Regenerating insulin-producing cells the next big thing in diabetes

Jonathan Gardner

Novo Nordisk’s cell therapy collaborations are a sign that serious work is under way.

Restoring the function of pancreatic beta cells would represent a leap forward in treating diabetes, potentially allowing insulin-dependent patients to wean themselves off frequent blood sugar monitoring and injections. But work has been hampered by difficulties in developing differentiated cells that can respond to the body’s need for glucose modulation and protecting these from the autoimmune response that is the hallmark of type 1 diabetes.

Novo Nordisk’s recent partnerships with the University of California-San Francisco and Cornell University on pluripotent stem cells and an encapsulation technology are signs that an advance is nevertheless creeping closer to approval. The diabetes-focused Danish company is behind some small biotechs in pursuing pancreatic regeneration, but its moves in this area ought to make others take notice (see table below).

Differentiation and protection

Researchers have known for some time that cadaveric pancreatic tissue could be implanted in diabetic patients to generate insulin; the first such cases were reported in 1990. However, the lack of tissue and the regimen of immunosuppressive drugs necessary for success – called the “Edmonton protocol” – limited its use. And very few diabetics showed sustained insulin independence.

Novo believes that it has cracked issues that have held this space back. Its deal with UCSF allows it to access technology for producing good manufacturing practice-compliant human embryonic stem cell lines and license their use for human treatments. The group says it has “preclinical proof of concept” on a process for differentiating pluripotent stem cells into insulin-producing beta cells.

With Cornell, Novo has developed an encapsulation device that can protect the beta cells from autoimmune attack, which is how type 1 diabetics end up with depleted insulin-producing capacity.

A candidate could enter the clinic within the next few years, Novo’s science chief, Mads Krogsgaard Thomsen, recently told EP Vantage: “Over the last two years we’ve made two breakthroughs. One is the ability to create the most difficult cell of all, namely the beta cell. Beta cells have to respond and make insulin only when blood sugar is high and not when it’s normally low, so it’s one of the most complicated cells to differentiate from stem cells.
“When we also started to understand how we could shield the cells from the immune system, so as to avoid getting destroyed immediately after being injected into the human body, we realised that we were in a good situation.”

Nothing like the real thing

In improving type 1 diabetes care, the life sciences sector has of late been more focused on the “artificial pancreas”, or a combination of glucose monitor, insulin pump and software that can detect and even predict swings in blood-sugar levels and prevent episodes of hyper and hypoglycaemia. The comparative benefit of a cell therapy is that exogenous insulin would no longer be needed, representing potential savings over the course of a patient’s life.

Cell therapies in type 1 diabetes generally fall into two categories: regeneration of insulin-producing beta cells or protecting residual cells from autoimmune attack. On the former, two companies, Viacyte and Sernova, appear to have advanced into the clinic.

### Selected cell therapies in development for type 1 diabetes

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<th>Company</th>
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Source: EvaluatePharma.

Viacyte has two candidates that have progressed as far as phase I: VC-01 or Pec-Encap, and Pec-Direct. At the American Diabetes Association meeting in June the group presented two-year data from the first cohort of 19 patients, who received a sub-therapeutic dose.

The Encaptra device prevented immune attack on cells and, when engraftment did occur, viable insulin-producing cells were formed, some persisting for two years. The company acknowledged that “consistent and robust engraftment was limited”, however.

Viacyte has also initiated dosing of a “potentially efficacious” version of Pec-Direct, which does not use the immune-shielding technology. Patients in this trial must use Edmonton Protocol immunosuppressives, and as such Viacyte reckons it might be best used in kidney transplant patients, who already require immunosuppression, or in severe patients such as those with hypoglycaemia unawareness, extreme glycaemic lability, and/or severe hypoglycaemic episodes.

Sernova, a Canadian group, last month began recruitment and screening for a phase I/II trial of Cellpouch, which it describes as a “prevascularised implantable medical device”. Patients with hypoglycaemia unawareness will first be implanted with this device, and after vascularised tissue development an initial dose of purified islet cells will be implanted.

A sentinel pouch also will be implanted and removed early to test islet transplant. At six months patient safety and efficacy will be measured and, if necessary, a second islet transplant will be performed.

Meanwhile, privately held Semma raised $114m last year in anticipation of filing an IND application for its technology, which came from the Harvard University Stem Cell Institute.

Retraining immune cells

On the protective cell therapy side, Caladrius and Tianhe aim to alter the autoimmune response of T cells. For this approach to work patients need to have some residual immune cell function, and they must also undergo apheresis. Tianhe uses a closed-loop system, while Caladrius isolates, activates and expands T regulatory cells, which have an immunosuppressive effect.

Caladrius has been awarded fast-track and orphan drug status from the FDA, suggesting that the agency is paying close attention to the development of its project, CLBS03. Its ongoing phase II trial is expected to read
Still, since all these candidates are invasive and will likely be very expensive, even if they are approved insurers will probably be reluctant to pay for their use in anyone but the most severe patients at risk of costly hospital stays and complications. Insulin and insulin analogues might be a $21bn budget line, but payers appear to have at least arrested spending growth.

Novo and its rivals will need to demonstrate that pancreatic cell regeneration can be a durable treatment that averts complications and reduces demand for insulin and other glucose-lowering medications. They have much to prove.