Cardiovascular disease is the No. 1 killer in the United States, with one death every 39 seconds. Ischemic heart disease is the predominant contributor to cardiovascular morbidity and mortality. In a myocardial infarction (MI), coronary occlusion leads to death of part of the heart muscle. While conventional therapies aim to limit the initial injury and to block maladaptive pathways, regenerative therapy for MI seeks, instead, to regrow healthy heart muscle. Over the last three years, in collaboration with colleagues at Johns Hopkins, the Cedars-Sinai Heart Institute has spearheaded the CADUCEUS trial, designed to test the idea that cardiosphere-derived cells (CDCs) are capable of inducing regeneration of the infarced human heart. The very notion is traditionally considered heretical: Once the damage is done, no therapy has ever been shown to be capable of healing scar and regrowing healthy heart tissue. Such was our ambitious goal.

In the CADUCEUS trial, recently reported in The Lancet, human subjects received either infusion of autologous CDCs or conventional treatment by prospective randomized assignment. Contrast-enhanced cardiac MRI was used to distinguish living heart muscle from scar, an approach that has been extensively validated.

Continued on page 4 (see “CDCs”)

Cardiosphere-Derived Cells and Therapeutic Regeneration of the Heart

Eduardo Marbán, MD, PhD

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Figure 1: CDCs regenerate the infarcted heart. Intracoronary infusion of CDCs in humans with MI leads to significant reduction of scar mass and increase of viable myocardium compared to controls.¹
Induced Pluripotent Stem Cells Open New Possibilities in Treatment, Drug Development

Clive Svendsen, PhD

One of the most exciting recent scientific findings is that adult cells from the human body can be reprogrammed back in time to a pluripotent state that is almost identical to embryonic stem cells. These blank-slate induced pluripotent stem cells (iPSCs) can then be expanded indefinitely while retaining the potential to be differentiated back into any tissue types of the human body. This remarkable discovery opens up possibilities for personalized medicine, where the cells may be used to both model and treat human diseases.

One example of how iPSCs may be used in the medicine of the future is related to the heart. When a doctor sees a patient with heart disease, the first question is: Why did it happen? Was it genetic, environmental, stress? By the time the patient reached the hospital, the damage had probably already been done; the doctor is looking at the accident that has already happened. What would be remarkably useful is the ability to replay the disease in a petri dish to get a better understanding of what led to the accident.

Making iPSC lines from a skin biopsy is now possible, and these skin cells can be reprogrammed back in time to a pluripotent state and expanded to large numbers. They can then be coaxed into cardiac tissue, and scientists can begin to discover why, in this patient, their heart tissue did not function properly. This so-called “disease in a dish” is opening up whole new ways to learn about heart disease. When further combined with studies probing the genetic makeup of the patient, it provides a rich source of information to begin understanding why diseases of the heart occur and potential new treatments.

Another example relates to a shocking finding in the world of drug discovery. Remarkably, only a handful of new drugs (for any human condition) make it onto the market each year, generally less than 15. One of the reasons is that a small number of patients suffer from serious side effects, very often involving changes in the rhythm of the heart. Prospectively identifying these patients would allow the drug to be used for all other patients, dramatically increasing the number of drugs that could be used to treat heart conditions. Amazingly, human iPSCs can be pushed into beating cardiomyocytes in the petri dish. These clusters of beating cells can survive for weeks, and some research groups have already shown that drugs that cause heartbeat abnormalities in patients also cause beating changes in these cells in the petri dish. If doctors could test a drug on the patient’s own beating heart cells before prescribing it, the dangers would be reduced, while the number of patients who could benefit from the drug would be increased—a revolution in treatment.

Of course, these same cells have great potential for heart disease therapy. While adult heart stem cells are being investigated to treat heart attack patients at Cedars-Sinai, there is a great interest in exploring how cardiomyocytes from iPSCs fare following transplantation. By starting from an earlier stage of development (the iPSC), it is possible to generate very primitive heart cells that may have a greater capacity to survive transplantation into the damaged heart and produce new beating tissues. Clearly there are many challenges ahead for this approach. The cells need to beat in rhythm with the patient’s own heart cells, otherwise they may have negative effects. They must also stop dividing, and not migrate too far into other tissues. However, the idea of making new heart tissue from iPSCs is a very powerful concept and the focus of many studies at Cedars-Sinai and around the world.

The Regenerative Medicine Institute and the Cedars-Sinai Heart Institute are working together to learn more about iPSC-derived cardiac tissues and how they may help us understand and treat heart disease in the future.

Human iPSC cells in a dish form beating heart cells...which happened to grow in the shape of a heart.
Photo by Howon Kim, PhD, Cedars-Sinai Regenerative Medicine Institute.

Dr. Svendsen is a Professor of Biomedical Sciences and Director of the Cedars-Sinai Regenerative Medicine Institute.
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Biological Pacemakers: Are We Closer to the Clinic?
Eugenio Cingolani, MD

Electronic pacemakers have been used for the treatment of symptomatic bradyarrhythmias for more than 50 years. Despite continuous refinement, devices are still prone to hardware malfunction of the generator or implanted leads, device-related infections and infrequent procedure-related complications. Device-related infections have been rising in the past decade, not only due to the increase in device implantations but also due to a higher incidence of bacterial infections in the United States and worldwide.

The challenge: device-related infections in pacemaker-dependent patients

Patients with device-related infections often require complete removal of all hardware until they become infection-free on systemic antibiotics. For those patients who are pacemaker-dependent, a temporary transvenous pacing device needs to be utilized during antibiotic treatment, which typically requires about two weeks to clear the infection. The temporary device requires hospitalization and continuous monitoring, and can potentially undermine the ability of systemic antibiotics to clear the infection due to the presence of an indwelling catheter. A hardware-free temporary pacing alternative would be desirable in these patients to support circulation in the interval between removal of the infected hardware and implantation of a new permanent electronic pacemaker.

Biological pacemakers, or “biopacers,” could provide temporary pacing, eliminating the need for indwelling hardware during antibiotic therapy and improving the efficacy of such therapy by removing any possible reservoir of infection associated with temporary transvenous leads. Although short-term biological pacemakers have been successfully created in large animals by both gene and cell therapy, the delivery methods have been extremely invasive open-chest or left-sided approaches. Translating this approach to humans requires a minimally invasive delivery technique accessible to practicing cardiac electrophysiologists using an off-the-shelf biological pacemaker capable of maintaining adequate heart rates.

Percutaneous delivery for potential biological pacemaker therapies

Different gene- and cell-based biological pacemaker strategies are being studied at the Cedars-Sinai Heart Institute with this very objective in mind. For the first time, we have successfully delivered a biological pacemaker in a preclinical model of complete heart block using a minimally invasive, right-sided technique. By advancing a magnetically-guided catheter through the right femoral vein, a combination of two pacemaker-related genes were delivered to the atrioventricular junctional region. The combined overexpression of HCN2 channels responsible for the pacemaker current (If) and suppression of the inward rectifier current (Kir2.1 genes) resulted in junctional pacemaker activity for up to two weeks (Figs. 1 and 2). A consequent decrease in backup electronic pacemaker utilization rates was seen, and no adverse effects were observed during the short follow-up period. Interestingly, three-dimensional electro-anatomical mapping of the newly generated impulse revealed a septal activation pattern and conduction velocities identical to those seen during sinus rhythm (Fig. 3). In contrast to the changes seen in right ventricular pacing with electronic devices, this ventricular activation pattern (through the normal conduction system) is unlikely to cause dyssynchrony or detrimental changes in the systolic function.

The delivery system, using a catheter-based technique similar to the one we routinely use today in our clinical cases, would allow for these novel technologies to be rapidly translated to human subjects.

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Pacemaker: continued from page 3

Additional biological pacemaker strategies are being actively studied at the Cedars-Sinai Heart Institute. The potential of pluripotent stem cells (which have been previously shown to exhibit biological pacemaker activity) are being tested using our minimally invasive delivery technique and preclinical platform. Moreover, by injecting specific factors (T-Box transcription factors), we are now able to focially reprogram the normal cardiac cells and induce differentiation into sinus node-type cells with spontaneous pacemaker activity. The ultimate goal of this novel approach is to regenerate an individual’s sinus node by reprogramming his or her own cardiac cells.

Development of a clinically applicable temporary biological pacemaker has the potential to significantly impact the treatment paradigm for device-related infections. We would expect to see improvement in device-related infection clearance due to absence of an indwelling transvenous pacing catheter, along with improved stability and safety relative to the current standard (external generator connected to a temporary pacemaker wire via a central veinous line). Development of a biological pacemaker for the focused bridge-to-device application, if successful, will open the way for more ambitious applications, such as definitive replacement of electronic pacemakers by biological surrogates. Our minimally invasive delivery technique will allow comparison of the different strategies, and will hopefully yield a clinical therapeutic candidate for study in Phase I clinical trials.

CDCs: continued from page 1

Patients randomized to receive CDCs underwent endomyocardial biopsy for tissue harvesting, and returned for intracoronary infusion of autologous CDCs 1.5 to 3 months post-MI.

Control subjects experienced no change in scar mass or viable heart mass over the 12 months of follow-up, but MRI revealed sizable reductions of scar mass (~13 grams) and increases in viable heart mass (~22 grams) in CDC-treated subjects (Fig. 1). Scar size (defined as scar mass/total left ventricular mass) was significantly smaller in CDC-treated human subjects compared to controls (Fig 2). The new heart muscle appeared to be functional, in that regional function was normalized in the area of injury in the CDC-treated patients (but not in controls). CADUCEUS is the first controlled clinical trial to demonstrate regrowth of living heart tissue as a result of cell therapy.

To date, cell therapy with CDCs is the only intervention that has been shown to be clinically effective in regenerating the infarcted human heart. CDC therapy produced not only a decrease in scar tissue but also a sizable increase in viable myocardial mass. Approximately half of the lost tissue was restored. These unprecedented findings challenge the traditional view that scar, once established, is irreversible and that healthy heart muscle, once lost, cannot regrow.

The ability to achieve therapeutic regeneration in convalescent post-MI patients opens up heady new prospects. Among the avenues we will be pursuing in soon-to-be-launched clinical trials are the following:

- The use of “universal donor” allogeneic CDCs, avoiding the need for biopsy and the attendant delays to therapy.
- Extension of the CADUCEUS trial to Phase II in the ALLSTAR trial.
- Testing whether CDCs work equally well in patients with longstanding ischemic cardiomyopathy.
- Consideration of alternative delivery methods, such as magnetically guided catheters that can inject directly into the heart muscle via the endocardium.
- Adjunctive therapy in patients with clinically indicated surgical procedures and left ventricular dysfunction.

Disclosure: The process to grow cardiac-derived stem cells was developed by Dr. Marbán when he was on the faculty of Johns Hopkins University. Johns Hopkins has filed for a patent on that intellectual property and has licensed it to Capricor, a company in which Cedars-Sinai and Dr. Marbán have a financial interest. No funds from that company were used to support the CADUCEUS clinical study at Cedars-Sinai; all funding for CADUCEUS was derived from the National Institutes of Health and Cedars-Sinai. Capricor is providing funds for the ALLSTAR clinical study at Cedars-Sinai.


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