will undoubtedly be necessary in achieving meaningful translation to human disease, and the authors take an important step in that direction. With steady work, the dream of true cardiac regenerative therapy may one day be fully realized. The authors have made a fine sandwich, and we cautiously await the next course.

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Commentary: Cardinal virtues of multifarious hydrogel implant in cardiac resurrection

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Permeant loss of cardiomyocytes, the “beating elements,” in the myocardium following myocardial infarction (MI) leads to irreversible cardiac damage, suggesting the need for myocardial restoration and regeneration to rescue the cardiac function.¹ Even though the existing management

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CENTRAL MESSAGE

The combinatorial approach of hybrid hydrogels decorated with ADSC sheets significantly improves myocardial regeneration following acute myocardial infarction.

strategies have been successful in preventing early mortality, protecting the surviving myocardium and reducing the further threat of cardiac arrest, the approaches for the replacement and rejuvenation of cardiac cells in the infarct zone to accelerate the regeneration of a functional myocardium remains to be achieved.² For instance, we recently reported that approximately 50 g of an injured myocardium reflects the irreversible loss of ~1 billion cardiomyocytes

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following an MI, suggesting the incompetency of the inherent regenerative mechanisms to replenish the lost cells.³ Interestingly, the growing advancements in stem cell-based regenerative technologies offer promising hope for myocardial restoration and regeneration by replenishing the lost cells.

The last 2 decades brought a broad spectrum of research achievements in cell delivery approaches to improve cardiac performance following MI. However, the replenishment of terminally differentiated cardiomyocytes (CMs) in the surviving myocardium remains a herculean task. For instance, the delivery of 100 million CMs induced only a ~4% increase in the ejection fraction, warranting the search for a promising strategy to sustain the CM density at the infarct zone.⁴ To address this issue, mesenchymal stem cells (MSCs) from diverse sources, including bone marrow, umbilical cord, blood,

and adipose tissue, have the ability to replicate many times through cell cycle with versatile cardiac differentiation strategies.⁵

After being introduced by Zuk and colleagues⁶ in 2001, the use of adipose-derived stem cells (ADSCs) has been recommended by the Internal Fat Applied Technology Society owing to their excellent regenerative potency and self-renewal capacity to be phenotypically similar to MSCs.⁶ In addition, the ease of and abundance in harvesting, potential to differentiate to multiple lineages in the cardiovascular system, abundance of paracrine and regenerative mediators, exceptional cytoprotective capacity, antiscarring ability and extreme immunomodulatory potential make ADSCs the most clinically attractive type of stem cells in regenerative cardiology.^{6,7} The wealth of data from more than 130 ongoing clinical trials support the application of ADSCs in cardiac regeneration.⁷

FIGURE 1. The overall scheme for accelerated regeneration of the infarcted myocardium following the implantation of multifarious hydrogel fabricated using porcine cardiac extracellular matrix (ECM), poly(ester-carbonate-urethane)urea (PECUU), and adipose-derived stem cell (ADSC) sheets.

In this context, the original findings reported in this issue of the *Journal* by Kashiyama and colleagues⁸ provide scientifically relevant insight into the effective application of ADSCs in regenerative cardiology.

The minimal retention and extremely low survival rate of the delivered cells in the hostile microenvironment of the myocardium following MI pose a major hurdle for direct cell injection strategies.⁷ In one study, more than 90% of the administered MSCs died within 24 hours and continued to decline thereafter.⁹ Hence, ineffectiveness of cell injection led to the evolution of scaffolding to ensure the bioretention and improved performance of the injected cells to accelerate cardiac tissue regeneration.¹⁰ Alternatively, the cell sheet technology described by Takezawa and colleagues¹¹ represents a promising scaffold-free system, using cell–cell junctions and extracellular matrix (ECM) components to form clusters/sheets¹¹; however, this technology also faces challenges, including poor mechanocompatibility and biointegration. The combinatorial approach of stem cell sheet technology along with a hydrogel template in a rat MI model make the study by Kashiyama and colleagues⁸ interesting and unique, and their findings undoubtedly will continue to advance the field of regenerative cardiology. Moreover, it is appropriate to applaud the fabrication of the multifarious hydrogel system by amalgamating synthetic poly(ester-carbonate-urethane)urea and porcine decellularized cardiac ECM using electrospinning technology decorated with ADSC sheets. The encouraging findings of Kashiyama and colleagues⁸ support a strong platform for translating the novel combinatorial approach in cardiac regeneration. The overall message of the study is depicted in Figure 1.

This study has some limitations. Unfortunately, the authors do not provide data on the cell infiltration and quantification of the translocated cells. Information on the anterograde and retrograde infiltration/migration of seeded and host cells is crucial for defining the integration of the scaffolds to accelerate the regenerative/healing responses. What are the fate and the mechanism of action of the transplanted ADSCs? Do they differentiate to CMs or elicit any paracrine effect? What is the status of host cells on encountering the transplanted cells? Is there any phenotype drift? Moreover, the conclusions were drawn mainly by considering growth factor expression, but further supporting studies are needed. In addition, the finding that the fibrotic area obtained from the hydrogel alone was same as that obtained from cell sheet–loaded hydrogel raise the possibility that the protective effect may be due to the scaffolding, with the cell sheet having a

minimal regenerative effect. Furthermore, the concerns regarding the application of biomaterials, including immunocompatibility, biointegration, biodegradation, and biological performance, warrant further attention. These perturbations need to be addressed from a clinician/cardiologist standpoint to obtain reproducible outcomes in the translational arena.

Despite the limitations of this study, the findings reported by Kashiyama and colleagues have introduced a novel multifarious approach for myocardial regeneration by effectively using a hybrid hydrogel system and ADSC sheets. Fundamentally, the incorporation of prohealing mediators to such a hydrogel system would add more flavors to this approach. The findings are novel and promising; however, further evaluation of other comorbidities, including diabetes and hypertension, and other confounding factors in clinically relevant large animal models is needed before human clinical trials.

In conclusion, myocardial restoration using combinatorial approaches incorporating multiple cell phenotypes, diverse regenerative mediators, and appropriate therapeutic agents in biocompatible templates marks the beginning of a new era of translational regenerative cardiology to resuscitate the failing myocardium.

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