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Editorial

Islet Transplantation: How Much Have We Advanced and How to Keep Moving Forward?

Braulio A. Marfil-Garza [1], Tatsuya Kin [1, 2, *]

1. Clinical Islet Transplant Program, University of Alberta, Edmonton, Alberta, Canada; E-Mails: marfilga@ualberta.ca; tkin@ualberta.ca
2. Alberta Islet Distribution Program, Clinical Islet Laboratory, Edmonton, Alberta, Canada

* **Correspondence:** Tatsuya Kin; E-Mail: tkin@ualberta.ca

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Special Issue: Current Advancement of Islet Cell Transplantation in the Treatment of Diabetes Mellitus

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As we celebrate the 100th anniversary of the discovery of insulin and reflect upon the myriad medications and technologies that are now part of the therapeutic arsenal to tackle diabetes, it is inevitable to ask whether a cure for this devastating disease is in the cards for humanity. To date, the closest resemblance to a cure can only be achieved with β-cell replacement therapies, including islet transplantation. This therapy has been in continuous refinement for more than half a century and is now able to consistently improve quality of life by improving glycemic control and, in many cases, enable insulin independence. However, many challenges remain for its widespread application.

This special issue of ***OBM Transplantation***, entitled **"Current Advancement of Islet Cell Transplantation in the Treatment of Diabetes Mellitus"**, comprises a broad and timely collection of articles of key relevance in the field of islet transplantation and β-cell replacement therapies. Overall, the included works focus on four main themes: 1) advances and remaining challenges with islet isolation, 2) cellular, molecular, and physiological characterization of cellular products for

transplantation, 3) current issues with pre-, peri- and post-transplant care, and 4) strategies to optimize islet transplantation and advance novel β-cell replacement therapies. Herein, we provide a brief synopsis of the works included in this special issue.

1. Advances and Remaining Challenges with Islet Isolation

An important aspect to advance islet transplantation concerns the process of islet isolation. Although islet isolation protocols have advanced considerably over the last 30 years, there are several areas of opportunity to improve islet quality and quantity. In this special issue, a comprehensive multicenter and multi-year report by Scharp et al. [1] summarizes several factors that have been shown to be consistently associated with improved islet yield, as well as insulin responsiveness and content, including active enzyme digestion time (i.e., switch time), older age and longer ischemia time. This relevant work by Sharp et al. challenges the notion that islet isolation techniques have 'reached their peak' and are unlikely to be amenable to substantial improvements. McCarthy et al. [2] present an outstanding review striving to correlate biochemical characteristics or doses of collagenases and proteases to islet yields following an islet isolation. The authors provide a comprehensive framework of advances to foster an understanding of how collagenases and proteases enable the release of islets from the pancreas. Importantly, this framework could also serve as a foundation for further development of a model for optimal enzymatic tissue dissociation and based on these concepts, the authors concisely outline potential future directions for research. Overall, the works by renowned figures and experts in the field such as Scharp et al. and McCarthy et al. constitute indispensable and extremely valuable resources for novice, but also seasoned specialists working in islet isolation.

2. Cellular, Molecular, and Physiological Characterization of Cellular Products for Transplantation

While recent reports on long-term clinical outcomes following islet transplantation are emerging [3-7], there is a lack of characterization of the islets before and after transplant. Dissecting these aspects is vital for the development and implementation of novel β-cell replacement therapies. In this regard, two timely articles are provided in this special issue. In their review on islet identity in transplantation procedures, Beamish and Sabek [8] succinctly dissect current evidence on β-cell heterogeneity, and the importance of islet cell characterization in terms of their genetic programs and how these could determine function after transplantation. The authors also discuss the role and implications of cellular differentiation in normal and pathophysiological states, including the post-transplant period. A common theme among these phenomena concerns metabolic stress (e.g., islet isolation, insulin resistance, etc.), and the authors propose several ways to tackle this, highlighting an interesting and relatively unexplored pathway involving osteocalcin. On the other hand, Holzer et al. [9] provide a concise discussion on the potential of microfluidic devices as tools to study the physiology and pathophysiology of human islets, as well as their individual cells. In this review, the authors elaborate on basic principles for device design and fabrication. Further, they describe contemporary technologies, current challenges, and limitations, while simultaneously introducing future applications, as well as specific directions to move forward.

3. Current Issues with Pre-, Peri- and Post-transplant Care

Many centers worldwide are rapidly gaining experience with islet transplantation. Hence, clinical outcomes are improving globally. However, there are several unanswered questions regarding the pathophysiological events occurring at the pre-, peri- and post-transplant moments. In this regrad, Shindo and Kanak [10] discuss the deleterious events impacting islets along the process of transplantation, including enzymatic and mechanical stress, cytokine-mediated injury, ischemic- and hypoxia-mediated cell death, peri-transplant inflammation, allo- and autoimmune responses, as well as immunosuppression-induced β-cell toxicity. Furthermore, the authors synthesize past and ongoing efforts to tackle these issues, including clinical trials. Similarly, Quintana et al. [11] elaborate on chemical strategies to improve islet transplant outcomes and provide a thorough and well-referenced recapitulation of molecular therapeutics and encapsulation strategies to protect islets from innate and adaptive immune responses. Finally, Darden et al. [12] contribute with a more focused review on the innate and adaptive immune responses and their impact on long-term graft function. It is an unequivocal fact that a comprehensive knowledge of the issues surrounding the initial inflammatory processes and immune responses is indispensable for researchers and clinicians working in islet transplantation and the works of Shindo and Kanak, Quintana et al., and Darden et al. represent an excellent starting point.

The following articles in this theme introduce two somewhat unexplored issues with peri- and post-transplant care following total pancreatectomy and autologous islet transplantation (TPIAT): *de novo* onset of autoimmunity and the potential for portal hypertension. Ali et al. [13] present two cases in which β-cell autoimmunity developed months following a TPIAT. In these cases, sudden deterioration of graft function was accompanied by elevated titers of typical β-cell autoantibodies (i.e., GAD, insulin, and islet cell), which were previously negative. The authors present a review of the literature and advocate for routine autoimmune testing in patients who present with a rapid worsening of glycemic control following TPIAT. It is unknown whether any potential interventions could be implemented in such cases, however, it reinforces the notion that inflammatory and innate immune responses might facilitate autoimmune recurrence. Regarding the impact of TPIAT on portal vein pressure, Lim et al. [14] report the first case of persistent non-cirrhotic portal hypertension presenting with hematemesis from variceal bleeding occurring two years after this procedure. With this report, the authors identify another area of research to be explored in future studies including patients undergoing TPIAT, but that could also have some repercussions for allogeneic islet transplantation, specially because these patients typically receive multiple infusions, which could put them at a potential risk of portal hypertension.

4. Strategies to Optimize Islet Transplantation and Advance Novel β-cell Replacement Therapies

The future of islet transplantation demands that researchers and clinicians push the limits of what is possible. As a final theme in this special issue, connotated researchers in the field propose several approaches to advance cutting edge technology and novel surgical techniques, as well as potentially limitless sources of tissue for β-cell replacement therapies. In an exhaustive review of the literature, Coughlan et al. [15] provide a balanced assessment of the current evidence with extrahepatic islet transplantation, including past and ongoing clinical trials. This article underscores the fact that, whilst preclinical evidence shows efficacy, much work remains for the successful clinical translation of extrahepatic islet transplantation. In this regard, Sato et al. [16] present new

preclinical data supporting the pancreatic parenchyma as a potential site for islet transplantation, which is a relatively unexplored approach.

In terms of improving accessibility to islet transplantation and β-cell replacement therapies, there are two approaches that are discussed in this special issue. First, consolidated researchers Shimoda and Matsumoto [17] present their expert review of the history and current progress with islet xenotransplantation and provide valuable insight into future directions. Second, Chhabra and Brayman present a well-rounded and rich discussion on cell-based approaches to advance β-cell replacement therapies, including the use of mesenchymal stem cells and pluripotent embryonic and inducible stem cells, while also elaborating on a key aspect that remains to be fully explored, the potential immunogenicity of autologous stem cell-derived β-cells.

Finally, Lv et al. [18] contribute with a thought-provoking review exploring the possibility of developing a combined bio-artificial system including a pancreatic islet graft and an automated insulin delivery system. Beyond a discussion of the literature, the authors introduce *in silico* studies using FDA-approved platforms and simulate post-transplant glycemic patterns and the impact of automated insulin delivery control strategies according to different levels of islet graft function. It should be emphasized that both islet transplantation and automated insulin delivery systems can be complementary in the management of patients with diabetes and severe hypoglycemia, particularly during the early post-transplant period. However, further research is needed to validate the proposed models, but also define the patient's perspectives regarding this combinatorial strategy.

Overall, the works compiled in this special issue in OBM Transplantation provide an up-to-date and fresh outlook on the ongoing and future challenges with islet transplantation. The interested readers will certainly encounter a curated collection of articles that provide an excellent platform and starting point to revise established paradigms in the field and develop novel strategies to advance islet transplantation as a true cure for diabetes.

Author Contributions

Braulio A. Marfil-Garza drafted the manuscript. Tatsuya Kin critically revised the manuscript.

Competing Interests

Braulio A. Marfil-Garza and Tatsuya Kin declare no conflict of interest with regard to this article.

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