CHAPTER II.6.11
Cardiac Muscle Tissue Engineering

QUESTIONS
1. Describe the tissue engineering paradigm as it relates to generating the myocardium. Consider the role of each component.

2. What is the advantage of regenerating the heart using tissue replacements rather than direct cell injection into the heart?

3. Describe the ideal properties of a scaffold for cardiac muscle engineering. Propose how you would develop such a scaffold. Include materials and fabrication methods, and how you would anticipate culturing cells on the scaffold.

4. What challenges will researchers face when implanting cardiac grafts in patients? Focus on both general and cardiac-specific issues.

5. Describe the rationale behind using perfusion systems for cardiac tissue engineering, and the importance of the properties of scaffolds used in these systems.

6. Propose a method that helps cardiac grafts connect to host vasculature once in vivo. Consider biophysical stimuli, cell sources, scaffold design or pre-implantation culture to facilitate the integration of the graft with the native muscle.

ANSWERS
1. Tissue engineering using the combination of cells, scaffold, and a bioreactor to impart biophysical stimuli to cells. The cells are the building blocks of the tissue and must be able to electromechanically couple to one another, and respond as native cells do to changes in their environment. Scaffolds must be conductive to cell attachment, promote alignment of the cells, permit mass transport through the cells, and be both stiff and elastic to encourage physiological cell contraction. Bioreactors must provide environmental control (pH, O₂, metabolites, and nutrients) and mimic cardiac conditions in a spatiotemporal manner – integrating electrical or mechanical stimulation, fluid flow, and presence of appropriate biochemical factors to sustain the cells.

2. The principle advantage of using a cell–matrix combination over injecting a cell suspension is to protect and maximize cell function in vivo. When individual cells are injected into the heart, they are unshielded from the ischemic environment and must form cell–matrix and cell–cell connections to electromechanically couple with the host myocardium. In contrast, implanting a functional cardiac tissue over the injury site eliminates the need for individual cells to survive and couple in the injury site, but relies on integration of the whole functioning muscle with the host myocardium. In this case, cell attrition due to anoikis and the ischemic environment are no longer significant concerns.

3. All scaffolds should promote cell attachment, degrade at a comparable rate to cell ECM remodeling, and have mechanical properties similar to that of the native tissue. For cardiac tissue engineering, scaffolds that induce cell alignment and cell–cell connections, and facilitate oxygen and nutrient transport, are particularly important. The mechanical properties of the scaffold should promote cell pulling – stiff enough to encourage cells to pull on it, and elastic enough to respond to deform under cell tension. You may include properties that encourage signal propagation or gas diffusion while shielding cells from shear stress, as well as hybrid biomaterials that take advantage of one or more physical properties of different materials.

4. As with any biological graft, researchers must select components that do not elicit immune responses from the recipient. This must be a consideration for the cells, scaffold, and any components included in the culture system (i.e., animal-derived products in the culture media). Scaffolds must be considered for their ability to elicit a response, as well as the potential side-effects of their degradation products once they begin to be remodeled in vivo. Specific to cardiac tissue is the need for the highly metabolic tissue graft to connect to a host vascular supply to sustain the graft. It must also electromechanically couple with the host tissue to ensure complete integration and avoid the initiation of arrhythmias. This is a significant challenge, as the infarct region onto which grafts would be implanted is typically void of functional cardiomyocytes.
5. Perfusion of culture medium through scaffolds can improve the distribution of cells throughout the scaffold during cell seeding, and further enhance oxygen and nutrient transport to cells within the scaffold throughout in vitro culture. Scaffolds must be able to withstand the shear rates due to the perfused culture without disintegration, and facilitate fluid movement through the scaffold either via interconnected pores or channels.

6. Answers may vary. Some suggestions include engineering vascularized cardiac grafts with endothelial cells that build an intact vasculature that can be extended to the infarct once implanted. Chemottractants may be included in the graft or scaffold to attract host cells to rapidly vascularize the tissue. An engineered vascular conduit embedded in the engineered muscle may be physically connected to a host conduit to allow immediate vascular integration.