

Editorial



Cardiac Patch as a Superior Clinically Translatable Approach for Cardiac Regenerative Medicine

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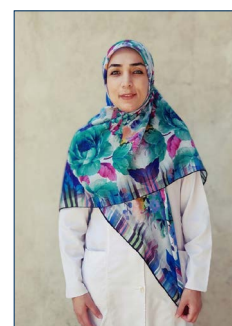
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A failing heart is far more challenging than a single organ insufficiency, as it can progress to a deteriorating condition with multi-organ impact and life-threatening outcomes.¹ Current therapeutic approaches focus on decelerating disease progression rather than restoring or preserving cardiac function.² Therefore, a shift toward more restorative biomedical approaches, including regenerative medicine, is necessary.³

Considerable research has been dedicated to cell-, gene-, and tissue-based therapies for heart failure. Over the past two decades, multiple cell types have been used for cardiac stem cell therapy, including bone marrow-derived multipotent stem cells, human pluripotent stem cells (hPSCs), and hPSC-derived cardiac progenitor cells and cardiomyocytes.⁴ However, according to available reports, the observed therapeutic effects have not been clinically significant, and this approach has not become standard therapy. Limited retention and no signs of remuscularization have been suggested as underlying reasons, because a failing heart requires a substantial number of new contracting cardiomyocytes to restore sufficient pumping function. In contrast, tissue-based models have appeared promising in this regard. Engineered heart tissue, or cardiac patch, is a three-dimensional (3D) laboratory-grown model comprising different types of heart muscle cells as well as extracellular matrix. In principle, these tissues are formed from pre-differentiated cells derived from cardiogenic differentiation of hPSCs. Signs of remuscularization have been observed following implantation of 3D tissue-engineered allografts and xenografts in small and large animal models.⁵⁻¹² Importantly, large animal studies—particularly the 2025 report by Jebran and colleagues on allograft engineered heart muscle (EHM)—provided early proof-of-concept for the safety and efficacy of this new approach in heart failure, findings that could not be conclusively derived from small animal studies alone.¹²⁻¹⁷ In xenograft models, the observed effects were determined to be partially

Author's Biosketch

Sara Pahlavan is a member of Cardiovascular Group at Royan Institute for Stem Cell Biology and Technology. She studied Biology in her B.Sc and graduated in M.Sc of Physiology from Shiraz University. During her undergraduate studies, she got interested in physiology of cardiac cells, specifically excitation-contraction coupling. To pursue her interest, she moved to Germany and started her graduate studies in Professor Peter Lipp's lab at Universitäts Klinikum des Saarlandes. There, she learned state of the art technologies such as simultaneous "patch-clamp" and "Ca²⁺imaging" to study excitation-contraction coupling in cardiomyocytes. Furthermore, she used transgenic mice to study pathophysiology of inherited cardiac diseases with respect to electrophysiology and/or Ca²⁺machinery. Toward the end of her PhD studies, she got interested in using patient-specific iPSC-derived cardiomyocytes to study cardiac disease in human cardiac cells and to test new drugs. To pursue this goal, she moved to United States and started her postdoctoral fellowship in Professor Martin Morad's lab at Medical University of South Carolina. There she could develop a new genetically-encoded Ca²⁺probe to study Ca²⁺induced Ca²⁺release and Ca²⁺sparks in cardiomyocytes of healthy and patient-specific iPSC-derived cardiomyocytes. She joined Royan Institute at 2015 and currently she works as an Associate Professor in cardiovascular Group.



induced by immune responses¹⁸ or paracrine mechanisms^{19,20}, rather than by remuscularization.

These findings led to the authorization of the first-in-patient Phase 1/2 clinical trial (ClinicalTrials.gov NCT04396899), named BioVAT-HF-DZHK20 in Germany, which aims to explore the safety and efficacy of allograft EHM. Primary results from an early BioVAT-HF patient receiving 10 EHM implants recapitulated large animal findings with respect to safety and remuscularization of the failing heart.¹² Furthermore, these results provided the basis for protocol revisions,



such as increasing the dose of EHM implants to up to 20.¹² Unlike intramyocardial injections, epicardial EHM implants have shown no signs of arrhythmia, reducing concerns regarding this major adverse effect.¹²⁻¹⁶

In a nutshell, EHM studies have revived hopes for a novel cell-based therapy for heart failure and have demonstrated that these tissue-engineered models are superior to other non-myocyte grafts, as they result in functional remuscularization.^{5,21} The findings of the currently ongoing clinical trial will be critical for future decision-making regarding next-generation therapies for advanced heart failure.²²

Competing Interests

None declared.

Ethical Approval

Not applicable.

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Intelligence Use Disclosure

None.

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