Ultra-rapid Manufacturing of Engineered Epicardial Substitute to Repair Ischemic Heart Tissue

Vahid Serpooshan[1], Ke Wei[2], Mingming Zhao[1], Scott A. Metzler[1], Parisha B. Shah[1], Yuka Matsuura[1], Wenqing Cai[2], Andrew Wang[1], Wenhong Zhu[2], Morteza Mahmoudi[1], Manish J. Butte[1], Phillip C. Yang[1], Daniel Bernstein[1], Mark Mercola[2], and Pilar Ruiz-Lozano[1]

[1] Stanford Cardiovascular Institute (CVI), School of Medicine, Dept. of Pediatrics-Cardiology, Stanford, CA

[2] Sanford-Burnham Medical Research Ins., La Jolla, CA

Statement of Purpose: The adult mammalian heart retains only a limited ability to regenerate after injury[1]. A modest stimulation of the innate regenerative capacity has been achieved by re-activating the cell cycle of normally quiescent adult cardiomyocytes in mice and by stimulating endogenous progenitor cells. To achieve therapeutic enhancement of innate regeneration, we explored whether an engineered epicardium might enhance cardiac healing after injury.

Recent evidence suggests that the epicardium promotes myocardial regeneration; however, the mechanism remains largely unknown. In this study we demonstrate that an engineered acellular type I collagen scaffold[2] with biomechanical properties approaching those of the *embryonic epicardium* can be utilized as a cardiac patch in order to improve heart function following acute myocardial infarction. Furthermore, incorporation of epicardial cell-derived paracrine factors into the matrices markedly augmented their restorative effect, protecting the cardiac tissue from injury at the anatomical and functional levels.

Methods: Engineered patches seeded with epicardial paracrine factors were grafted onto the infarcted area in adult murine hearts immediately after the LAD artery ligation and the physiological outcomes were monitored by echocardiography and MRI, and by hemodynamic and histological analyses four weeks post injury.

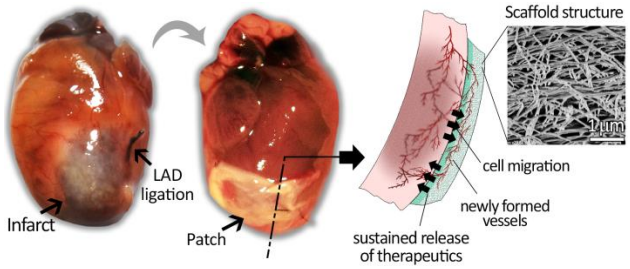

Figure 1. Application of the patch onto the infarcted myocardium in the mouse heart. The inset on the right shows electron microscopy of 3D collagen structure[2].

Results: Application of the engineered graft preserved myocardial contractility and blocked left ventricular remodeling. This was accompanied by formation of a network of interconnected blood vessels and evidences of proliferating pre-existing cardiomyocytes at the border zone of the infarct. Immunostaining confirmed the presence of proliferating myocytes, fibroblasts, smooth muscle, and epicardial cells within the grafted area.

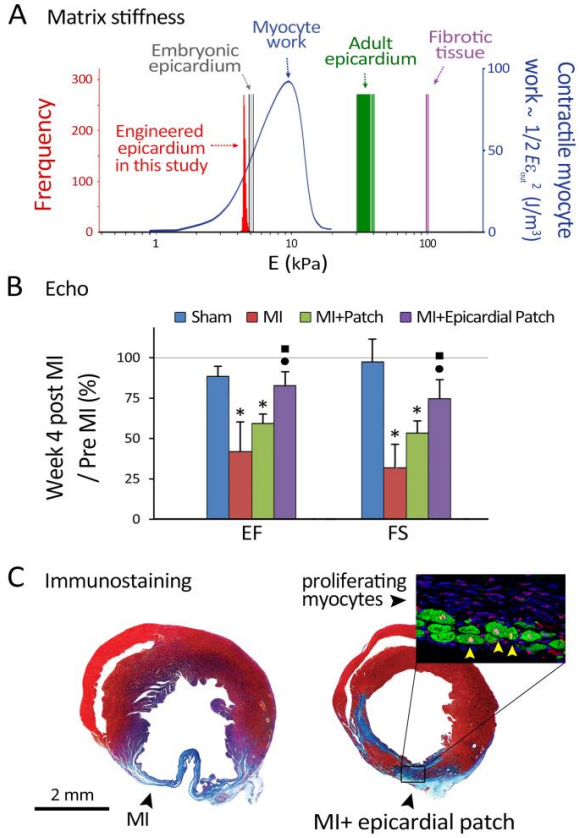

Figure 2. A: comparison of elasticity of the engineered patch (red) with that of epicardium at different stages and optimal stiffness for myocyte contractility (blue)[3]. B: echo data four weeks post infarct. C: histology (trichrome staining) and immunostaining of heart sections.

Conclusions: In summary, we developed a novel, embryonic epicardium-like patch that promotes myocardial regeneration independent of added cells, and demonstrated that incorporation of epicardial factors into the patch augments this effect, most likely by restoring an endogenous epicardial regenerative activity. In addition to its intrinsic beneficial mechanical effect, the engineered epicardium can be utilized as a local sustained delivery device to induce regeneration and preserve cardiac function, thus constituting a novel platform for treating heart disease.

References

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