A future beyond insulin injections? Regenerative medicine for type 1 diabetes

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For people with type 1 diabetes, frequent blood glucose measurements and insulin injections are a part of daily life. While immensely beneficial, this is unfortunately an imperfect, time–consuming treatment with its own inherent risks. Over the last two decades, researchers have made significant strides in the development of alternative cell–based therapies that have the potential to circumvent the need for insulin injections. In particular, stem cells may be able to provide an infinite supply of insulin–producing cells for use in transplant therapies. Fierce pursuit of this technology is underway by research groups at academic institutions and biotechnology companies. These groups hope to apply regenerative medicine to type 1 diabetes, with the first clinical trials now in progress in Canada and the United States.

Background

In Canada, approximately 300,000 people are living with type 1 diabetes.[1] The most common age of onset is ten years old; however, onset can be at any age.[2] The condition is characterized by autoimmune destruction of insulin–producing pancreatic beta cells, leading to dysregulation of glucose homeostasis.[3] Beta cells are present in the pancreas in clusters of endocrine cells known as pancreatic islets. In humans, remarkably only approximately 1.3 grams of beta cells are responsible for regulating blood glucose for the whole body.[4] The small number of essential beta cells presents type 1 diabetes as an attractive target for cell replacement therapies.

Insulin–based therapies

Type 1 diabetes was not always managed by insulin injections. Canadian scientists Frederick Banting and Charles Best's discovery of insulin in 1922 led to the emergence of this treatment. Before their discovery, children who developed type 1 diabetes typically only lived for one to two years after diagnosis.[5] It is not an overstatement to say insulin injections have saved millions of lives.

However, insulin injections fall short of a cure. Among other challenges, quality of life is impaired, and over–administration of insulin can lead to life–threatening hypoglycemia. Newer products such as insulin–pumps and long–acting insulins are addressing some of the limitations of insulin injections, though even with these products a meticulous patient cannot achieve the ultimate goal of diabetes therapy: perfect regulation of blood glucose levels.[6] Therefore, the risk of long–term complications such as cardiovascular disease, neuropathy, and nephropathy cannot be fully eliminated by current insulin replacement therapies. Nevertheless, in 2016 the Food and Drug Administration (FDA) approved the first ever "artificial pancreas", a hybrid closed–loop insulin delivery system, for patients aged 14 and up.[7] This system monitors blood glucose and automatically administers insulin; however, it still requires users to input details about upcoming meals. Another therapeutic avenue under research is gene–based therapy. Gene–based therapies primarily involve *in vivo* viral delivery of genetic material to coax non–beta cells into producing insulin.[8] However, this approach is limited by the inability to perform controlled, multistep cell reprogramming as could be performed *in vitro*.

Regenerative medicine therapies

The idea to directly replace lost pancreatic beta cells, instead of lost insulin, drove research at the University of Alberta in 1990s. This lead to the development of the Edmonton Protocol. The Edmonton Protocol is a method to isolate pancreatic islets from a cadaveric organ donor and transplant them into a type 1 diabetes patient. This method has proven successful, with approximately 50% of patients remaining insulin–independent at five years post transplant.[9,10] While this method is limited by the scarcity of donors and challenges such the need for immunosuppressive drugs, it has established a precedent for cell–based diabetes therapies.

Building on this precedent, stem cells have the potential to serve as an alternative source of pancreatic beta cells for cell–based therapies.[11] The generation of beta cells from human stem cells is challenging, however, with the *in vitro* development of true beta cells remaining elusive.[12,13] The most recent major breakthroughs came in 2014, when two research groups in Canada and the United States independently published for the first time evidence of glucose–responsive insulin production in cells derived from stem cells.[14,15] These derived cells notably lacked several characteristics of human beta cells, such as the ability to rapidly turn off insulin production once glucose levels dropped. Nevertheless these "beta like" cells rapidly reversed diabetes when implanted into diabetic mice.

It remains unclear whether true beta cells are required for reversal of diabetes in humans, or whether insulin–producing "beta like" cells are sufficient.[8] ViaCyte, a clinical stage biotechnology company based in California, is using the latter strategy to differentiate allogeneic human embryonic stem cells into pancreatic progenitor cells, which are developmental precursors to beta cells. These pancreatic progenitor cells are loaded into a device for subcutaneous implant into a patient, anticipating final maturation of the cells to occur *in vivo*.[11,16] In 2014 this group launched a combined phase 1 and 2 clinical trial to evaluate the safety and efficacy of this therapy.[17] The trial is run from several locations, including the University of California San Diego and the University of Alberta, with the goal to treat over 50 patients. For now, this trial is limited to adults who have been living with a diagnosis of type 1 diabetes for several years. However, as their implantation device circumvents the need for immunosuppressive drugs, a similar therapy could eventually be suitable for youth as well.[18] More recently, ViaCyte has launched a second clinical trial to test an alternative non-immunoprotective device for cell delivery, tailored for patients at high risk for severe hypoglycemic episodes.[19] The University of British Columbia (UBC) is participating in this second trial, led by UBC endocrinologist Dr. David Thompson and based on research pioneered by UBC professor Dr. Timothy Kieffer.

While the results of these trials are awaited, researchers are also working to address other challenges associated with cell transplantation. In California, ViaCyte is employing cell encapsulation, a technique to

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immobilize cells in a semipermeable polymer, to isolate the cells from the immune system and to provide convenient cell retrieval. However, cell encapsulation also reduces blood supply, thus starving the transplanted cells of oxygen. Researchers are exploring methods to mitigate this issue by promoting vascularization within the encapsulation device. For example, Pepper et al. temporarily placed a vascular access catheter into a subcutaneous site to stimulate vascularization of the site prior to cell transplantation.[20] As well, researchers are exploring a strategy to mitigate the foreign body immune response by encapsulating cells with alginate, a polysaccharide derived from algae.[21-23] There is also ongoing investigation to identify the most optimal site for transplant.

The cost of a stem cell–based diabetes therapy could also prove to be a significant barrier to its usage. Islet cell transplantation by the Edmonton Protocol is estimated to cost $100,000 CAD per transplant, and it is likely a stem cell–based therapy would cost significantly more due to expenses related to the long and complex cell preparation procedure.[24] In 2017, the FDA approved the first ever chimeric antigen receptor–T cell (CAR–T) cell therapy to treat cancer, with a high price of $475,000 USD per patient.[25] Interestingly, this CAR–T therapy will employ a new "outcomes–based" pricing model, with the company only receiving reimbursement for patients who respond to the therapy. It is possible a similar policy could be applied to future stem cell–based diabetes therapies. Treatment prices may also decrease in the long–term with further manufacturing innovations. Regardless of the initial price of treatment, the lack of need for insulin injections following transplant, and a reduction in diabetes–associated complications could lead to significant long–term savings.

It is possible further basic science advances will be needed prior to progression to larger–scale clinical trials. There remains room for improvement in the stem cell differentiation protocol, with the goal to develop true beta cells *in vitro* still unrealized. Advancements in scale–up and manufacturing of cell–based therapies are also needed if the treatment is to be accessible to the millions of people living with type 1 diabetes worldwide. With the Edmonton protocol, clinicians observed a decrease in function of the transplanted cells after several years. Long–term clinical studies are therefore needed to assess if there are similar decreases in the function of stem cell–derived therapies. Also, if the need for lifelong immunosuppressive therapy were avoided, this would more readily allow the treatment of pediatric patients who are more susceptible to the side effects of such therapy. This could be achieved by immunoisolation of the transplanted cells, or by using autologous stem cells obtained from the patient instead of an allogeneic stem cell line.

For almost 100 years, insulin injections have been the mainstay of therapy for type 1 diabetes. While numerous challenges remain, it appears regenerative medicine may eventually replace insulin injections. It is exciting to see the large contributions of Canadian researchers to the field. Canadians played a key role in the discovery of insulin in 1922, the discovery of stem cells in 1961, and the development of islet transplantation in the 1990s. It is fitting that Canadians are now leading the development of stem cell–derived therapies for diabetes. Close collaboration by clinicians and expert scientists in the fields of stem cell biology, diabetes, biomaterials, and cell manufacturing will be essential moving forward to create an optimized final product that provides the greatest overall benefit to patients.

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