2011 Annual Report: Mimicking the pancreas

News at CIRM

Mimicking the pancreas

Chris Stiehl has already beaten the odds. Living with type 1 diabetes, Stiehl recently celebrated his 62nd birthday. To put that in perspective, when he was diagnosed he was only expected to live to 53. Stiehl is proud of this accomplishment, but it hasn't been easy. Though regular blood sugar monitoring and insulin injections keep him alive, they are no substitute for the 24/7 efficiency of beta cells in the pancreas that would normally give him insulin.

"I'm like a passenger on an ocean liner who falls overboard," says Stiehl. "I have a lifeline—insulin—but I'm still in the ocean. I'm still in danger."

The 3 million people in the U.S. with type 1 diabetes must maintain a delicate balance. For reasons we don't entirely understand, the body's immune system turns on itself, killing off pancreatic beta cells, which monitor blood sugar (glucose) and produce insulin when glucose is high. Insulin tells cells it's time to take in sugar, reducing the amount in the bloodstream. Too much blood sugar can damage nerves, kidneys and the cardiovascular system. Too little can cause coma or death.

Stiehl has to be his own pancreas, a fulltime job. He must constantly monitor his blood sugar, food intake, exercise, even his moods. If he's happy, grouchy, hungry, he must consider the part insulin could play. He checks his blood sugar ten or more times a day, titrating his response based on years of experience. Despite his diligence, he has lost toes, received a kidney transplant and experienced numerous health issues. He uses an insulin pump and twice a pump has failed, nearly killing him.

Insulin keeps Chris alive, but it's no picnic. Like millions of others suffering from diabetes, he wants a better option. He wants a cure.

Diabetes: Progress and Promise in Stem Cell Research

A Two-Part Problem

How do you cure type 1 diabetes? The simplistic solution would be to engineer cells to produce insulin. Unfortunately, it's not enough to produce insulin, you have to produce the right amounts at the right times. Beta cells constantly monitor the blood stream and produce insulin only when blood sugar levels are high.

Beta cell transplants would be ideal, but there are two problems. First, there needs to be a steady supply of cells to transplant. Then, once transplanted, these fragile cells must be protected from the immune system, which still mistakes them for non-self. Immunosuppressive drugs provide some protection, but the risks of inhibiting the immune system often outweigh the benefits. Any potential treatment has to address both issues.

Stem Cells to Beta Cells

CIRM has long recognized that embryonic stem cells would be an excellent source for transplantable beta cells, but the technical requirements have been daunting. Moving an embryonic stem cell through various stages of development to become a beta cell (or a heart cell or a neuron) is a painstaking process. Researchers must mimic the chemical signals found in the body to force the stem cell to gradually become more specialized, until after several steps it becomes a mature beta cell.

In 2008, Evert Kroon and colleagues at ViaCyte, Inc., (formerly Novocell), located on Torrey Pines Mesa in San Diego, succeeded in using stem cells to create progenitor cells, just shy of mature beta cells. These cells could mature in an animal and produce insulin in response to blood sugar. This was a huge step forward, as stem cells could provide a virtually unlimited source of beta cells.

“This was an amazing breakthrough,” says Allan Robins, acting CEO at ViaCyte. “We were one of the first groups to take human embryonic stem cells, make pancreatic cells and show they function in animals.”

However, technical difficulties remained. Moving progenitor cells to fully mature beta cells proved difficult. In addition, efforts to transplant donor beta cells had been problematic, as mature cells are fragile and don’t always survive.

A few blocks away from ViaCyte, Pamela Itkin-Ansari, Ph.D., a researcher with joint appointments at Sanford-Burnham Medical Research Institute and UC San Diego School of Medicine, was looking for ways to safely transplant beta cells and overcome the immune response. Because type 1 diabetes often strikes children in grade school—Chris Stiehl was diagnosed at ten—she felt immunosuppression was not an option.

“We were never going to transplant young kids if they were going to be immunosuppressed for the rest of their lives,” she says.

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Itkin-Ansari became intrigued by a pouch-like device made of polytetrafluorethylene (PTFE), a material akin to Gore-Tex, which is porous enough to allow glucose and insulin through, but fine enough to bar immune cells. The device had been around for a while, but had fallen out of favor because encapsulated beta cells often didn’t survive transplantation.

Itkin-Ansari had an idea. What if you transplanted pancreatic progenitor cells, which are hardier than beta cells, inside the protective device and allowed them to mature in the body? Would they become fully functioning beta cells? Would the device thwart the immune system? In research funded in part by the Juvenile Diabetes Research Foundation (JDRF), she set out to answer these questions.

“The results exceeded our expectations,” says Itkin-Ansari. “Not only did the cells mature inside the device, but we found no evidence of an active immune response. The cells in the device were invisible to the immune system.”

ViaCyte had been investigating the potential benefits of encapsulating insulin-producing cells in a PTFE device for some time. The company and Itkin-Ansari began a collaboration and successfully applied for a CIRM Tools and Technology grant to advance the technology.

A Team of Everyone

In 2009, CIRM continued their support with a $20 million Disease Team loan to ViaCyte, working with researchers at UC San Francisco and the La Jolla Institute for Allergy and Immunology. Groups that had been working separately on the same problem came together to move the research forward.

The loan has had an enormous impact on the research, allowing the team to advance through the so-called Valley of Death, the period between lab discovery and clinical trials where many promising treatments are tabled for lack of funding.

“CIRM has been absolutely instrumental in helping us get where we are,” says Robins.

"This type of innovative therapy could revolutionize the way people live with type 1 diabetes."

Now on the last leg before clinical trials, ViaCyte has refined the technology to create an encapsulation device that can be implanted just under the skin. In addition to protecting beta cells from the immune system, it also keeps the transplanted cells sequestered from the body. This is a great advantage. If there is ever a problem, the cells can be easily removed.

With the encapsulation technology verified by labs around the world, the next step is scaling up production.

“Our normal manufacturing is on the order of billions of cells,” says Robins. “Now we need to think about trillions of cells. We have shown proof of concept that we can do this in bioreactors. There will probably be some hurdles scaling up, but we won’t have to invent anything new.”

Based on the CIRM Disease Team’s success, JDRF has stepped in to help fund the work as part of the organization’s collaborative funding partnership with CIRM.

“This type of innovative therapy could revolutionize the way people live with type 1 diabetes,” says Julia Greenstein, JDRF’s assistant vice president for Cure therapies.

With academia, biotech, government and patient advocates all coming together to push this therapy forward, Robins anticipates clinical trials should begin sometime in 2013. Chris Stiehl knows there is still a long road to an approved treatment but remains confident.

“When I was first diagnosed, at ten, the doctor took me aside and told me how my life was going to be. He said, ‘you’re going to die before you’re 50; you will be blind and you will be on dialysis before you die.’ I have outlived that doctor and his predictions. I’m very excited about this research.”
