Pancreatic islets find a new transplant home in the omentum

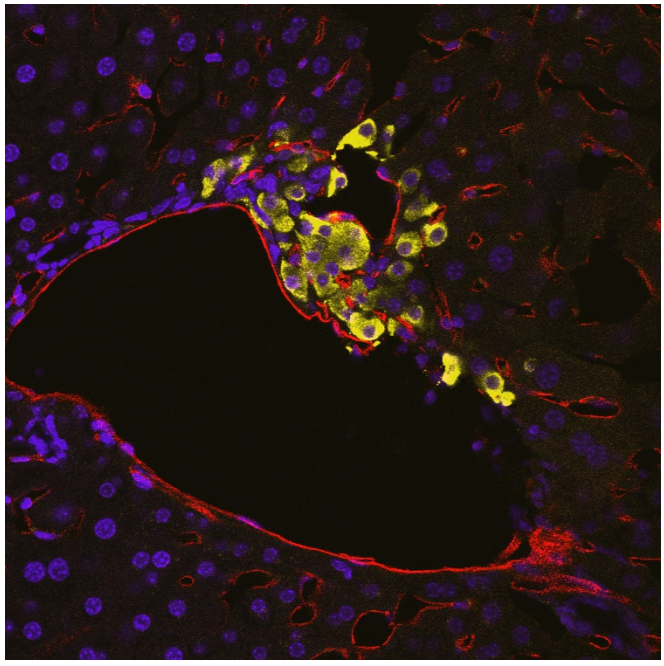
In 2017, the FDA will begin evaluating a Biological License Application for pancreatic islet transplantation to the liver—a treatment for severe type 1 diabetes that's now approved in Canada, Australia, the UK and several European countries. But even as the US Food and Drug Administration (FDA) reviews the clinical data for anticipated approval of the procedure in the US, investigators are exploring a different transplant site that may allow for better long-term outcomes. So far, two patients have undergone islet transplants to the omentum, a layer of visceral peritoneum that covers the abdominal organs. "Both are still completely off insulin," says Camillo Ricordi, scientific director of the Diabetes Research Institute (DRI) in Hollywood, Florida, and a professor at the University of Miami, who developed the surgical protocol.

Islets are clusters of cells in the pancreas that regulate blood glucose by producing the hormones insulin and glucagon. Clinical islet transplantation involves harvesting islets from deceased organ donors and infusing them through the portal vein into the liver. The treatment has been provided to small numbers of patients, just over 1,100 worldwide, who cannot be stabilized successfully with insulin and have a history of hypoglycemia unawareness. The best responders may be freed of having to take daily insulin shots for years, but all recipients require lifelong immunosuppressive drug therapy with its risks of side effects, including cancer.

The liver and the omentum are each highly vascularized, and thus provide transplanted islets with plenty of blood flow, oxygen and nutrients. But as a transplant site, the liver presents certain limitations. It's prone to inflammatory reactions against the islets, and it also concentrates oral immunosuppressive drugs that are toxic to the cells. Roughly 60% of transplanted islets are killed off in the liver within hours, and it generally takes two infusions or more with purified islet cells to reach a stable population that can adequately control glucose levels in the blood.

Ricordi says the omentum could be more hospitable to transplanted islets than the liver, with the added advantage of easy access by minimally invasive laparoscopic surgery. In the procedure, surgeons drip a mixture of islet cells and the patient's own plasma onto the omentum and add thrombin to create a gel-like biodegradable scaffold that sticks to tissue and holds the islets in place. Omental tissue is then folded over the scaffold to create a pouch that protects the cells from inflammatory attack. With time, the gel gets absorbed while newly forming blood vessels sustain the transplants.

Whether islet cells will engraft in the omentum as well as or better than in the liver "only time will tell," says James Shapiro, director of the Clinical Islet Transplant Program at the University of Alberta, in Canada. Shapiro developed the Edmonton protocol, which is now the dominant method for islet delivery to the liver. He has treated more than 250 patients with the protocol since it was first published in 1999. Shapiro collaborates with Ricordi and the DRI, and says he plans to perform islet transplants to the omentum at his own facility. "The omentum is an alternative for patients with liver disease, and it may also be easier to remove the islets laparascopically from the omentum if there's a problem with them," he says.



Per-Ola Carlsson, Uppsala University.

Islet cells transplanted into the wall of a portal vein tributary show signs of disrupted integrity (yellow depicts insulin, red is staining for blood vessels).

Per-Ola Carlsson, a professor of medical cell biology at Uppsala University, in Sweden, says mouse experiments show the omentum is superior to the liver in terms of graft function and revascularization. "We also find that transplanted beta cells (the subgroup of islets that release insulin) maintain their differentiation better in the omentum than after transplant to the liver." Islets tend to change gene expression after transplantation, says Carlsson, referring to unpublished studies, in ways that depend on where they're placed. Islet cells transplanted to the liver show a decrease in the expression of *Pdx1*, which is important for beta cell differentiation. Conversely, when transplanted to the omentum, islets increase the expression of *Pdx1* and two insulin genes known as *Ins1* and *Ins2*. "This [may have consequences] for their long-term functioning," Carlsson says.

Ricordi is currently conducting a phase 1/2 clinical safety/efficacy trial investigating functional and clinical outcomes in patients who receive islet transplants to the omentum. The first recruit for this trial, which has an enrollment goal of six patients, received a transplant at the DRI in September, 2015. A second patient was treated at Niguarda Hospital, in Milan, last May in a separate European study using the same protocol. Meanwhile, the FDA is reviewing data from a phase 3 trial testing islet cell preparation and portal system delivery to the liver. "We don't think we need to do another phase 3 trial for the omentum," Ricordi says. "Ideally the agency will accept the omentum as an alternative transplantation site of an approved product."

On that point, Shapiro is skeptical. "If the phase 1/2 trial shows safety, then a phase 3 trial would still be required for the omentum to show superiority to the liver," he says. "That will be up to the FDA and the rest is speculation." Although some patients treated with the Edmonton protocol have been off insulin for up to 18 years, he says, "a significant proportion of cells in the liver don't survive. If we could get a higher proportion surviving in the omentum that would be a significant advantage. But it needs to be proven."

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