Cells for the Treatment, Prevention, and Cure of Cardiovascular Disease

Cell therapy is a 21st-century approach to the intractable problem of heart failure. Yet 9 years after the 1st patient was treated, stem-cell–based repair of myocardium is not a panacea. Instead, it is a partial solution—usually early after ischemic injury—to prevent progression to heart failure.1-7

Our group has chosen to focus on cell therapy for the prevention, treatment, and (ultimately) cure of disease. Prevention, in our hands, means early delivery of cells to reverse early injury—often prior to symptomatic disease and often in the vasculature. In the case of vascular injury, we have been able to intervene with bone marrow mononuclear cells to either prevent8 or reverse9 atherosclerosis in apolipoprotein E (ApoE) knock-out mice. Early preliminary clinical data suggest that in patients with increasing degrees of endothelial dysfunction, there are decreases in the numbers of stem or progenitor cells circulating in the blood. Our goal is to define these cell populations and to provide the missing cells as we move our preclinical data into clinical use.

For the treatment of disease, often the goal is delivery of autologous and possibly even allogeneic cells to prevent the disease progression. In the case of cardiovascular disease, such delivery is often made after an ischemic insult, in order to prevent cardiac remodeling that leads to heart failure.

Finally, cells hold the potential for cure, if in fact we can use them to affect positively the almost 22 million individuals who are living with heart failure. However, for those with end-stage disease, cell therapy alone is probably not sufficient to completely reverse or remodel scarred, failing myocardium.

An allograft is the only definitive treatment for end-stage heart failure; yet each year, thousands of individuals in need of a transplant die due to a lack of viable donor organs. In addition, patients who receive a transplant require harsh anti-rejection drugs that often lead to hypertension, renal disease, and other side effects. To begin to compensate for this scarcity of donor tissues and to overcome the need for harsh anti-rejection drugs, we propose to build new bioartificial transplantable organs.10

To express this in the simplest way, generating an organ requires 3 things: cells, a scaffold, and blood vessels to feed the cells. To build a heart requires cells that can give rise to both myocardial muscle and to the vasculature that perfuses the resulting tissue; and it requires an underlying matrix—a 3-dimensional scaffold reminiscent of heart on which to place the cells to generate a whole organ. Of course, the new organ also has to be physiologically capable of the function associated with a performing heart.

Cells with the capability to make myocardium and vessels are now available. Patient-derived adult stem cells, umbilical-cord blood cells, and induced pluripotent stem cells or human embryonic stem cells may all in fact be future solutions. At present, we have identified stem cells from adult myocardium11 that can give rise to both cardiac muscle and vascular components. Embryonic stem cells, likewise, can give rise to the multiple cell types required for engineering new myocardium; more recently, inducible pluripotent stem cells derived from fibroblasts have shown the same capability.

Scaffolds have been a more problematic issue. Generating a 3-dimensional perfusable scaffold that comprises the native cardiac-matrix proteins and manifests cardiac geometry and architecture in its entirety, including valves and vessels, has not to date been accomplished. Neither has the construction of such a scaffold from individual artificial matrix components been imagined feasible. However, we have developed a method for perfusion “decellularization” (removing cells) of cadaveric organs that
gives rise to such a scaffold, as shown in Figure 1. The resulting scaffold is made of extracellular matrix and has the following elements:

- a geometrically and spatially appropriate organ structure;
- vascular conduits for tissue perfusion and maintenance;
- an adjustable microenvironment that can be manipulated with genes or molecules to alter cell physiology and function; and
- a capacity for enabling tissue and organ maturation in vitro.

When combined with cells—either the patient’s own stem cells or allogeneic cells from someone else—this scaffold provides a potent structure for re-creation of a new organ, as we showed recently. The next few years will be dedicated to understanding the physiology, the cell biology, and the pharmacology—as well as the bioengineering—that are required to generate human-sized complete organs and to mature them in ways that provide transplantable tissues for the future. By using a patient’s own cells, we should be able to generate autologous organs that require minimal anti-rejection drugs.

Our goal is to generate hearts, lungs, livers, kidneys, and pancreata—whatever is needed for patients who have chronic disease. Decellularized scaffolds, stem cells, and the science of the future provide an opportunity to treat chronic disease in a manner never before possible.

References

5. Brehm M, Darrelmann E, Strauer BE. Stem cell therapy in acute myocardial infarction [in German]. Internist (Berl) 2008;49(9):1068-78.