

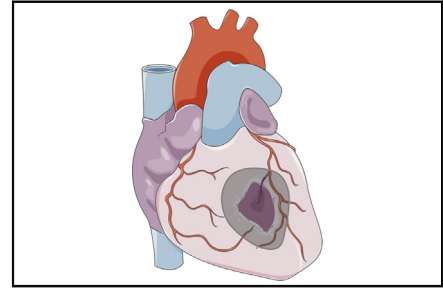
# Tissue engineering of the heart: An evolving paradigm



Gordana Vunjak-Novakovic, PhD

## ABSTRACT

Tissue-engineered regeneration of a failing human heart remains a major challenge, while cardiovascular disease continues to take more lives than all cancers combined. Much has been learned from the basic and clinical studies, with the most interesting developments happening at the interfaces of disciplines. This seems to be the right time to step back and rethink the evolving paradigm of tissue engineering, and to reflect about the most promising directions to take. We clearly need new therapeutic modalities that are effective and yet simple enough to be practical, and the field is looking into the therapeutic potential of stem-progenitor cells, cardiac and vascular, that are enabled by bioactive factors and functionalized biomaterials. (J Thorac Cardiovasc Surg 2017;153:593-5)



A patch for heart repair: cell therapy, or induction of endogenous repair?

### Central Message

New therapeutic modalities are now emerging through the use of technologies that can mobilize the regenerative potential of cardiac and vascular stem-progenitor cells.

### Perspective

The state of the art of cardiac tissue engineering is an evolving paradigm: from cell therapy to the induction of endogenous repair mechanisms by bioactive factors and functionalized biomaterials.

See Editorial Commentary page 596.

**Feature Editor's Note**—Near the end of her insightful and highly authoritative Expert Opinion, under the general heading of “functionalized biomaterials,” Dr Gordana Vunjak-Novakovic mentions the publication in *Nature Materials*<sup>1</sup> that stimulated this Feature Editor to ask her to highlight new possibilities in tissue engineering. Yu and colleagues<sup>1</sup> reported “synthesis and application of an elastic, wearable crosslinked polymer layer that mimics the properties of normal, youthful skin,” accompanied by stunning photographs of cosmetic

results around the eyes of human females. Virtues of this polysiloxane-based polymer include delivery of pharmaceuticals. Unsurprising is that the *Los Angeles Times*<sup>2</sup> and the *New York Times*<sup>3</sup> picked up the story. Surprising is that the *Palm Beach Post* missed it. But even those who've given up worrying about bags under the eyes might wonder if there is something in this for the cardiovascular system. Isn't the endothelium a kind of “skin”? Even more so, the epicardium, pericardium, aortic adventitia? Could the right drug cocktail, delivered under a patch of polymer, heal atherosclerosis? Worst case, there are always those bags under the eyes!

**Craig R. Smith, MD**

It is now almost 30 years since tissue engineering has been officially established, to offer “the application of principles and methods of engineering and life sciences toward fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain,

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or improve tissue function.” With end-stage heart and lung disease representing major medical problems worldwide, tissue engineering is focused on providing definitive solutions by repairing the heart, lung, and many other organs, in a way not limited by the shortage of donor organs. This issue of *The Journal of Cardiovascular and Thoracic Surgery* is focused on tissue engineering, giving us opportunity to reflect on the state of the art of the field and some recent developments.

Much has been learned during this time. Current tissue-engineering approaches are increasingly based on biologically inspired environments designed to inform and guide cell differentiation and functional assembly toward re-establishing the organ function lost to injury or disease. Although the 3 key components: cells (the actual “tissue engineers”), biomaterial scaffolds (structural and logistic templates for tissue formation), and the environmental signals (in vitro in bioreactors or in vivo in the body) are still a basis of all tissue-engineering systems, each of them has changed quite substantially. Young animal cells have been replaced by patient-specific stem/progenitor cells that are being derived from a number of tissues, differentiated into desired lineages, and gene edited to study mechanisms of disease. Inert biomaterials, once considered ideal for cell culture and transplantation, have been replaced with biomaterials interacting with the cells via biochemical, mechanical, and electrical signals. Bioreactors, used for the culture of human cells on advanced scaffolds, are now able to capture many aspects of the native context of development or disease.

For over 2 decades, the main focus of cardiac tissue engineering, to develop a standard of care based on cell therapy of the heart, is still without clinical application, largely due to the lack of understanding of the underlying mechanisms of action. A most interesting result of clinical studies that were mostly done using mesenchymal stem cells (MSC) to treat ischemic injury, is the discrepancy between the scarcity of cell engraftment and functional benefits, a finding strongly suggesting paracrine effects. In particular, the allogeneic and autologous MSCs had similar functional outcomes despite more rapid rejection of allogeneic MSCs.<sup>4</sup>

These findings bring up a logical question: is cell engraftment necessary for heart repair, and if so, for how long? The collective experience with better outcomes of cell injection into the heart compared with intravenous infusion suggests that the paracrine action requires some residence time for the cells in the zone of injury. It is possible that (1) improving cell retention (eg, using a hydrogel to inject cells into the heart) and (2) providing transient immunosuppression to allogeneic cells (derived from donors with high expression of CD34 and used off the shelf) may be an interesting option to explore.

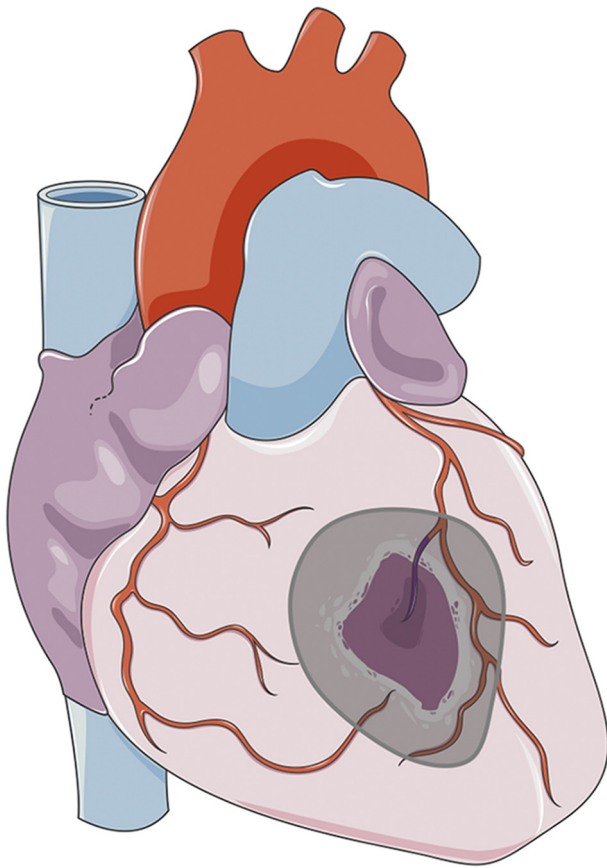
In parallel, cardiac progenitor cells are being explored in primate studies<sup>5</sup> and the first clinical trials of heart repair. Again, the question is if these cells need to engraft and

form new muscle, or just provide paracrine signals that would initiate repair. Clearly, if cells are not used, or not required to engraft, this would also help avoid the arrhythmias encountered in animal studies.

Other approaches are focused on cell-free therapies: if cells are acting through the factors they secrete, can we just use factors? There is growing evidence that paracrine factors are clustered in cell-secreted vesicles that are rich in  $\mu$ RNAs and other biological cargo. Notably, a study comparing the effects of cardiac cells and secreted vesicles on heart repair could not find much difference,<sup>6</sup> supporting the “paracrine hypothesis.” This opens the possibility of introducing an entirely new paradigm: cell-free heart repair using cocktails of cell-secreted factors that can be mass-produced in cell culture, isolated from culture medium, and delivered in a hydrogel patch. It would be of great interest to evaluate in more detail the paracrine effects of cardiac and non-cardiac therapeutic cells and learn more about the key factors that can induce heart repair.

A related question is if biomaterials alone could be functionalized to provide the necessary regulatory cues. A recent study showed that epicardially derived follistatin can rebuild heart muscle.<sup>7</sup> This simple and elegant approach utilized a collagen patch loaded with a single cardiokine, which has multiple developmental and cardiogenic roles and is depleted from the heart after myocardial infarction. Whereas previous studies showed the cardioprotective and vasculogenic effects of follistatin, this study resulted in an unexpected finding that follistatin secreted from the hydrogel patch induced proliferation of resident cardiomyocytes. One can envision a new cell-free approach to sustained delivery of regulatory factors, controlled over time by the degradation and release kinetics of the collagen patch. Clearly, patch delivery could be extended to clusters of cardioprotective, cardiogenic, and vasculogenic factors; to the delivery of cell-secreted vesicles to provide more comprehensive paracrine effects; and to studies of the paracrine effects of various cell types and the mechanisms of their paracrine action.

As many times in the past, the cardiac field is being informed by advances in other fields of tissue engineering. A recent study<sup>1</sup> reported development of an elastic “second skin” that can be applied topically to reduce skin herniation, re-establish barrier function, or deliver drugs. One can envision that a similar “epicardial skin” could be used for sustained delivery of biological cargo (such as the secretome from immature cardiomyocytes) (Figure 1). The most attractive features are the adherence of such “second skin,” the possibility of using both encapsulation and immobilization chemistry, and the possibility of implementing minimally invasive treatment modalities. These 2 articles,<sup>1,7</sup> from 2 very different areas of tissue engineering, show us that tissue regeneration could indeed



**FIGURE 1.** A patch for heart repair: cell therapy, or induction of endogenous repair?

be achieved using simple methods that have evolved from lessons learned in the past.

In summary, regeneration of the myocardium is certainly an area of great potential for therapeutic applications. Interestingly, the initial focus in the field is moving from revascularization into revascularization, and from myocardial infarction into nonischemic cardiac diseases. However, cell and tissue therapies also carry risks—most notably arrhythmia, a complication observed in primate studies of cardiac repair using human stem cells. To avoid arrhythmia, the implanted tissue (or cells) would need to be matured to cease beating spontaneously, and instead start to display synchronized contractions in response to electrical signals. Development of protocols for maturation and

synchronization of cardiac cells is one of the key challenges in the application of tissue-engineering methodologies to heart repair. Another challenge of cell/tissue therapies is the incorporation of a vascularized network that can be anastomosed to the circulatory system of the host to provide the immediate blood supply needed for cell survival. These increased risks and the higher cost of cell-based treatment modalities—during all phases of their development, preclinical and clinical studies, and implementation in patients—suggest that the clinical experience will continue to evolve using cell-free approaches whenever possible. In principle, one can envision the use of just a biomaterial incorporating biologic factors that activate endogenous cells (cardiac and vascular) by triggering specific signaling pathways. Finally, the treatment modalities need to be simple enough to be adopted and to support efficient use of therapeutic agents: cells, factors, or biomaterials, alone or in combinations. One of the future challenges will be the combination of tissue engineering and endocardial delivery.

#### Conflict of Interest Statement

Author has nothing to disclose with regard to commercial support.

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**Key Words:** tissue engineering, heart, stem cells, biomaterials, endogenous repair