

COMMENTARY

β -cell replacement therapy for type 1 diabetes: closer and closer

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The widespread publicity last year for the centenary of the discovery of insulin demonstrated what a wonderful, life-saving treatment insulin is for people with type 1 diabetes, but it also served as a reminder that a century later we are still largely treating the symptoms of diabetes with exogenous insulin rather than offering a cure. Perhaps for not much longer: Islet transplantation has the potential to cure type 1 diabetes by delivering physiological glycaemic control without dependency on exogenous insulin which should avoid the development of secondary complications.¹ However, current human islet transplantation protocols are normally dependent on islets isolated from pancreases harvested from heart-beating, brain-dead donors who comprise a very limited donor pool of a few thousand, at best, in the UK. Allogenic human islet transplantation is therefore currently confined to a subset of people with type 1 diabetes who also suffer from severe and intractable hypoglycaemia.¹ This is proof of concept of the therapeutic potential of human islet transplantation, but the limitations of donor graft material means that this approach will make little overall clinical impact on the wider population of the hundreds of thousands of people with type 1 diabetes in the UK.

Over the past two decades, much research effort has therefore been directed towards generating in vitro essentially unlimited amounts of β -cell substitutes for transplantation therapy.² To date, most success has been reported in studies using pluripotent stem cells as the

starting material, either human embryonic stem (hES) cells derived from the inner cell mass of human blastocysts or induced pluripotent stem (iPS) cells generated by reprogramming adult cells. These in vitro differentiation studies have been informed by extensive studies of pancreas development, mostly in experimental animals, which have identified signalling factors driving the sequential developmental stages and have mapped gene expression signatures for those stages. The most successful in vitro differentiation protocols have imposed versions of in vivo development cues onto hES/iPS cells in vitro, albeit with greatly telescoped time frames when compared to normal human pancreas development.

The first convincing reports of the generation of functional β -cells came from Novocell, a biotechnology company based in California, which published in vitro protocols designed to drive the differentiation of pluripotent stem cells via definitive endoderm, foregut, pancreatic progenitors and endocrine progenitors to mature β -cells.³ It soon became apparent that these stem cell-derived ' β -cells' were most likely immature endocrine cells because they were polyhormonal and unresponsive to glucose, although glucose responsiveness could be achieved by a further in vivo maturation phase after implantation into experimental animals.⁴ It took more years of intense effort before the first report from Melton's group at Harvard of a differentiation protocol which could generate mature, glucose-responsive β -cells solely using defined in vitro treatments, by which time Novocell had changed its name

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to ViaCyte, Inc. but was still focused on using stem cells to treat type 1 diabetes.

ViaCyte's initial approach was to immunoisolate their hES cell-derived pancreatic progenitor cells (PEC-01 cells) in a macroencapsulation device (Encaptra), where they matured into functional β -cells on implantation, consistent with the requirement for the in vivo maturation stage reported in earlier experimental studies.⁴ Subsequent refinements in macroencapsulation technology led to a preclinical trial using PEC-01 cells in the smaller VC-01 immuno-isolating device, which depended on diffusion across cell impermeant, semipermeable membranes for the movement of nutrients and insulin (<https://clinicaltrials.gov> NCT02239354). Although results were encouraging in terms of cell survival and maturation, the decision was made to modify the macroencapsulation device (VC-02) to allow the host vasculature to directly revascularize the graft to enhance engraftment and insulin production,⁶ albeit at the clinical cost of having to immunosuppress the graft recipients which is the current practice when transplanting primary human islets.¹

Two recent reports from a Phase 1 multicentre study using PEC-01 cells in the VC-02 revascularizing device described encouraging results which move the field closer to a wider therapeutic roll-out (NCT03163511).^{7,8} This study is ongoing and the report are of results from a limited number of participants in their first cohorts (17 and 15 respectively). The subcutaneous implants were well tolerated with only minor adverse effects, and mature endocrine cells were detected in >60% of cells in the devices after surgical retrieval. Circulating C-peptide was detected in a substantial number of previously C-peptide-negative graft recipients, consistent with the presence of mature β -cells. Importantly, some of these C-peptide-positive participants showed elevations in circulating C-peptide in response to a mixed meal test, indicative of nutrient-responsive insulin secretion from the engrafted cells.^{7,8} One study⁸ reported moderate clinical benefits with ~20% reduction in insulin requirements, 13% more time in target blood glucose range and improved hypoglycaemic awareness: The other study⁷ reported no statistically significant clinical benefit at the time of reporting, but attributed this to a likely insufficient number of engrafted cells. Nonetheless, both studies have demonstrated the capacity of pancreas progenitor cells derived from hES cells in vitro to survive and engraft in the VC-02 device in vivo, and to mature into functional, nutrient-responsive β -cells. ViaCyte now plans to address the issue of immunosuppression by gene editing their progenitor cells to evade recognition by the host immune system.⁹ They have recently announced a Phase 1 trial (NCT05210530) which, if successful, may enable the use of the VC-02 device without immunosuppressing the graft recipient.

Meanwhile, the glucose-responsive β -cells generated from hES cells in vitro by Melton's group^{2,5} have also entered Phase 1 clinical trials (NCT04786262). In a recent press release,^{10,11} Vertex Pharmaceuticals Inc. reported on the outcomes of the first participant from 17 to be recruited into a Phase 1/2 clinical trial of VX-880, described as a '*stem-cell derived, fully-differentiated pancreatic islet cell replacement therapy*'.¹⁰ The unencapsulated VX-880 cells were delivered via hepatic portal vein infusion, as for primary human islets, into the immune-suppressed participant. In contrast to Viacyte's PEC-01 cells in the VC-02 device, VX-880 cells delivered intraportally are ir-retrievable, so the ethical approval for this route of delivery presumably considered the teratogenic potential of pluripotent stem cells to be minimal in the VX-880 cells. The day 90 results were impressive: a 91% reduction in insulin requirement, HbA1c reduced from 8.6% to 7.2% and mixed meal test-responsive elevations in circulating C-peptide, indicative of successful engraftment and function of the implanted VX-880 cells. These remarkable clinical benefits are so far limited to one graft recipient and a relatively early time point, so it will be interesting indeed to see how effective VX-880 is in the remainder of the trial cohort.

So, in the space of a few months, we have proof of concept of the safety and (potential) efficacy of β -cell substitutes generated from pluripotent stem cells using two different strategies: subcutaneous implantation of immature progenitor cells in a revascularizing microencapsulation device⁷⁻⁹; or intraportal delivery of in vitro matured, glucose-responsive cells.^{10,11} Both approaches have advantages and disadvantages and we have no information yet about longer term effects, but the race is now on, and these are exciting times for β -cell replacement therapy: Two decades of intensive laboratory science are now translating into clinical trials which may soon open up the option of β -cell replacement to everyone with type 1 diabetes.

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