Researchers Coax Leftover Pancreatic Cells to Morph Into Insulin-Producing Cells

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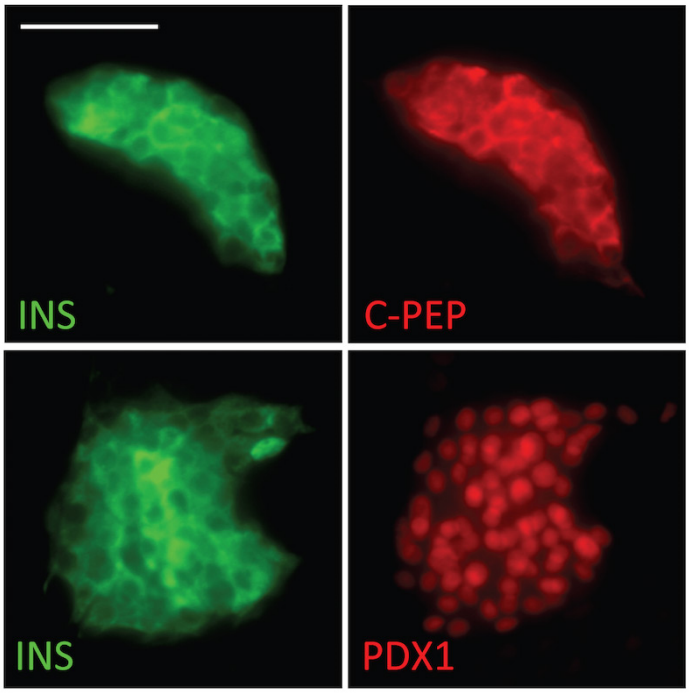
With commentary by Juan Dominguez-Bendala, Ph.D., director of stem cell development for translational research at the Diabetes Research Institute.

Using a growth factor produced naturally by the human body—and used in spinal-fusion surgeries—scientists from the Diabetes Research Institute (DRI) at the University of Miami Miller School of Medicine have coaxed “leftover” cells from the pancreas to morph into insulin-producing islet cells. In a study set for publication in the December issue of the journal *Diabetes*, the reprogrammed cells churned out about as much insulin as healthy human islet cells.



Using BMP-7, the research team induced islet-like clusters from the exocrine cells as shown by several markers, including insulin expression (green, top left) and C-peptide (red, top right). C-peptide is a by-product of insulin expression by the cells and is used to demonstrate the production of natural insulin as opposed to the possibility that cells are simply absorbing insulin from the culture medium. Additionally, the reprogrammed cells show the expression of PDX1, a key marker of beta cell function (red, bottom right).

Transplanted into lab mice and rats, the new islets released their blood sugar-lowering hormone in response to increases in blood glucose levels—just like the real thing. “That’s the hallmark of functioning islet cells, the ability to sense and respond to blood glucose levels,” notes the study’s co-lead investigator Juan Dominguez-Bendala, Ph.D., director of stem cell development for translational research at the DRI. “The

reprogrammed cells in our study produced 50 to 250 times more insulin than pancreatic cells reprogrammed by other teams using genetically-engineered viruses and other compounds. We're hopeful that this technique will one day provide islet cells for people with type 1 diabetes whose own islets have been destroyed by their immune system."

The recipe developed by Bendala, co-leader Ricardo Pastori, Ph.D., Director of the Molecular Biology Laboratory at the DRI and their team, uses BMP-7 (bone morphogenetic protein-7), a growth factor produced in the kidneys and other organs. The version they use is currently approved by the U.S. Food and Drug Administration (FDA) as atreatment for knitting bones back together. Surgeons use it as a paste or implant in difficult bone surgeries.

In the study, BMP-7 transformed cells from the pancreas that don't normally produce insulin. Researchers used non-endocrine pancreatic tissue (NEPT)—cells leftover after islets are removed from the pancreas for transplants. "Ninety-eight percent of the pancreas is NEPT," he explains. "This includes cells that produce digestive enzymes, cells that make up ducts and progenitor cells. BMP-7 reprograms the progenitor cells. If we can improve the efficiency of our process, one pancreas could provide enough cells for several islet-cell transplants in the future."

Bendala says his team discovered this almost by chance. "We wanted to improve our methods for converting NEPT into endocrine cells. We knew BMP-7 could have an effect and we started out using it as the control while testing other agents. We found that it worked better than any of them," he says.

Ahead of the Islet-Cell Shortage

Right now, islet-cell transplants for type 1 diabetes are approved only as experimental procedures in the U.S. If and when islet-cell transplants are OK'ed by the FDA for widespread use, experts expect demand forislets to outstrip supply. Right now, researchers use cells from deceased organ donors. But one transplant requires about a half-million islet cells. "Not all pancreases provide use-able cells and one person may need cells from two or more organs," Bendala says.

The race is on to turn other cells into islets. Bioengineered stem cells are another option that many researchers are pursuing. "With more than one million people worldwide with type 1 diabetes, there will be long waiting lists for transplants. Answering the question of where you get all those islets will be a major accomplishment," notes says F. Charles Brunicardi, M.D., F.A.C.S., Professor and Vice Chair of Surgical Services at the David Geffen School of Medicine at UCLA and Chief of General Surgery at, Santa Monica Hospital.

"We'll have to see which process gets to the finish line first," Bendala notes.

There are two more reasons Bendala's rooting for the reprogrammed NEPT cells: "The process is simple. It doesn't involve sending new genes into cells with Trojan horse viruses. It uses a compound that's already FDA-approved and that our own bodies make. And one day, it may allow us to grow new islet cells right in the pancreas of a

person with type 1. We would still have to shield them from destruction by the immune system, but no transplant would be needed.”
Researchers hope to test that idea soon in animal studies.