Inducing β -cell expansion

By Lauren Martz, Staff Writer

A group at **The Scripps Research Institute** has identified two classes of small molecules that induce β -cell expansion and could potentially treat diabetes by restoring natural insulin secretion and improving glucose management.¹ The small molecules, which include L-type calcium channel agonists, could potentially address the problems with existing therapeutics for both type 1 and type 2 diabetes.

Both forms of diabetes are characterized by a loss in β -cell mass or function that leads to insufficient or improper insulin secretion and glucose management.² In type 1 disease, an immune reaction destroys insulin-producing β -cells in the pancreas, whereas type 2 diabetes involves resistance to insulin and frequently includes decreased insulin secretion. Many type 2 diabetics progress to insulin dependence.

For type 1 diabetes in particular, islet cell transplants could achieve more precise control of blood glucose than insulin injections, but the utility of this method has been limited by a lack of available donors, the need for simultaneous use of immunosuppressants and a lack of efficacy that leads many patients to become insulin-dependent following surgery.³

In a paper published in the *Proceedings of the National Academy of Sciences*, Peter Schultz and colleagues at Scripps reported on a screening study they conducted to find molecules with new, disease-modifying mechanisms. The group screened about 850,000 compounds against growth-arrested mouse pancreatic β -cells to identify molecules that could restore replication of the cells.

Among the identified compounds were thiophene-pyrimidines that activate the Wnt signaling pathway and dihydropyridine (DHP) derivatives that function as L-type calcium channel (LTCC) agonists. One LTCC agonist also restored replication of growth-arrested human β -cells.

Although the Wnt pathway is being targeted in cancer and LTCCs are being targeted to treat Alzheimer's disease (AD), neither has previously been targeted in diabetes.

The paper also suggests that the new compounds could play well with molecules already on the market, including Byetta exenatide, a glucagon-like peptide-1 receptor (GLP1R; GLP-1R) agonist that is sold by **Amylin Pharmaceuticals Inc.** and **Eli Lilly and Co.** Indeed, the *PNAS* authors showed that the LTCC agonist plus glucagon-like peptide-1 (GCG; GLP-1), which promotes cellular viability, had additive

effects on proliferation.

Cord Dohrmann, CEO of **DeveloGen AG**, told *SciBX* that the β -cell proliferative effects of the identified LTCC agonists make them good starting points for further drug development.

DeveloGen's DG770, a β -cell regeneration factor, is in preclinical testing to treat both type 1 and type 2 diabetes.

Selective targeting

Although the Scripps screen brings new mechanisms into play for treating diabetes, selectivity issues could hamper development because compound classes targeting LTCCs and the Wnt pathway interfere with signaling cascades that are not specific to pancreatic cells.

Stephen Doberstein, VP of research at **Xoma Ltd.**, noted that "the most important thing is that the two classes of molecules studied in the paper are both agonists of growth control pathways. Small molecules tend to be inhibitors of cellular processes, and whenever you start turning on pathways, you need to be careful about what other tissues you are affecting."

Xoma's lead diabetes compound is XOMA 052, a mAb against IL-1 that is in Phase I testing to treat type 2 diabetes.

Yoshio Fujitani, associate professor in the Department of Medicine, Metabolism and Endocrinology at **Juntendo University School of Medicine**, shared the caution: "One of my great concerns is target specificity of the compounds characterized in the study."

For example, Fujitani noted that activators of the Wnt pathway could be tumorigenic. In addition, he told *SciBX* that LTCC is broadly distributed in various organs such as vascular

walls. Thus, "LTCC agonists might cause unknown, unfavorable effects on vasculature such as inducing hypertension or diabetic complications in the kidney by contracting blood vessels," he said.

Douglas Muchmore, VP of endocrinology clinical development at **Halozyne Therapeutics Inc.**, said getting compounds to the pancreas "hasn't yet been nailed down. Maybe cross-linking to another compound that has the ability to target that particular area or tissue type is a potential solution."

Halozyne's PH20-Insulin, a recombinant human hyaluronidase (rHuPH20) coformulated with Humulin insulin human injection and Humalog insulin lispro, is in Phase II testing to treat type 1 diabetes.

A future step, according to Fujitani, is "to examine whether these compounds are indeed effective in lowering blood glucose levels by increasing β -cell mass" in animals.

Room for small molecules

If the safety and selectivity issues of the LTCC agonists are resolved, researchers said the compounds might be better suited to treat type 2 diabetes rather than type 1.

Both Doberstein and Muchmore noted that β -cell regenerators could have limited efficacy in type 1 disease.

"One of my great concerns is target specificity of the compounds characterized in the study."

—Yoshio Fujitani,
Juntendo University
School of Medicine

“The use of β -cell regeneration in type 1 diabetes is still a difficult road because even as you expand the number of cells, there is still the immune response that originally caused the disease and pancreatic destruction,” said Doberstein.

Without long-term immunosuppressive therapy, which has its own side effects, Muchmore suggested it is possible that neither transplants nor β -cell regeneration is likely to be completely effective.

Thus, he thinks inducers of β -cell expansion could be more useful in maintaining and prolonging β -cell function and insulin signaling in type 2 diabetes.

“It is likely that this strategy will have to exist as a combination therapy” in type 1 disease, Doberstein concluded.

Indeed, Dohrmann suggested that “stimulating β -cell proliferation in patients with type 1 diabetes has the potential to restore β -cell function in part or completely in diabetic patients and thus reduce or even spare routine insulin injections as well as reduce the likelihood of developing diabetic complications.”

Fujitani suggested that using the small molecule inducers with existing treatment might be a good path forward in either form of the

disease. “When functional β -cell mass is preserved thanks to the compounds, patients have a better chance to achieve good glycemic control with multiple insulin injections,” he said.

Martz, L. *SciBX* 2(6); doi:10.1038/scibx.2009.213
Published online Feb. 12, 2009

REFERENCES

1. Wang, W. *et al. Proc. Natl. Acad. Sci. USA*; published online Jan. 19, 2009; doi:10.1073/pnas.0811848106
Contact: Peter G. Schultz, The Scripps Research Institute, La Jolla, Calif.
e-mail: schultz@scripps.edu
2. Pipeleers, D. *et al. Diabetes Obes. Metab.* **10**, 54–62 (2008)
3. Serup, P. *et al. BMJ* **322**, 29–32 (2001)

COMPANIES AND INSTITUTIONS MENTIONED

Amylin Pharmaceuticals Inc. (NASDAQ:AMLN), San Diego, Calif.
DeveloGen AG, Goettingen, Germany
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Halozyne Therapeutics Inc. (NASDAQ:HALO), San Diego, Calif.
Juntendo University School of Medicine, Tokyo, Japan
The Scripps Research Institute, La Jolla, Calif.
Xoma Ltd. (NASDAQ:XOMA), Berkeley, Calif.