www.idosr.org Mangen, 2025
©IDOSR PUBLICATIONS
ISSN: 2550-7931
International Digital Organization for Scientific Research IDOSRJAS1020000
IDOSR JOURNAL OF APPLIED SCIENCES 10(2):16-22, 2025.
https://doi.org/10.59298/IDOSRJAS/2025/102.1622

Beta-Cell Regeneration and Stem-Cell-Derived Islet Transplantation

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ABSTRACT

Diabetes mellitus, particularly type 1 diabetes (T1D), results from a loss or dysfunction of insulin-producing pancreatic β-cells. Restoration of β-cell mass and function remains a major therapeutic goal. Two complementary strategies hold promise: endogenous β-cell regeneration, through stimulating proliferation, neogenesis, or transdifferentiation, and exogenous replacement using stem-cell-derived islet (SC-islet) transplantation. This review synthesizes recent advances in both areas, delineates key challenges including functional maturation, immune rejection, scaling, and safety, and explores bioengineering and immunomodulatory strategies designed to enhance outcomes. It examines in vitro differentiation protocols, in vivo regeneration stimuli, results from preclinical and early clinical trials, and technological innovations such as encapsulation, immune evasion, and gene editing that may help make SC-islet replacement a safe, durable therapy. Finally, future research directions are proposed to guide progress in this field.

Keywords: β-cell regeneration; Stem cell-derived islets; Transplantation immunomodulation; Differentiation and maturation; Type 1 diabetes therapy

INTRODUCTION

The pancreatic β-cell is a central regulator of glucose homeostasis because it senses changes in blood glucose levels and secretes insulin in response. In type 1 diabetes, autoimmune destruction of β-cells leads to absolute insulin deficiency[1]. In advanced type 2 diabetes, dysfunction and loss of β-cells also contribute to impaired insulin production. The current standard of care, consisting of exogenous insulin delivery, glucose monitoring, and lifestyle interventions, has saved countless lives but does not replicate the fine control exerted by native β-cells[2–4]. Patients remain at risk of both acute hypoglycemia and chronic complications despite therapy. This has created strong interest in strategies that can restore endogenous insulin production by regenerating or replacing β-cells[5, 6]. Endogenous β-cell regeneration represents one major therapeutic pathway. The idea is to stimulate the body's own capacity to generate or replenish β-cells, either by inducing existing β-cells to replicate, promoting neogenesis from progenitors, reprogramming other pancreatic cell types into β-cells, or guiding dedifferentiated cells back into their insulin-secreting state. Research in animal models demonstrates that β-cells can replicate under conditions of high demand such as pregnancy, obesity, or partial pancreatectomy[7]. Molecular signals, transcription factors, and epigenetic regulators have been identified that influence this process. However, spontaneous regeneration in humans is limited, and translating these findings has been difficult. Key hurdles include the risk of uncontrolled cell proliferation, the challenge of preserving functional competence, and the need to protect regenerated cells from autoimmune destruction in T1D[7–9].

Exogenous replacement represents a second promising avenue. For decades, islet transplantation from cadaveric donors has been attempted with some success, allowing recipients to achieve insulin independence. Yet donor scarcity, variability in islet quality, immune rejection, and the burden of lifelong immunosuppression have limited its widespread application[10]. This has driven interest in generating β-cells or islet-like clusters from stem cells, whether embryonic stem cells or induced pluripotent stem cells. Stem-cell-derived islets promise an essentially unlimited source of cells, the potential for autologous or genetically matched grafts, and the opportunity to engineer cells for improved survival and immune evasion[11].

Over the past decade, protocols have been refined to direct pluripotent cells through pancreatic developmental stages into endocrine lineages that include insulin-producing cells. The quality of these stem-cell-derived β-cells has improved considerably, with many now capable of glucose-responsive insulin secretion. In animal models, transplanted SC-islets can normalize blood glucose[12]. Nevertheless, significant issues remain. Many cells retain fetal-like characteristics, with less robust metabolic capacity and slower secretory dynamics

compared to mature human β-cells. Immune rejection, autoimmunity, hypoxia, inflammation, and vascularization challenges further limit outcomes. Production must also meet rigorous safety standards, avoiding tumorigenic cells and ensuring genetic stability[13].

At the same time, advances in bioengineering have created opportunities to improve outcomes. Encapsulation devices and immune-protective scaffolds have been developed to shield transplanted cells. Co-transplantation with endothelial or mesenchymal cells may enhance vascularization and survival[14–16]. Extracellular matrix scaffolds and gene editing strategies offer further ways to optimize integration and reduce immunogenicity. First-generation clinical trials of SC-islet products have begun, providing early safety and feasibility data. Lessons from pancreas and islet transplantation continue to shape expectations regarding optimal sites of implantation, graft monitoring, and patient-relevant outcomes such as insulin independence and avoidance of severe hypoglycemia[17].

This review focuses on recent progress in endogenous β-cell regeneration and stem-cell-derived islet transplantation. It evaluates the biological principles, current successes, limitations, and future directions of each approach. Together, these efforts form a dual pathway toward therapies that could restore physiological insulin production and transform diabetes management.

Endogenous β-Cell Regeneration: Mechanisms, Challenges, and Therapeutic Prospects

Endogenous β-cell regeneration refers to strategies aimed at stimulating the pancreas to replenish its own insulin-producing β-cell mass, thereby restoring glucose homeostasis without the need for transplantation. This concept is highly attractive because it seeks to mobilize the body's intrinsic repair mechanisms rather than relying exclusively on exogenous cell replacement[18, 19]. Several potential mechanisms for β-cell regeneration have been proposed, each supported by varying degrees of experimental evidence, but all face significant biological and translational challenges.

Self-Replication of Existing β-Cells

The most direct and well-documented mechanism of β-cell regeneration is the replication of existing β-cells. This has been observed robustly in rodent models, particularly during periods of increased insulin demand such as pregnancy, obesity, and insulin resistance. In these states, β-cells re-enter the cell cycle and undergo proliferation, expanding islet mass to meet metabolic needs[20]. Molecular pathways regulating this process include cyclins and cyclin-dependent kinases, growth factor signaling cascades such as insulin-like growth factor (IGF) and epidermal growth factor (EGF), and nutrient-sensitive pathways such as mTOR and Wnt. Epigenetic regulators and chromatin remodeling factors also play roles in modulating β-cell plasticity and proliferative potential[21–23]. However, in adult humans, baseline replication rates of β-cells are extremely low, estimated at less than 0.5% per day. Attempts to pharmacologically stimulate replication have achieved only modest success[24, 25]. Compounds that push β-cells into the cell cycle often raise concerns about long-term safety, particularly the risk of uncontrolled proliferation or tumorigenesis. Furthermore, induction of proliferation can compromise specialized β-cell functions, such as glucose-stimulated insulin secretion, if cells fail to redifferentiate fully after division[26]. Thus, while self-replication remains a promising avenue, strategies must carefully balance proliferative drive with maintenance of mature β-cell identity and function.

Neogenesis from Progenitor Niches

A second proposed mechanism of β-cell regeneration is neogenesis, defined as the formation of new β-cells from pancreatic progenitor cells or from the ductal epithelium[27]. During embryonic development and early postnatal life, neogenesis plays a major role in building the β-cell population. Lineage-tracing studies in animal models suggest that a degree of progenitor activity may persist into adulthood, particularly following pancreatic injury. However, the extent of this contribution in adult humans remains hotly debated.[28] Some studies show ductal markers associated with new islet formation, while others argue that replication of existing β-cells, not neogenesis, accounts for most expansion in adult tissues.

Therapeutically, activating progenitor niches in situ would offer a major advantage, as it bypasses the need for transplantation and instead reactivates intrinsic developmental programs. Yet this approach requires precise control of signaling pathways such as Notch, Hedgehog, and Hippo, which govern differentiation and lineage allocation during pancreatic organogenesis. Because these pathways are incompletely understood in the adult context, efforts to harness neogenesis risk producing immature, dysfunctional, or non-β endocrine cells. Greater insight into the regulation of progenitor plasticity is essential before this mechanism can be clinically viable.

Trans differentiation of Non-β Pancreatic Cells

A third mechanism involves trans differentiation, where other pancreatic cell types are converted into insulin-producing β-like cells[29]. Experimental models have shown that α-cells, δ-cells, and ductal cells can be reprogrammed into β-like cells by altering transcriptional and epigenetic programs. Key transcription factors, including PDX1, MAFA, and NEUROG3, play central roles in this reprogramming process. Inflammatory or metabolic stress environments may also enhance cellular plasticity and facilitate fate switching[30].

In rodent studies, forced expression of β-cell transcription factors has generated insulin-secreting cells capable of improving glycemic control. Nonetheless, in humans, evidence for efficient and durable trans differentiation remains limited. Questions remain about the stability of reprogrammed cells, their capacity for long-term

survival, and whether they achieve the functional sophistication of native β-cells, including glucose-sensing and pulsatile insulin secretion[31, 32]. Moreover, large-scale conversion of α-cells could disrupt glucagon regulation, leading to dangerous hypoglycemia. Thus, while trans differentiation offers conceptual appeal, translation into safe and effective human therapies requires significant refinement.

Preserving Functionality and Identity

Beyond generating new β-cells, regenerative strategies must ensure the survival and proper functioning of both newly formed and existing β-cells. This is particularly challenging because β-cells in diabetes are subjected to multiple stressors[33]. In type 1 diabetes (T1D), autoimmune destruction by T cells and autoantibodies remains the dominant barrier, while in type 2 diabetes (T2D), metabolic, oxidative, and inflammatory stress progressively impair β-cell health. Stress-induced dedifferentiation, in which β-cells lose their specialized identity and revert to a more progenitor-like state, further reduces insulin secretory capacity[12, 34–36]. Preserving β-cell identity, protecting cells from immune attack, and enhancing resilience to metabolic stress are therefore critical components of any regeneration strategy.

Current Progress in Human β-Cell Proliferation

Despite these obstacles, significant progress has been made in identifying factors that can stimulate human β-cell proliferation. Small molecules such as harmine, a DYRK1A inhibitor, and related analogues have been shown to induce replication in vitro and in animal models[37]. Growth factors, incretin mimetics like GLP-1 receptor agonists, and systemic proteins such as SerpinB1 have also been implicated in promoting β-cell survival and expansion. In addition, signals from endothelial cells, stromal components, and immune niches appear to influence β-cell regenerative potential, pointing toward the importance of the microenvironment[38].

Nevertheless, the magnitude of regeneration achieved in human systems remains modest. New β-cells generated in vitro or in vivo often fail to undergo full functional maturation, limiting their ability to dynamically secrete insulin in response to glucose fluctuations. Moreover, safety concerns remain paramount: agents that promote proliferation could inadvertently increase the risk of neoplasia, while immune rejection or autoimmunity could quickly destroy regenerated cells in T1D patients[39]. Delivering regenerative stimuli specifically to the pancreas without affecting other organs remains another technical challenge.

Translational Outlook

The concept of harnessing endogenous β-cell regeneration is compelling because it offers a potentially lifelong, self-sustaining therapy for diabetes. However, translation from preclinical discovery to clinical application is hindered by several unresolved issues [40]. These include species differences between rodents and humans, limited replication efficiency in human islets, the difficulty of controlling complex developmental pathways, and safety concerns surrounding long-term proliferative induction. Advances in drug delivery systems, gene editing tools, and immunomodulatory therapies may help overcome some of these barriers. In parallel, improved in vitro human islet models and single-cell profiling technologies are expanding our understanding of β-cell biology, offering insights into how regeneration might be more effectively stimulated[41, 42].

Endogenous β-cell regeneration encompasses a spectrum of mechanisms—self-replication, neogenesis, and transdifferentiation that together offer promising routes to restore insulin-producing capacity[43]. Yet, each mechanism faces substantial biological and translational hurdles. To realize the therapeutic potential of this approach, future research must integrate insights from developmental biology, regenerative medicine, immunology, and bioengineering to design interventions that not only generate new β-cells but also preserve their long-term survival and functionality[44]. While substantial progress has been achieved, the journey from concept to clinic remains ongoing, and endogenous regeneration should be viewed as a frontier area of diabetes therapy rather than an imminent clinical reality.

Stem-Cell-Derived Islet Transplantation: Advances, Barriers, and Future Directions

Stem-cell-derived islet transplantation has emerged as one of the most exciting avenues for diabetes therapy, aiming to provide patients with functional insulin-producing cells through exogenous replacement. Differentiation protocols for embryonic stem cells and induced pluripotent stem cells have improved substantially[45]. By guiding pluripotent cells through pancreatic developmental stages, researchers now routinely generate insulin-positive cells with measurable glucose responsiveness[45]. These cells not only express insulin but also improve glycemic control in animal models once transplanted. Importantly, maturation often continues after transplantation, with cells acquiring more adult-like functionality in vivo.

The progress achieved has paved the way for clinical translation. Early human trials of stem-cell-derived β-cell products are underway, focusing on safety, engraftment, and reduction of insulin requirements[46]. Parallel advances in bioengineering are enhancing the potential of transplantation. Encapsulation devices are being developed to shield grafts from immune attack while allowing diffusion of oxygen, nutrients, and insulin. Other approaches include genetic engineering to reduce immunogenic markers, co-transplantation with vascular or mesenchymal support cells, and scaffolds that mimic the native pancreatic niche[47].

Despite these achievements, barriers remain. One major problem is the functional immaturity of many stem-cell-derived β-cells. While capable of secreting insulin, their response to glucose is often slower and less robust than that of adult human β-cells. Metabolic coupling pathways remain underdeveloped, and differentiation

outcomes vary significantly across cell lines, creating variability in quality[48]. Immune rejection is another central issue. Transplanted SC-islets face allogeneic rejection as well as recurrence of autoimmunity in T1D patients. Lifelong immunosuppression is not a practical solution, given associated risks. Encapsulation and immune engineering strategies offer hope but can impair vascularization and oxygen supply, limiting long-term viability[49].

The transplantation site itself is a critical determinant of success. Traditional sites such as the hepatic portal vein expose cells to inflammatory stress and poor oxygenation. Alternative sites and engineered vascularized scaffolds are being explored to provide better environments. Additionally, scaling production for widespread use demands robust good manufacturing practice pipelines. Cells must be generated at large scale with consistent quality, avoiding contamination with undifferentiated cells that could form tumors. Genetic and epigenetic stability must also be ensured to minimize risks[50].

Beyond biological hurdles, regulatory, ethical, and cost issues complicate implementation. Embryonic stem cell sources raise ethical concerns, while iPSCs mitigate some issues but carry risks related to reprogramming and epigenetic memory. Regulatory approval for cell therapies is complex, and manufacturing and transplantation costs may limit patient access[51, 52].

Future progress will depend on continued refinement of differentiation protocols to produce consistently mature β-cells. Incorporating supporting niche cells and optimizing environmental conditions may further enhance outcomes. Immune protection strategies must strike a balance between graft survival and immune tolerance. Identifying optimal transplantation sites, developing non-invasive monitoring tools, and establishing reliable biomarkers of graft health will also be important. Clinical trials will need to demonstrate long-term efficacy, durability, and patient-centred outcomes such as sustained insulin independence and protection from hypoglycemia. The ultimate goal is to combine biological advances with engineering, immunology, and clinical innovation to produce therapies that are safe, scalable, and accessible.

CONCLUSION

Beta-cell regeneration and stem-cell-derived islet transplantation are complementary strategies that hold significant promise for the treatment of diabetes. Regeneration strategies appeal because they would repair the pancreas in situ and may involve fewer complications related to transplantation and immune rejection. However, their capacity in humans remains limited and is unlikely to produce sufficient functional β-cells without additional support. Stem-cell-derived islets, in contrast, can supply large numbers of insulin-producing cells and are already entering clinical testing, but they face barriers related to maturation, immune rejection, safety, and cost. The pathway to clinical success will require fully mature SC-β cells, effective immune protection without toxic systemic immunosuppression, robust vascularization and survival, and scalable manufacturing pipelines that ensure safety and consistency. Ethical, regulatory, and economic concerns must also be addressed. Advances in developmental biology, stem cell science, immunology, and bioengineering are converging to bring this vision closer to reality. Together, β-cell regeneration and SC-islet transplantation provide a roadmap toward restoring physiological insulin production and improving the lives of individuals with diabetes.

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CITE AS: Mangen Joshua Fred (2025). Beta-Cell Regeneration and Stem-Cell-Derived Islet Transplantation. IDOSR JOURNAL OF APPLIED SCIENCES 10(2):16-22, 2025.
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