct remodeling. This can be implemented using regulatory elements from genes highly upregulated in activated fibroblasts after MI, such as periostin (Postn), a widely used marker of activated cardiac fibroblasts during infarct

remodeling[24], and collagen type I alpha 1 (Col1a1), which is strongly expressed in fibrosis-associated fibroblasts[25].

Layer 4: Post-Transcriptional De-Targeting

SYNCARDIA further reduces off-target expression through post-transcriptional de-targeting. miRNA binding sites are incorporated into untranslated regions (UTRs) of therapeutic RNAs. In tissues where those miRNAs are abundant, the therapeutic RNA is degraded or silenced before producing meaningful protein[26]. For example, miR-122 binding sites are integrated into 3'UTRs. In the liver, where miR-122 is abundant, any stray SYNCARDIA RNA is immediately degraded. This strategy has been demonstrated in LNP-based RNA delivery systems and has been used to reduce off-target expression in high-uptake organs[26].

Epigenetic Priming (PHF7)

SYNCARDIA begins with epigenetic priming to reduce fibroblast epigenetic resistance. The first active regulator is PHF7, which has been reported to enhance adult murine and human fibroblast cardiac reprogramming by modifying chromatin accessibility at cardiac super-enhancers when added to reprogramming cocktails[27]. Mechanistically, PHF7 has been described to localize to cardiac super-enhancers and cooperate with chromatin remodeling machinery, increasing chromatin accessibility and enabling stronger transcription factor binding at cardiac regulatory regions[28].

In SYNCARDIA, PHF7 is delivered as a transient expression to create a limited priming window. This is intended to shift key cardiac regulatory DNA from closed to permissive before transcription factors are expressed. To ensure this window is temporary, the PHF7 protein is tagged with an Oxygen-Dependent Degradation (ODD) domain. This is a molecular timer that

ensures the protein is recycled by the cell after 48 hours, preventing uncontrolled chromatin remodeling[29].

Cardiomyocyte Conversion (GMT)

After priming, SYNCARDIA initiates cardiomyocyte conversion using GMT (Gata4, Mef2c, Tbx5). GMT has been shown to reprogram fibroblasts into cardiomyocyte-like cells directly and induce cardiac marker expression and cardiac beating behavior in vitro [9].

However, SYNCARDIA does not treat GMT as sufficient. Evidence indicates that GMT-mediated conversion can remain inefficient and incomplete, with partially reprogrammed intermediate states that show immature electrophysiology and poor survival in vivo.[7] SYNCARDIA's PHF7-first architecture is designed to reduce this failure mode by increasing accessibility at cardiac regulatory regions, increasing the probability that GMT activates a coherent cardiac gene network.[27]

Electrical Integration Support (Cx43)

SYNCARDIA is also designed to reduce arrhythmia vulnerability during and after conversion. Electrical instability can occur when newly formed cardiomyocyte-like cells remain electrically isolated or conduct abnormally within the infarct border zone. SYNCARDIA therefore includes a coupling support module using connexin-43 (Cx43), the primary gap junction protein in ventricular myocardium. Cx43-based gap junctions enable direct intercellular ion transfer and synchronized contraction, and disruption of Cx43 expression or localization contributes to conduction abnormalities and arrhythmia risk.[30]

This module is designed to activate during the transition window when cardiac identity begins to emerge, reducing the chance that reprogrammed tissue behaves like electrically heterogeneous islands. Support for this concept includes evidence that increasing Cx43

expression in infarct border tissue can improve conduction velocity and reduce ventricular tachycardia susceptibility in large-animal models[31].

To avoid inappropriate coupling in immature cells, Cx43 expression is placed under the control of a cardiomyocyte-specific Troponin T (TNNT2) promoter. This ensures the "electrical bridge" only forms once the cell has successfully established a contractile cardiac identity[32].

Breakthroughs

While the components of SYNCARDIA are grounded in biology, several critical breakthroughs are required to move from laboratory proof-of-concept to a 2045 clinical reality.

1. Nano-Acoustic Shell Engineering and Sonoporation Precision

Currently, lipid nanoparticles (LNPs) are designed for systemic absorption (like vaccines) or liver-targeting. The technology to create an LNP that remains inert in the bloodstream but reacts to specific, localized ultrasound frequencies (Focused Ultrasound/FUS) is in its infancy. As of 2025, researchers have achieved early success with sucrose-stabilized liposomes that respond to ultrasound in brain tissue.[33] However, we require a sub-100nm shell that can undergo "sonoporation", specifically in the high-pressure environment of the coronary microvasculature.

2. Calibration of the "ODD-Degron" Molecular Timer

The Oxygen-Dependent Degradation (ODD) domain is a natural biological sensor, but using it as a precision "timer" for PHF7 requires synthetic tuning. While we understand the basic mechanism of ODD-mediated proteolysis[34], we cannot currently guarantee the exact half-life of a protein in the human heart. We need further Proteomic Engineering research to calibrate the ODD sequence so it degrades PHF7 at the exact moment of cardiac reperfusion (re-oxygenation) to ensure the “priming window.”

3. Large-Scale Synthetic Logic Gate Reliability

Our project relies on a four-input "AND gate." Current synthetic biology often suffers from "leaky" expression, where genes turn on slightly even if all conditions aren't met. Transcriptional Gating needs to progress to ensure that GMT conversion factors have an absolute "zero-leak" threshold, preventing accidental reprogramming of healthy heart cells or organs.

Our proposed investigation is to make SYNCARDIA safe by ensuring that the PHF7 "priming" protein vanishes exactly 48 hours after reperfusion to prevent uncontrolled chromatin remodeling and cellular instability. We will engineer a library of 500 synthetic ODD-domain variants, each attached to a Green Fluorescent Protein (GFP) reporter. These will be delivered via LNPs into human-induced pluripotent stem cell-derived fibroblasts (hiPSC-Fibs). We will place these cells in a "Hypoxia-Reoxygenation Chamber" to simulate a heart attack and subsequent medical intervention.

To validate the precision of this system, we will utilize automated flow cytometry to monitor Fluorescence Decay Kinetics, measuring the Mean Fluorescence Intensity (MFI) of the reporter at two-hour intervals over a 96-hour period. This high-resolution temporal data will allow us to conduct a Half-Life Analysis by plotting a proteomic decay curve, identifying the specific ODD-variant that achieves a protein half-life of 48 hours with a standard deviation of less than 30 minutes. Finally, to ensure the entire therapeutic payload is being processed, we will perform Western Blotting to verify that the PHF7 protein itself is being degraded by the cell’s proteasome system in response to rising oxygen levels, rather than just the fluorescent marker.

Design Process

Our team looked at three alternative features before finalizing the current design. First, we considered calcium-based mechanosensing to activate therapeutic gene expression in the infarct border zone. This approach was rejected because calcium plays overlapping roles in

cardiac excitations, contraction, and electrical signaling.[35] Using calcium as a regulatory switch could be dangerous, as therapeutic activation could disrupt normal rhythm or induce arrhythmias.[36] Our final design uses YAP/TAZ-TEAD mechanotransduction, which responds to cytoskeletal tension without interfering with calcium-dependent electrical processes.

Second, we looked at systemic delivery of lipid nanoparticles (LNPs) with liver-specific microRNA binding sites to suppress hepatic expression. This was rejected because systematically delivered nanoparticles accumulate mainly in the liver and spleen, and only a small fraction reaches the myocardium.[37] Getting to therapeutic levels in the infarct zone would require high doses with increased risk of toxicity. Our final design instead combines localized cardiac delivery with mechanosensitive TEAD-responsive promoters, improving specificity for mechanically abnormal border zone cells. Local delivery achieves much higher cardiac concentrations than systemic administration.[38]

Third, we considered expressing Gata4, Mef2c, Tbx5, and Connexin 43 from a single promoter. This idea was rejected because early Connexin 43 expression would electrically couple immature and partially reprogrammed cells to host myocardium, creating a risk of arrhythmias.[6] Simultaneous GMT expression also fails to overcome chromatin accessibility barriers, leading to inefficient and incomplete reprogramming. Our final design regulates gene expression over time, with PHF7 driven by TEAD-responsive promoters to prime chromatin and enhance GMT-mediated reprogramming, followed by Connexin 43 expression restricted to cells that have established cardiac identity, which helps ensure safe electrical integration.

Consequences

For many Americans, surviving a heart attack doesn't mark a full recovery but ongoing health decline[39]. Approximately 38% of post-myocardial infarction patients die within nine years, and nearly 30% develop heart failure, highlighting the limitations of current treatments[40].

Reprogramming fibroblasts with scar tissue into cardiomyocyte-like cells, the approach aims to reduce electrically inactive tissue while improving coordination of heart muscle contraction. For patients, this could mean fewer symptoms of heart failure, such as fatigue, and potentially a lower risk of arrhythmias[9].

For hospitals and clinics, successful cardiac reprogramming could reduce emergency readmissions and the need for intensive interventions such as implantable cardioverter-defibrillators (ICDs)[6]. It could also lower long-term treatment costs since it avoids expensive cell grafts, immune matching procedures, and repeated hospitalizations. However, gene-based therapies carry uncertainty, including unintended genetic or epigenetic changes, incomplete cellular reprogramming, and cancer risks that could emerge later. Past gene therapy trials have resulted in severe outcomes, including patient mortality and leukemogenesis[37]. Clinics must also prepare for potential complications and ongoing monitoring. Additionally, the leakage of LNPs could allow therapeutic material to accumulate in non-target tissues, potentially causing unintended side effects outside the heart.

Another important concern is access, as gene therapies typically cost over $2 million per patient. While sometimes accessible to patients with commercial insurance, most Medicaid programs lack the capacity to cover such interventions. Given that 85% of uninsured MI patients face catastrophic medical costs, SYNCARDIA risks widening health disparities without aggressive policy intervention to ensure equitable access.[41]

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