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Hope injections: the promises of regenerative medicine in curing type 1 diabetes mellitus

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LETTER TO THE EDITOR

One evening of 2006, my mother announced that scientists had made a groundbreaking discovery. By 2012, we would be having the first “vaccine” against type 1 diabetes mellitus (T1D), and so my chronic disease would finally come to an end. It was the most fascinating news I had heard as a 9-year-old.

T1D is a chronic autoimmune endocrine condition, caused by a faulty recognition of self and foreign antigens by the immune system[1]. It attacks the insulin-producing beta cells of the islets of Langerhans in the pancreas; insulin is a vital hormone for blood glucose control. Without it, patients must turn to insulin injections multiple times daily, adjusting doses to fluctuations in food, activity and numerous other

interdependent factors. Blood sugar monitoring is also imperative. But oftentimes, exogenous insulin will not act as deftly as the pancreas, causing the unpleasant symptoms and dangerous consequences of hypoglycaemia: fatigue, dizziness, trembling and even seizures and coma[2].

The truth is, life with T1D requires constant adaptation and planning ahead. I may not have known at the time, but walking out of the hospital with my diagnosis, I had acquired a monkey on my back, for life. Today, nearing the end of my medical studies, I realize that T1D management resembles applying evidence-based medicine 24/7. Contrarily to common belief, experience does not always automate management, while type 1 diabetic patients lead a life with the astonishing number of up to 180 extra health-related decisions per day[3]. Nutritional training and constant alertness are vital, day in, day out.

2012 came and went. Today, more than 1.25 million Americans are affected[4], a reality that seems odd, considering the massive accomplishments in Regenerative Medicine. Upon the recent outbreak of the COVID-19 pandemic, individuals with T1D have been reported to be at higher risk for severe illness[5] and in-hospital death[6] due to COVID-19. On top of that, the endocrine tropism of SARS-CoV2, the virus causing COVID-19, offers a potential explanation for the observed link between the infection and increased incidence of T1D[7]. Beyond health complications, for many low or middle-income countries (LMICs), and even for patients in high income countries with private healthcare systems, T1D constitutes a heavy financial burden, with essential insulin and technology often being unaffordable[8]. More often than not, physicians are faced with diagnostic challenges regarding the pathophysiological mechanism of diabetes mellitus. For example, some patients are erroneously diagnosed with T1D and treated with insulin, while having a different, rare form of monogenic diabetes: Maturity onset diabetes of the young (MODY), which often manifests with comparable clinical characteristics to T1D, but without an autoimmune origin. Genetic testing is required and treatment usually involves diet, sulfonylureas or metformin[9]. Evidently, MODY should be included in the differential diagnosis of every case of atypical manifestation of T1D.

Even though my medical background has now enabled me to grasp why unimagined roadblocks would not have allowed for a cure of T1D in 2012, the cumulative global progress seems poised to ultimately take the disease to meet smallpox in history books. Planning to specialize in diabetes research and management, I wish to contribute to finding a cure for the disease that has been my life's greatest challenge.

The leading strategy today is beta cell replacement, though only therapeutically available for a small fraction of patients [10-12]. It can be achieved by transplanting self or allogeneic stem cells, differentiated into specialized insulin-producers. Replenishing pancreatic islets will theoretically reverse the deficiency, but certainly, that is easier said than done. Difficulties appear from *in vitro* stages. The engineered beta cells often exhibit immature metabolism and insulin kinetics which deviate from the normal glucose-dependent secretion pattern. A key point, yet to be clarified, is whether the artificial islets should include beta cells only, or other endocrine islet cells, too. Embracing the idea that all these types of cells were phylogenetically preserved in adjacent sites advantageously, most protocols include integral islet-like clusters, but the optimal ratio remains an open question[13].

However, even if we inject the best, functional islets, there are further setbacks ahead. One risk is the development of malignancy, if incompletely differentiated cells are accidentally co-transplanted[14]. Moreover, transplants can be

immunogenic, meaning that, the immune system will lurk on two sides. The new cells might be *different enough* from the host's to provoke an allogeneic rejection response, or *similar enough* to trigger the autoimmunity roller-coaster again[15]. So far, the only option has been immunosuppression, with the well-known severe risk of susceptibility to infections and malignancy[16].

An elegant alternative is wrapping transplants in immune-proof devices (macro-encapsulation) or hydrogel-based biomaterials serving as molecular coats (micro-encapsulation) [17-19]. Yet, it remains a bioengineering challenge, as the desirable composition must be impermeable to attack, but permissive to the secretion of insulin and the exchange of oxygen and nutrients. Over time, capsule architecture has been debated. Previously, microcapsules were larger than islets, allowing poor contact. Improved designs have now hit the labs, able to wrap around islets and conform to their shape and size[19,20].

Even without coats, transplants can be processed with the help of gene-editing tools such as CRISPR-Cas9 to "ninja cells", which are devoid of surface proteins and evade immune recognition and attack[21]. These might have another advantage: They could constitute universal cell donors, with minimal immunogenicity, taking us closer to industrial islet production. However, escaping immune surveillance must not be taken too far: If cell division aberrations occur, the immune system would not be able to prevent malignancy stemming from the transplants. Subsequently, scientists are attempting to add a suicide protein, activated upon administration of a certain drug, to serve as a safety valve[22].

Moving from disguise to adaptation, immunomodulation trials have been in place[23], and may reduce the need for immunosuppression more promptly than encapsulation. Such an agent, Teplizumab, has reached final stages in multinational clinical trials[24], both to reverse overt T1D, and to prevent clinical manifestation in individuals at-risk of developing it, meaning siblings of T1D patients with a considerable titer of islet-specific autoantibodies but so far preserved islet function[25].

But where to plant our little insulin factory? So far, experiments have involved the omentum (a large membrane covering the intestines), subcutaneous tissue and the portal vein, as locations differ in their ability to generate vasculature[22]. Especially the portal vein, although a convenient choice for transplantation, entails exposure of the islets in maximum concentrations of nutrients and drugs, as per human physiology, and that can be harmful to cells used to surviving protected in the pancreas. Another interesting approach involves the interaction of islets with the host microbiome[26]. Among other institutions, the Joslin Diabetes Center is testing this, after their striking Medalist Study revealed a percentage of patients, who were somehow protected against complications, after 50 years with the disease[27]. This leads to the hypothesis that Precision Medicine may have an important role in creating effective cures. As exciting as it may sound, it introduces a new level of challenge, with growing evidence that T1D immunopathology varies among patients[9]. Table 1 shows a summary of the main therapeutic targets and approaches to restore or preserve beta cell function in T1D currently under laboratory development or in clinical trials, discussed in this article.

Nevertheless, while we wait for definitive therapies, we luckily have the technologies of continuous glucose monitoring (CGM) and insulin pumps making life with T1D easier[28]. Still, as exquisite as they are, they entail a heap of information for the patient. The dual-hormone iLet Bionic Pancreas pump seems like an "external electronic version" of our previously described mixed-cell islet: Along with insulin, the pump delivers glucagon - the insulin counteracting hormone, micro-adjusting their balance every

few minutes, just like a real pancreas. Its goal is to automate glucose control and it may soon enter the market, now that the stability of glucagon in room temperature is finally optimized[29].

Overcoming all these diverse obstacles may be frustrating, but the concepts we are now handling seemed like science fiction twenty years ago. I speculate that the cure, once perfected, will seem to future generations like Oedipus' solution to the riddle of the Sphinx: a solution so sensical, which however, only he was able to conceptualize. A prominent scientist devoted his career to T1D research after his two children were inflicted[30]. My life motto will be his answer when asked whether he thinks we will find a cure: "I am not going to give up until we do". In fact, I already feel as part of the efforts of the T1D scientific community. When reading original research and hitting the key message, a little internal voice shouts "Eureka!", as if it were my own discovery to celebrate. These are hope injections, and thankfully they don't hurt.

Eventually, my disease came with an appreciation that healthy individuals own a miraculous pancreas. Still, while life-threatening[31], T1D is manageable. Interning in hospitals, I often see fatally ill patients, inflicted with ailments that can be destroyers. But me? I have the precious chance to fight. My gift was the inexhaustible desire for a cure, combined with the physical and mental ability to search for one.

My fervent hope is that someday, I will be privileged to know life without diabetes[32]. It is also that my patients will, too. I view my challenge as to continuously evolve *from a chronic worrier to a chronic warrior*, as one of my mentors put it. Can a system with such complexity be modified to work harmoniously, with no component falling short? The tools are all on our hands, and we are only facing an "assembly" puzzle. Personally, I can see myself tightening some screws, as we make this dream reality.

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Table 1 **Main therapeutic targets and approaches to restore or preserve beta cell function in T1D currently under laboratory development or in clinical trials**

Target	Approach
Islet cell replacement	Transplantation of embryonic, mesenchymal or induced pluripotent stem cells in various stages of differentiation into pancreatic islets
Protection from immune destruction	Micro- or macro- encapsulation
Development of minimally immunogenic transplants	Transplant cell engineering through gene editing
Mitigation of autoimmunity in T1D confirmed patients Prevention of clinical disease for at-risk individuals	Selective immunosuppression – immunomodulation (eg, Teplizumab)

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