Chemistry & Biology, Vol. 12, 609–610, June, 2005, ©2005 Elsevier Ltd All rights reserved. DOI 10.1016/j.chembiol.2005.06.003

Innovations

Can Scarred Hearts Be Repaired? MG Biotherapeutics Is Testing Cell Therapy for Heart Repair

In a myocardial infarction, more commonly known as a heart attack, heart cells die from a lack of oxygen. Just as in a simple cut, scar tissue forms. This scar tissue does not contract and does not have the strength of the heart muscle tissue. As a result, the heart enlarges and loses its ability to pump blood efficiently. This condition, known as congestive heart failure, is progressively fatal. Currently, only the symptoms of congestive heart failure can be treated by drugs or surgery. There is no cure because heart tissue does not spontaneously regenerate and no manner of inducing it to do so exists. According to the American Heart Association's 2004 figures, over five million Americans experienced congestive heart failure that year.

In a new treatment undergoing a large clinical trial, muscle cells biopsied from patients' own thigh muscles are implanted in the damaged tissue in an attempt to at least partially mend damaged hearts. This innovation comes from MG Biotherapeutics, a 50-person virtual joint venture inaugurated in 2004 by Boston-based Genzyme and Minneapolis medical device company Medtronic.

Genzyme brings extensive experience in cell therapy to the partnership, and Medtronic has wide expertise in conventional cardiology treatments. Genzyme already has two autologous cell-therapy products on the market: Epicel (cultured epidermal autografts) skin replacement, which is grown from severely burned patients' own skin cells to eliminate tissue rejection, and Carticel (autologous cultured chondrocytes), which repairs damaged knee cartilage. Medtronic's cardiology portfolio includes devices such as catheters, stents, heart valves, and pacemakers. However, Medtronic has been following the potential of skeletal myoblast cells as a method of improving heart function since the mid-eighties. "We have had a program for years on electronically stimulating skeletal muscle wrapped around the heart," says Dr. Maura Donovan, Clinical Director of BioSciences R&D and Bakken Fellow at Medtronic.

MG Biotherapeutics is faced with competition from research institutions and commercial rivals such as Vascular Genetics in North Carolina, BioHeart in Florida, and Maryland-based GenVec, which has teamed up with Johnson & Johnson for catheter expertise.

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In a phase II clinical trial dubbed MAGIC (Myoblast Autologous Graft in Ischemic Cardiomyopathy), skeletal myoblast (muscle) cells will be biopsied from patients' legs. After being expanded in the lab for 21 days, the cells will be directly injected into and around the scar tissue during bypass surgery. A control group of patients will be injected with a placebo of transfer media. A previous ten-patient trial conducted by Dr. Phillippe Menasche of the Department of Cardiovascular Surgery at the Hospital European George Pompidou in Paris indicated that grafting the muscle cells onto the damaged tissue can improve heart function. Menasche measured metabolic activity by PET scans as well as ultrasound to check behavior of the tissue.

So far, 78 patients have been recruited for the MAGIC trial, which is projected to have 300 participants. "All the patients have suffered relatively large infarcts [scarring]. The scar has to be well healed," says Dr. Ralph Kelly, VP of Clinical Affairs at Genzyme. The trial is being conducted in European countries, including France, Belgium, the UK, and Germany, under the supervision of Dr. Menasche.

After a heart attack, the remaining heart tissue takes up the load. As a result, the "overworked" heart degenerates more quickly than normal. Overall heart function declines exponentially. The aim of this treatment is to arrest this heart-remodeling process and reduce the body's stress response to the damage. "There are also very high levels of adrenaline in the blood released by the brain and the sympathetic nervous system," said Kelly. "It is analogous to severe dehydration or the evolutionary fight or flight response. Doctors currently give drugs after a heart attack to 'dial down the heart function' in order to slow the degradation of the remaining heart tissue." Part of the hypothesis behind cell therapy is that implanted skeletal myoblasts, which ordinarily heal muscle as it is damaged, may spur release of cytokines, proteins that signal an inflammatory process to activate wound healing, blood-cell growth, and, hopefully, angiogenesis (proliferation of blood vessels).

The skeletal muscle cells do not actually differentiate into heart muscle or convey electrical impulses the way heart cells do, but they may help bolster a flabby heart structur-

ally. Although there is no observable direct electrical connection between the implanted cells and the rest of the heart, it does not mean that the cell does not contract in synchronicity with the heart. "It may be that the stretch of the muscles is enough," says Kelly.

MG Biotherapeutics is currently focusing on skeletal muscle cells because "they have been studied extensively preclinically and have been shown to be resistant to conditions of hypoxic stress," says Dr. Maura Donovan who adds that scar tissue is poorly perfused with oxygen-rich blood.

Trials conducted on animals confirm that about 10% of the injected cells survive. "Numerous laboratory studies have been done on animals, but it is extremely hard to conduct controlled studies in humans," says Dr. Gordana Vunjak-Novakovic, Principal Research Scientist at the Massachusetts Institute of Technology. A key issue is cell localization, which is how many cells go to the right place. How many stay there instead of migrating out or dying? If the dead muscle [scar tissue of the heart] becomes fibrous and stiff, it is a substrate for cells to adhere to but is not optimal."

Donovan explains that the mechanism of action by which transplanted cells may improve the function of scarred heart tissue is unclear; in the end, it may be a combination of many factors. "One theory is that transplanting cells into the myocardium may promote an angiogenic response and improve tissue perfusion," she says. "An alternative theory is that transplanted cells may secrete factors that recruit native stem cells into the area to repair tissue." The transplanted cells may prevent deleterious tissue remodeling. Interestingly, in transmyocardial revascularization procedures (TMR and PMR) clinicians improve blood perfusion and heart function by literally poking holes in the heart. In current clinical cell-therapy trials, surgeons implant cells into the heart via multiple injections, which may generate a positive response by increasing the blood flow to the affected area just like mechanically perforating scar tissue but have little to do with the cells themselves.

"Current clinical studies are focused on determining the safety of transplanting therapeutic cells into infarcted myocardium," Donovan says. "Complementary preclinical studies are needed to answer questions related to mechanism of action and to determine the fate of the transplanted cells." In preclinical controlled experiments, MG Biotherapeutics will look at what is the optimal way of delivering the cells. "Two things appear to be happening when you inject cells into infarcted tissue," Donovan says. "One is you get physical loss of cells. The second is not all the cells you inject survive in that location."

More than one research group have raised questions about the impact of the vast amount of cellular debris left over from the 90% of billions of cells that die after being injected into the heart. The debris could generate a helpful inflammatory response by stimulating angiogenesis or a harmful one by damaging healthy tissue. "You are injecting into the infarct. The inflammation response would be different if you are injecting into normal tissue," Donovan explains.

Another issue is that skeletal muscle cells that do not integrate with existing heart tissue may not transmit cardiac electrical impulses or, even worse, may respond to the electrical impulses of the heart in a completely different way. This could cause arrhythmias, or irregular heartbeats. This was not the case with animals, but there is concern that this could happen in humans. "There was early clinical evidence that there might be more arrhythmic events in these patients," Donovan says. "But the problem is that the patient population we are treating in these clinical studies is already at a high risk of ventricular arrhythmias. It is really unclear from current data whether the myoblast implantation is increasing that risk. Subsequent clinical studies will be needed to answer this question."

MG Biotherapeutics is also developing a portfolio of devices to deliver cells to the heart in a less invasive way, says Genzyme's Kelly, and the company is already working on the next generation therapies, including genetically modified cells, donor cells, and advanced biomaterials that will help cells stick better and live longer.

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