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Biological ways to achieve the correct insulin levels

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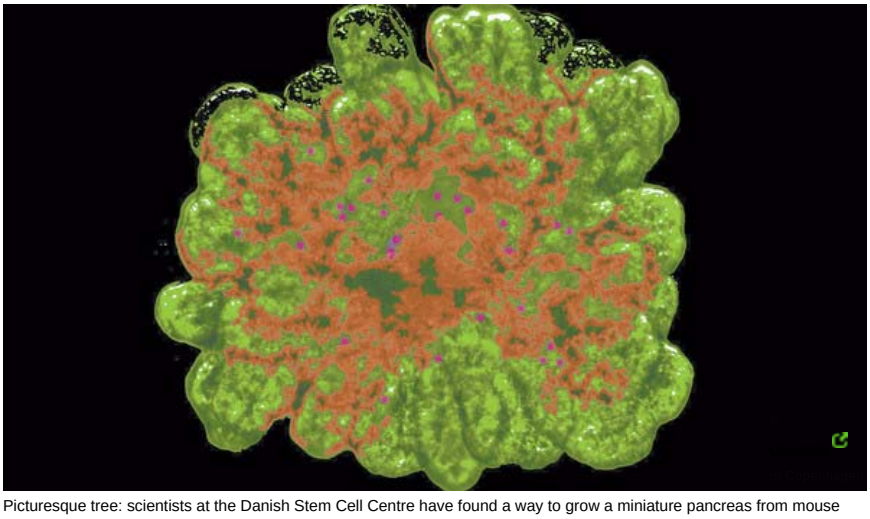

Picturesque tree: scientists at the Danish Stem Cell Centre have found a way to grow a miniature pancreas from mouse progenitor cells

When diabetics can no longer make enough insulin in their own pancreas, the normal treatment is to inject the hormone into their bloodstream. A better method in principle is to replace the failed insulin-producing "islet cells" by transplanting new ones that can produce a smoother flow of hormone without the need for injections.

Since the 1990s, clinicians have been transplanting islets from the pancreas of deceased donors into patients with the most dangerous form of diabetes, who fail to recognise potentially fatal changes in blood sugar levels.

The treatment works but suffers from two serious drawbacks. One is the severe shortage of suitable pancreases – so only about 1,800 people worldwide have had islet transplants. The other is the need for recipients to take immunosuppressant drugs indefinitely to prevent rejection, which inevitably increases the risk of developing other diseases.

Diabetes charities and biotechnology companies are running several research projects to overcome both problems, by developing new sources of insulin-producing cells, and finding ways to prevent the host's immune system from attacking them.

There are several competing technologies to stop rejection – all in animal testing or very early clinical trials. For example, Sernova, a Canadian company, uses Sertoli cells, which are normally made in the testes to protect sperm from immune attack. Its Sertolin technology mixes the islet cells with Sertoli cells in a matchbox-sized device implanted under the skin, where the "immune-privileged" environment makes systemic immunosuppression unnecessary.

Others are developing miniature capsules, made from various organic materials such as cellulose and alginate, to contain the transplanted cells. The idea is that nutrients can get into the capsule, and insulin can get out, but the patient's immune system cannot penetrate it. Companies following this route include Living Cell Technologies, based in New Zealand and Australia, and Nuvilex of the US.

In the Islet Sheet Project – a collaboration involving Professor Jonathan Lakey at the University of California Irvine, the Hanuman Medical Foundation and Juvenile Diabetes Research Foundation (JDRF) – the islets are the inner layer in a sheet just 0.3mm thick, encapsulated in alginate and strengthened with a micromesh.

Pigs have been considered as an alternative source of islet cells for several years, because their islets are physiologically very similar to those of humans, and purified porcine insulin has long been used to treat diabetes. Although researchers have bred pigs that are germfree and genetically engineered to be more compatible with the human immune system, regulators remain reluctant to endorse "xenotransplantation" to people from other species.

Meanwhile, research into human stem cells – including adult stem cells, embryonic stem cells and the more recently discovered "induced pluripotent stem cells" (iPSCs) derived from adult cells – is giving hope that these will eventually provide a plentiful new source of islets.

Although scientists have already had some success in driving stem cells to become insulin-producing beta cells – the most important component of islets – a lot more work will be needed to produce these reliably and safely.

ViaCyte, a Californian regenerative medicine company, is leading the development of a treatment based on human embryonic stem cells, with encapsulation to protect them from the recipient's immune system. If the US Food and Drug Administration agrees, its VC-01 product could begin clinical trials next year.

Further in the future is the prospect of moving beyond groups of islet cells to generate a functioning pancreas – an "artificial pancreas" in the biological rather than electronic sense.

At the Danish Stem Cell Centre at the University of Copenhagen, scientists have discovered how to grow a miniature pancreas, with a picturesque treelike structure, from mouse progenitor cells.

"Under optimal conditions, the initial clusters of a few cells have proliferated into 40,000 cells within a week," says Anne Grapin-Botton, project leader. "After growing a lot, they transform into cells that make either digestive enzymes or hormones such as insulin, and they self-organise into branched pancreatic organoids that are amazingly similar to the pancreas ... We are now trying to adapt this method to human stem cells."

The Diabetes Research Institute, based in Florida, is developing the BioHub, a "mini-organ" that mimics the human pancreas, containing thousands of insulin-producing cells that sense blood sugar levels and produce precisely the right amount of insulin, as it is needed.

However, Sarah Johnson, the JDRF's UK policy director, notes that none of these biological approaches to replacing islets can be regarded as a cure for type 1 diabetes, however well they work, because the new cells may be attacked by the immune disorder that destroyed the patient's own cells in the first place. "Ultimately, the cure will be to restore the function of insulin-producing cells and stop the autoimmune response," she says.

Although the ultimate causes of type 1 diabetes remain mysterious, Alasdair Rankin, research director of Diabetes UK, says it may soon be possible selectively to modulate the immune system so that the disease "goes into remission" for short periods. That could be the foundation for damping down the autoimmune response for longer, and eventually switching it off.