Islet transplants find the adrenal gland

By Lauren Martz, Staff Writer

German and U.S. researchers have shown that transplantation into the adrenal gland of islet cells preconditioned with an improved peptide agonist of growth hormone-releasing hormone may help normalize glucose levels in diabetic mice better than existing islet transplantation protocols.¹ The agonist has been licensed to **Biscayne Pharmaceuticals Inc.** for all indications, and the benefits of the intra-adrenal transplantation protocol will next be confirmed in large animal models.

Although transplantation of pancreatic islet cells has the potential to permanently correct dysfunctional insulin production and treat type 1 diabetes, current procedures require long-term immunosuppressive treatment, and progressive loss of islet functionality poses a big challenge.

Besides destructive autoimmunity, additional causes of post-transplant islet death include cell damage during isolation from donors and a lack of vasculature and oxygen supply at the hepatic transplantation site. Indeed, the standard intraportal infusion method of transplantation results in the liver quickly killing as much as 60% of the islet cell mass.²

To improve the long-term functioning of islet grafts, diabetes researchers have begun focusing on new sites of transplantation and new pharmacological approaches to improving islet survival.

In 2010, a team led by Andrew Schally and including most of the same principal German coauthors as the current study found that treatment of insulinoma or islet cells with an agonist of growth hormone-releasing hormone (GHRH) increased cell viability and decreased apoptosis in culture compared with vehicle treatment. The group also found that transplantation of GHRH agonist-treated islets into diabetic mice improved glucose tolerance better than transplantation of untreated cells.³

The team has now built on the previous work and designed a more potent GHRH agonist, MR403, and shown that the adrenal gland is a potential alternative transplantation site. The researchers chose the adrenal gland because it has easy surgical access, dense vascularization and high oxygen tension. It also provides an anti-inflammatory and immunoprotective environment.

Schally is head of the Endocrine, Polypeptide and Cancer Institute at the **Veterans Affairs Medical Center** and a professor of medicine

at the **University of Miami Miller School of Medicine**. The team included researchers from the **University Hospital of Carl Gustav Carus** and the **German Center for Diabetes Research**.

The team initially found that MR403 increased the survival and proliferation of cultured insulinoma cells and decreased apoptosis compared with vehicle. Coculture of agonist-treated rat islet cells and rat adrenal cells led to further survival improvements.

In nonobese diabetic mice, transplantation of islet cells pretreated with MR403 into the adrenal gland led to normal glucose levels a few days after transplantation that lasted until the grafts were removed at 30 days post-transplantation. The short-term transplantation efficiency was comparable to that of MR403-pretreated islet transplantation under the kidney capsule, the standard site of transplantation in rodent diabetes models. Adrenal gland transplantation also did not damage adrenal tissue, cause apoptosis of the islets or induce an inflammatory reaction.

Results were published in the *Proceedings of the National Academy of Sciences*.

“The shortage of donor islets and the need for lifelong immunosuppressive therapy remain major barriers to the adoption of islet cell transplantation,” said coauthor Stefan Bornstein, who is professor of medicine and director and chair of the Department of Medicine at the **Dresden University of Technology**. He added that the GHRH agonists and other modifications to the protocol may help overcome these obstacles and make islet cell transplantation a feasible therapeutic option.

“The shortage of donor islets and the need for lifelong immunosuppressive therapy remain major barriers to the adoption of islet cell transplantation.”
—*Dresden University of Technology*

Next steps

Diabetes researchers believe the new work is a step toward an improved protocol for islet cell transplantation but also say further *in vivo* testing is needed to confirm the benefits of the approach.

“As encouraging as these results are, GHRH-enhanced islet cell transplantation strategies require identifying suitable islet cell donors as well as subjecting diabetes patients to invasive procedures,” Hubert Chen, VP of clinical development at **Aileron Therapeutics Inc.**, told SciBX.

But, added Chen, it could also turn out that because GHRH may enhance the quality of islet cell harvests, the pool of eligible donors will be expanded.

With regard to the invasiveness of the procedure, coauthor Barbara Ludwig said that “transplantation into the adrenal gland could be envisioned either by laparoscopic procedure or via an intravascular approach. These options will be tested in the near future in a large animal model.” But she also acknowledged that “compared to the transhepatic approach that is currently performed in most centers for intraportal islet transplantation, this would generally be more invasive.”

Ludwig is a medical doctor at the University Hospital of Carl Gustav Carus.

Chen suggested that the invasiveness of the procedure could be reduced by directing islet cells toward the adrenal glands with X-ray-guided catheterization procedures, which are routinely used in hospitals.

Aileron's long-acting GHRH analog, ALRN-5821, is in preclinical testing to treat growth hormone deficiency, abdominal obesity and cardiometabolic conditions including lipodystrophy.

Finally, Ludwig added that long-term *in vivo* experiments to prove that GHRH pretreatment increases the survival of the transplants are ongoing.

Biscayne

The University of Miami has licensed several of Schally's GHRH-targeting compounds to Biscayne Pharmaceuticals. The company first plans to pursue indications in cardiovascular disease and cancer rather than diabetes because these indications have the most experimental characterization and documentation.

"We are in preclinical stages and getting ready for clinical testing. We have a peptide agonist that is being tested for ischemic heart disease and an antagonist for solid tumors," CEO Samuel Reich told *SciBX*.

Biscayne has raised \$1.5 million in seed-round financing for preclinical testing and expects to raise more financing in the next 12–18 months to move into clinical trials.

"Right now we want to remain as focused as possible on the chosen indications," said Reich.

"As those programs advance, Biscayne expects to develop other applications of the GHRH technology, including potentially its role

in islet cell regeneration and diabetes," said Biscayne scientific advisor Schally.

Schally told *SciBX* that the University of Miami has patents pending covering composition of matter of the peptides and methods of use in clinical applications including diabetes. The IP is licensed to Biscayne, and there may be opportunities to collaborate or partner.

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COMPANIES AND INSTITUTIONS MENTIONED

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