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A cell therapy to heal a broken heart

Researchers harvest stem cells from patients who have recently had a heart attack and use them to trigger regeneration of their cardiac muscle.

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For many people, surviving a heart attack is just the beginning. Within minutes after one or more areas of the heart stop receiving oxygen, cardiac muscle cells begin to die. Given the limited regeneration potential of the heart, its response to this destruction is to replace the lost cells with scar tissue.

“This scar is just there to save the patient,” said Matthieu de Kalbermatten, chief executive officer of the biotechnological company CellProthera. The heart won’t pump blood as efficiently as before, and if the damage is severe, it can result in chronic heart failure. “The [organ] becomes weaker and weaker, [leading to] a high mortality after three to five years, plus bad quality of life,” he explained.

Matthieu de Kalbermatten, CEO of CellProthera, said that their product, ProtheraCytes®, mimics one of the natural responses of the body after heart attack by mobilizing progenitor blood CD34+ stem cells towards the cardiac tissue.

CREDIT: STUDIO CHLOROPHYLLE

Drugs and therapies prescribed after a heart attack may improve patient survival rates, but they do not repair the injured cardiac tissue, said de Kalbermatten. His team at CellProthera aims to prevent this long-term damage by injecting patients with their own, lab-expanded, stem cells.

The promise of this cell therapy, called ProtheraCytes®, is to intervene early — within a month after the heart attack — and inject these cells in the hope that they will help regenerate the tissue, reducing the scar area and regaining partial heart function.

Stem cells directly into the heart

The researchers at CellProthera focus their efforts on the regenerative potential of CD34+ stem cells, which give rise to all types of blood cells in the body as well as the endothelial cells that line the insides of blood vessels. Since the early 2000s, studies have shown that CD34+ cells mobilize from the bone marrow into peripheral blood circulation shortly after a heart attack (1,2). These observations suggest that the human body naturally calls for these cells to come and help after such an event, but de Kalbermatten hypothesized that the migration might not be sufficient to heal after a severe heart attack. With Protheracytes®, he said, “We are trying to

mimic [this] natural phenomenon, but just making it bigger and stronger."

To achieve this goal, the team first obtains CD34+ cells from the patient a few weeks to a month after the heart attack. After administering a growth factor to the patient to stimulate the bone marrow's production of these cells, doctors take a blood draw from the patient and isolate the CD34+ cells. The team use their own cell expansion protocol and technology for in vitro proliferation to increase the number of these cells. Finally, nine days after the blood draw, there is a CD34+ suspension ready to be injected back into the patient, de Kalbermatten said. The cells are maintained fresh during that period. He noted, "We don't freeze them." Keeping the cells fresh allows for higher cell viability and potency, he explained.

A doctor then injects the stem cell suspension via a catheter directly into the left ventricle muscle wall of the patient. CellProthera partnered with the biotech company BioCardia, which designed a specialized catheter known as the Helix™ Transendocardial Biotherapeutic Delivery System. The goal was to deliver therapeutic agents — cells, genes, or proteins — directly into the heart muscle to offer better results than injecting them into the coronary arteries, while also avoiding cardiac surgery, explained Peter Altman, chief executive officer of BioCardia.

"Injecting them into the myocardium as opposed to just sending them down the capillaries [might be] better," concurred Robb MacLellan, a practicing cardiologist and physician scientist studying regenerative therapies at the University of Washington who is not associated with CellProthera or BioCardia. "With gene therapy, doing that leads to better delivery amounts."

The secretome of the patient's own cells is key

Using a patient's own cells for transplant comes with advantages and disadvantages. The alternative option, an allogeneic transplant, might be more efficient since the production of cells does not rely on the patient, and cell quantities may be less limited. Yet, using foreign cells poses rejection risks.

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Autologous transplantation, on the other hand, is very safe, de Kalbermatten said. Since cells are from the patient, rejection is unlikely, and there is no need for immunosuppressive drugs. However, using the patient's own cells has other requirements, such as a well-designed logistic bench-to-bedside process. "We have developed a technology that is totally automated," he said. "You take a kit; you take the blood; you put it in the machine; you get a product." That standardization also reduces costs, he added.

The benefits from the therapy do not rely on the stem cells differentiating into cardiomyocytes, but the secretion of factors makes the difference. The release of these factors may modulate endogenous repair processes (3). "It's the beauty about the cell as a drug, because the cell is a small factory that is able to react to the environment," de Kalbermatten said.

"This idea that cells can impact scar formation and scar resolution has been around for decades ... in cardiology," said MacLellan. Yet, he noted that while researchers have tried to use cell therapies to modulate the healing process post injury in the heart and other organs, "none of them have translated into standard of care."

A high bar for clinical translation

Translating preclinical studies of stem cell therapies to successful clinical trials to treat acute myocardial infarction has proved challenging. One reason for this is the lack of rigor and standardized protocols in many preclinical studies (4).

The various drugs — beta blockers, angiotensin-converting enzyme (ACE) inhibitors, aspirin — administered to patients after a heart attack may also account for this difference, said MacLellan. "If you get on that cocktail of medicines, your prognosis is then very good," he said. "That has really frustrated these cell therapy trials," he added. "[Most] preclinical trials never use the same medication background that we use in patients." Researchers need to prove that cell therapies add to these existing therapies, and "that's a high bar," he added.

Differences in the delivery methods between animal and human cell therapy protocols may also explain the inconsistencies between preclinical and clinical outcomes for acute myocardial infarction. Researchers often deliver the cells surgically into the heart muscle in small animal models, while for humans, they mostly use catheters that go into the coronary arteries. Using the BioCardia Helix™ catheter may help bring cell therapies in humans closer to achieving the positive results reported in preclinical studies, according to Altman.

Once the stem cell suspension is ready, scientists at CellProthera ship it from the manufacturing site to the clinical site where doctors prepare the patient for the cell injection.

CREDIT: CELLPROTHERA

In addition to the delivery system, MacLellan acknowledged that ProtheraCytes® has two more primary differences that stand out from what researchers have previously done, namely, the process for obtaining and expanding the CD34+ cells and the timing of the infusion.

CellProthera is currently conducting a clinical trial to reveal whether these variations in their protocol result in more successful clinical translation than previous attempts. Already in the 2000s, the founder of CellProthera, Philippe Henon, led a pilot study on seven patients who had suffered a severe heart attack. That first trial was nonrandomized, and the surgeons injected the cells directly into the cardiac tissue by open heart surgery, explained de Kalbermatten. The outcome for six of the patients was promising. “That’s why we decided to start this adventure.”

Now, the team’s Phase 1/2b randomized clinical trial evaluates the safety and efficacy of their therapy in 33 patients. For assessing the efficacy, they use primarily magnetic resonance imaging (MRI). “This is the most precise imaging system that you can have these days,” said de Kalbermatten. They compare, for instance, visible damage after the heart attack versus six months after injection of ProtheraCytes®. The aim is to determine whether the therapy reduces the area in the heart that became nonviable after the heart attack. The interim data based on this parameter is already very compelling, said de Kalbermatten. The team also

measures other markers that are predictive of the future outcome of the disease, he added.

Completing this assessment will provide enough information to potentially advance to the next stage and design a Phase 3 trial. In this study, they plan to assess survival rate and hospitalization for worsening heart failure.

“There is a lot of history to overcome in this field,” MacLellan said, but he is optimistic about the future. The scientific community may be emerging from the period of disappointment regarding cell therapies, he suggested, and well-designed randomized controlled trials will add important information about their value.

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