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Posted by Sarah Schwartz
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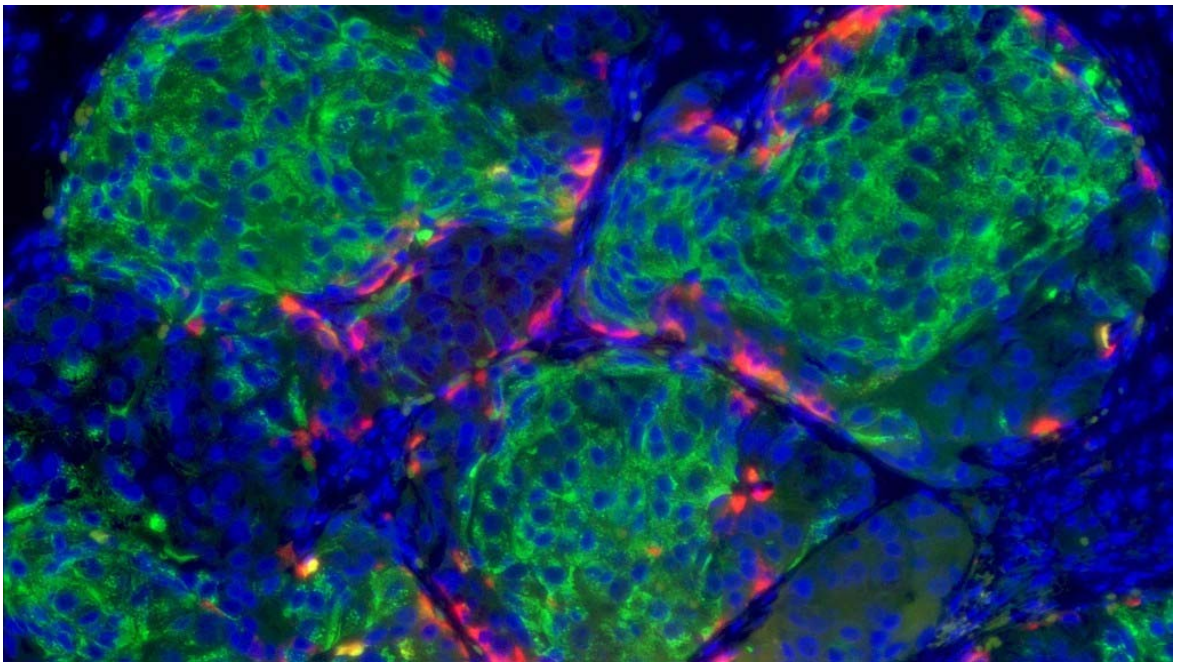
Insulin-Producing Stem Cells Could Provide Lasting Diabetes Treatments (http://dx.doi.org/doi:10.1038/nbt.3033)

Researchers have crafted what may be a powerful weapon in the fight against diabetes: A new line of insulin-producing cells that has been shown to reverse diabetes in mice within forty days. Scientists hope that these cells may someday do the same in humans.

The new cells, called “Stage 7” or “S7” for their seven-step production process, are the product of a study (http://dx.doi.org/doi:10.1038/nbt.3033) by researchers at the University of British Columbia and the pharmaceutical company Janssen. S7 cells are made to mimic human beta cells, which are damaged or destroyed in patients with diabetes. Healthy beta cells produce insulin and help regulate blood sugar; S7 cells are grown from human embryonic stem cells and are programmed to do the same.



A microscopic view of beta cells derived from stem cells

“The advance that they have made is that they’ve got better cells in the test tube, cells that have more insulin and can secrete insulin in response to glucose,” said Dr. Gordon Weir, a physician and researcher at Joslin Diabetes Center and Harvard Medical School. “People haven’t been able to do that before.”

Human embryonic stem cells, like those used to produce the S7 line, show great promise for producing beta cell replacements. Just last week, another team of researchers led by Dr. Douglas Melton at Harvard University announced their own line of insulin-producing cells (http://dx.doi.org/10.1016/j.cell.2014.09.040), also produced from human embryonic stem

cells. Like S7 cells, the Harvard team's cells produce insulin in response to high blood sugar and can reverse diabetes symptoms in mice.

The hope is that cells like these could be injected into diabetic patients, restoring normal beta cell function. Timothy Kieffer, head of the diabetes research group at University of British Columbia and a co-author of the S7 cell study, said that treatment with these cells could be curative, though other researchers caution that additional work has to be done before that's the case.

Cellular transplantation has already been shown to effectively combat diabetes. Since the late 1980s, beta cells extracted from cadaver pancreases have been used to normalize blood sugar in diabetics. But these treatments are not an option for many patients. In addition to the challenges of establishing a treatment program, Weir said, "there aren't enough pancreatic donors to even scratch the surface." These transplanted cells also tend to stop working over time, said Dr. David Nathan, the director of the Diabetes Center and Clinical Research Center at Massachusetts General Hospital. Whole organ pancreatic transplants usually last longer and have been increasingly successful in recent years, Nathan says. But both organ and cell transplants from cadavers require immunosuppressive treatments, which can cause tumors, skin cancers, and weakened immune systems.

Beta cells grown from stem cells could solve some of these problems. It is possible that stem cells could be developed to reduce or eliminate the need for immunosuppression, Nathan said. Plus, their supply is theoretically unlimited. "If you can make them in a test tube, in a dish, whatever—well, that gets rid of the problem of donor pancreases," Nathan said. While S7 cells are most efficient when made from human embryonic stem cells, they can also be made using induced pluripotent stem cells, which are reprogrammed adult cells. This, Weir noted, could eliminate "ethical issues" involved with embryonic stem cell use.

Kieffer believes that a stem cell-based treatment would also be superior to insulin supplementation, the current standard of treatment for type 1 diabetes. In type 1 diabetes, which Kieffer's research targets, beta cells are destroyed by an autoimmune attack, and patients require external insulin to survive. Even with advanced treatment options like insulin pumps, Weir said, it is challenging to keep blood sugar in a normal range. "And if you push hard enough to drive the blood sugar down, you end up getting into trouble with insulin reactions," Weir said. "The blood sugar goes too low and that's dangerous."

But S7 cells have some challenges to overcome before they can replace current treatments. For one, it can be difficult to control the development of stem cells, Nathan pointed out. Kieffer agreed that more research is needed to mature the cells, which are still not identical to human beta cells because they react more slowly to sugar and don't release as much insulin. Kieffer's collaborators are also working to scale up production of the S7 line. Meanwhile, the Harvard study uses a protocol that already seems to allow relatively large-scale development of insulin-producing cells.

There are also other challenges to treating type 1 diabetes with cells like S7 because of the autoimmune nature of the disease. If beta cell transplants are injected into type 1 diabetics, Weir said, "those cells are still going to be subject to the immune problem that killed the cells in the first place." Kieffer said that the "next hurdle" for his team is to see if S7 cells will work inside devices that prevent immune attack.

These “immunobarrier” devices are essentially capsules that contain implanted stem cells, allowing the exchange of nutrients and insulin while blocking attacking immune cells. Nathan and Weir expressed reservations about these devices. Nathan wondered if they can be designed to allow sufficient blood flow and nutrients to all the cells inside, while Weir questioned whether there could be a device large enough to hold the number of cells needed to control the disease. Still, in August, the company Viacyte started clinical trials with such a device, using a line of cells less developed than S7. “We’ll have to wait and see,” Weir said.

Because of the autoimmunity problem inherent in type 1 diabetes, Weir says that it may be easier to use beta cell transplantations to treat type 2 diabetes instead. Up to 95% of diabetic patients have this form of the disease, which involves no autoimmunity. Instead, in type 2, beta cells “wear out” such that the body stops responding to insulin.

“You can take a type 2 diabetic and give them insulin injections and normalize the sugar if you do it carefully,” Weir said. “So, a beta cell transplant is just the same thing as giving an insulin injection.” He feels the effects of such treatment could be profound. “You can put cells in and normalize the blood sugar for years,” he said. “So if you want to call that a cure, I’d go along with that.” Nathan disagrees: because type 2 diabetics have some pancreatic function, it can be simpler and easier to treat their symptoms. Because of this, he believes that cellular transplantations will mostly be useful to combat type 1 diabetes.

Nathan doesn’t think that beta cell transplantations are an “appropriate clinical option”—yet. “The balance between risk and benefit isn’t quite right,” he says. Still, he hopes that someday, a cellular treatment will be advanced enough to safely and effectively treat this disease. “To cure type 1 diabetes would be a godsend,” he says. “To actually do a single procedure that essentially takes away the disease at low risk would be great.”

Though several questions must be answered before they start curing patients, S7 cells are a promising step in the fight against a disease that affects 347 million people worldwide. The field is moving quickly towards its goal; as Kieffer writes, “I am very optimistic that we are narrowing down on a cure for diabetes.”

Image credit: Doug Melton/Harvard