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Review Article

The Future of Type 1 Diabetes: Can Stem Cells Provide a Cure?

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Abstract

Type 1 diabetes (T1D) develops when the immune system targets and destroys pancreatic β-cells responsible for insulin production, ultimately resulting in reduced insulin levels. Islet transplantation has garnered significant attention as a potential treatment, but it presents numerous challenges that hinder its effectiveness for T1D patients. A primary issue is the immune system's tendency to reject transplanted islets, leading to a gradual decline in their functionality. Furthermore, many individuals remain reliant on additional insulin therapy. These challenges are exacerbated by the global shortage of organ donors, which limits the availability of pancreata for transplantation. This review outlines several innovative strategies to regenerate insulin-producing β-cells for the treatment of T1D, with a primary focus on pancreatic progenitor and stem cells. The strategy of converting non-β cells, particularly pancreatic α-cells, into functional β-cells continues to show promise. Moreover, α-cells, which are less vulnerable to autoimmune attacks, present a distinct opportunity for β-cell regeneration in individuals with T1D. While the use of progenitor or stem cells for β-cell regeneration appears encouraging, various hurdles, such as immune rejection, suboptimal differentiation, and other challenges, still impede the implementation of this strategy. Nonetheless, this approach may ultimately pave the way for long-lasting treatment and potential cures for T1D.

Introduction

Type 1 diabetes (T1D) is an autoimmune disorder in which the immune system mistakenly attacks and destroys the β-cells in the pancreas that are responsible for producing insulin, resulting in inadequate insulin production.[1–3] The immune system often targets insulin itself or components that are essential for its synthesis, like pre-proinsulin, the insulin precursor.[4,5] Moreover, a combination of environmental and metabolic factors, along with genetic and epigenetic factors, contributes to the initiation and progression of this autoimmune response.[6–8] Its distinctive feature is this immune-mediated destruction of pancreatic β-cells.[1–3] Therefore, a person diagnosed with T1D requires continuous insulin therapy.[9] Hyperglycemia, or an increase in glucose in the blood without the conjunction of insulin, can result in a lethal condition known as diabetic ketoacidosis.[10,11] Although T1D is traditionally considered a childhood disease, more than half of the new cases now occur in adults, with diagnoses spanning from early childhood to well into middle age.[12,13] It is crucial to distinguish between T1D and type 2 diabetes, since type 2 diabetes primarily affects older individuals and is characterized by an initial insulin resistance instead of a complete absence of insulin.[14,15] Interestingly, in T1D, the immune system attacks β-cells only, leaving glucagon-producing α-cells unaffected.[16,17] Non-β cells may have innate resistance to autoimmune attack, making them suitable for transformation into β-cells by innovative techniques to promote evasion from autoimmunity.[18–20] In simple terms, the immune response affects specific types of cells, namely β-cells, confirming that the autoimmune mechanism in T1D has a degree of selectivity that can be utilized for future treatment approaches. In this context, the immune system's rejection of the recipient of transplanted cells poses a significant challenge to established treatments such as islet transplantation (IT).[21,22] This immune response can result in a gradual reduction of islet function over the subsequent years, and it may also prevent certain individuals from fully reducing their reliance on exogenous insulin therapy.[23,24]

Moreover, the worldwide shortage of organs is a major challenge that hampers progress in pancreatic IT. Annually, around 8,000 organ donations take place, yet fewer than one-third of the pancreases are considered suitable for transplantation.[25,26] Although IT can provide a provisional solution for T1D, it necessitates the administration of immunosuppressive drugs to prevent graft rejection.[27,28] However, these immunosuppressants can cause

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lymphopenia, which is associated with increased serum levels of the cytokines interleukin (IL)-7 and IL-15, contributing to the *in vivo* proliferation of autoreactive clusters of differentiation (CD) 8^+ T cells.[29,30] The resurgence of autoreactivity is likely a significant factor behind the long-term failure of islet transplants. Graft rejections, under normal circumstances, typically involve an immune response directed against donor antigens. However, in the case of T1D, the resurgence of autoimmunity is fundamentally different from these occurrences and indicates the reactivation of autoreactive T cells targeting self-antigens in the graft, thereby signifying another resurgence of the disease's original pathogenic mechanisms. In other words, rather than the typical rejection of foreign tissue, the immune system could activate the dormant autoimmune process that originally caused β-cell destruction in T1D. This revival of autoreactive immune responses likely plays a role in the eventual failure of the islet grafts.[31,32] It also underscores the complex immunological landscape that needs to be managed to achieve successful and lasting IT outcomes.

In light of these challenges, researchers are increasingly investigating the potential of pancreatic stem or progenitor cells to produce immune-tolerant β-cells, making them a logical option for T1D patients with autoimmunity. To elaborate, multiple experimental findings indicate that, under specific culture conditions or when triggered by key transcription factors, these progenitor cells can produce functional β-like cells that release insulin in response to glucose.[33–35] Moreover, there is a growing focus on whether stem cell-derived β-cells are more resilient to immune attacks or can be designed to promote immune tolerance.[36–38] Thus, immune modulation through stem cell-based approaches could help alleviate immune attacks, aiming to restore β-cell function and address the fundamental autoimmune response seen in T1D. Although identifying and isolating pancreatic stem cells remains technically challenging and they are available in limited quantities for research, these cells hold potential for modulating immune responses and preventing autoimmune destruction of β-cells in T1D. Pancreatic stem or progenitor cells are typically obtained from donated organs. Unlike transplanting entire organs, these cells can be expanded outside the body and may be modified for immune invisibility. Therefore, they offer a scalable and less resource-intensive solution that could alleviate the challenges associated with organ shortages.[39–42] Mesenchymal stem cells release anti-inflammatory cytokines such as IL-10, transforming growth factor-beta (TGF-β), and prostaglandin E2, which may slow effector T cell growth and promote the expansion of regulatory T cells (Tregs), thereby reducing immune responses.[43,44] These generate a protective environment for the neogenesis of β-cells formed from pancreatic progenitor cells to boost immunity against the immune attack.[45,46] A highly small number of pancreatic stem cells in the islets can differentiate into insulin-producing β-cells. They provide the possibility to restore endogenous insulin production through immune modulation and regeneration, with minimal rejection risk.[47–49]

However, a significant barrier is the ambiguity regarding the existence of specific pancreatic stem cells in adults. Pancreatic regeneration mainly occurs through β-cell division rather than through stem cells that self-renew.[50,51] Pancreatic progenitor cells play a critical role in building both exocrine and endocrine cells during embryonic development, but seem to lose this ability with age.[52,53] Recent studies suggest that progenitor-like cells in ductal and acinar regions may generate new β-cells, especially under injury or metabolic stress.[54,55] The mature pancreas lacks a dedicated stem cell niche like the intestines and bone marrow. Advances in regenerative medicine and stem cell research show that cells can be reprogrammed to act like pancreatic progenitors or stem cells from other tissues, generating functional β-cells.[56–59] This has led to new diabetes treatments, such as activating progenitor cells or using patient-derived stem cells to restore insulin production.[60–63]

Recent studies have also highlighted the potential of senescent or damaged β-cells—cells that endure an autoimmune attack yet lose their ability to replicate or produce insulin.[64,65] Although typically nonfunctional, these cells may possess significant flexibility in terms of differentiation and could potentially be reprogrammed under certain conditions. Genetic or drug-based strategies may help dysfunctional β-cells revert to a progenitor-like state, enabling them to grow and produce insulin.[66–70] This concept of cellular adaptability provides optimism for restoring insulin production in individuals with T1D. Interestingly, senescent β-cells may acquire progenitor-like characteristics in the presence of appropriate signaling cues.[71–74] Genetic or regulatory factors may drive the cells back to a more stem-like state and allow for the replacement and expansion of insulin-secreting cell mass.[75–77] Under certain conditions, studies on animals indicate that α-cells might transdifferentiate into a cell type reminiscent of a β-cell.[78,79] This suggests that, under appropriate signals, both α-cells and aged β-cells could be reprogrammed to perform the roles of insulin-producing cells. Some reprogrammed cells may arise from surviving β-cells, suggesting that senescent ones could regain a flexible, progenitor-like state to support regeneration.[80,81] Hence, reprogramming senescent β-cells into functioning insulin-producing cells represents a significant breakthrough in diabetes care.[82,83] This approach aims to restore β-cell function in T1D, moving beyond insulin replacement to regenerative therapies that address the disease's root cause. If successful, reprogramming senescent β-cells into functional β-cells, either directly or after turning them into progenitor β-cells, could provide a permanent solution for restoring insulin production.[84–86] This concept envisions a future in which persons with T1D will no longer rely on insulin injections.

Against this backdrop, this article aims to expand T1D research by critically analyzing past studies and forming hypothesis-driven insights. It explores alternative sources of insulin-producing cells, focusing on whether pancreatic stem or progenitor cells exist in islets, as adult stem cells are found in other organs. It also investigates why α-cells resist autoimmune attacks in T1D. A critical question is whether the distinctive property of their resistance to autoimmunity can help convert non-β-cell counterparts into 'normally' resistant β-cells. This research aims to uncover new approaches for T1D management and explore their broader societal impact.

Hence, the article opens with the search for elusive pancreatic stem cells and the inquiry into whether β-cell replication suffices for insulin regeneration. It subsequently explores the regenerative role of ductal epithelium and insights gained from single-cell transcriptomics.[87,88] It focuses on the immune resistance of α-cells, their role in β-cell protection, and approaches to replicate this immunity.[89,90] The final sections briefly examine important transcriptional and signaling pathways that could be utilized to combat T1D and regenerate β-cells: neurogenin-3 (NGN3), Hippo signaling pathway (Hippo)/Yes-associated protein (YAP), and glucagon-like peptide-1 (GLP-1).[34,91–94]

The hidden treasure island: The search for elusive pancreatic stem cells

Recent research shows that turning stem cells, like embryonic stem cells (ESCs) or induced pluripotent stem cells, into β-cells could help with cell replacement therapies.[95,96] For instance, studies have

indicated that researchers successfully produced glucose-responsive β-like cells from ESCs that managed blood glucose levels in diabetic mice.[97–99] Initial clinical trials conducted by ViaCyte using encapsulated pancreatic progenitors derived from ESCs showed their potential for application, although some challenges related to immune responses were encountered.[100] Building on this initial research, ViaCyte progressed its proprietary pancreatic endocrine cell (PEC)-01 cell line, sourced from human pluripotent stem cells, into Phase 1 and Phase 2 clinical trials (e.g., NCT02239354, NCT03163511). These clinical studies involved subcutaneous delivery of PEC-01 cells through macroencapsulation devices, such as Encaptra. While the results were encouraging regarding safety and partial engraftment, several problems arose, including limited oxygen and nutrient diffusion, excessive fibrosis growth, and insufficient insulin secretion, presenting major hurdles to achieving long-term functionality and immune compatibility. These findings underscore the need for ongoing enhancement in cell encapsulation and device innovation to optimize the survival and efficacy of transplanted cells. Vertex Pharmaceuticals, which acquired ViaCyte in 2022, recently announced favorable outcomes for its VX-880 treatment, inspired by Douglas Melton's foundational research, indicating a revival of spontaneous insulin production and reduced reliance on insulin in patients.[101,102] This approach offers major benefits, like scalability and the ability to modify cells so the immune system doesn't attack them after transplantation, which is crucial for treating T1D. It also suggests that we can trigger pancreatic stem cells, possibly in the islets, to become insulin-producing β-cells. By changing key biological signals and the pancreatic environment, we may activate this regeneration and restore β-cell function in people with T1D.[103,104] The main challenge is figuring out how to change these signals and control stem cells to encourage β-cell production while preventing immune system rejection. As a result, the quest for endogenous pancreatic stem or progenitor cells could significantly impact T1D management. If scientists could identify these cells and determine whether they have regenerative ability, there may then be the possibility of inducing the direct conversion of these cells into insulin-secreting β-cells in the pancreas of the subjects. This would usher in a new mode of replacement for β-cell functioning, which would be far more sustainable and personalized and would considerably reduce reliance on an external cell source as well as the immunorejection risk, which is currently a major hurdle for treatment.[105,106] Understanding the major mechanisms governing this important process will be crucial in devising efficient therapies for T1D and ultimately restoring normal insulin production.

Replicating β-cells: A limited solution or the future of insulin regeneration

Looking back at the history of scientific inquiry, groundbreaking research by Susan Bonner-Weir and colleagues showed that the number of β-cells in the pancreas progressively increases during normal development and continues throughout adulthood.[107] This growth links the formation of new, small islets to ductal progenitor cells in a process called neogenesis. Another finding was that while pancreatic cells, like β-cells, acinar cells, and ductal cells, can replicate, mature β-cells may have limited ability to do so due to two types: one that can replicate and another that has aged. It's noteworthy that while replicating β-cells may undergo slight dedifferentiation, they do not revert to progenitor or stem cell states. During replication, these β-cells might temporarily lose their functional capabilities. This suggests that using existing β-cells to produce insulin may be less effective at regulating blood glucose than converting pancreatic progenitor cells into stable, long-lasting insulin-producing β-cells.

Subsequent studies have confirmed the concept of neogenesis, particularly during physiological conditions such as pregnancy or stress from injury, where ductal cells are implicated in the regeneration of β-cells.[108–110] Notably, studies by Bonner-Weir and associates have provided histological and lineage-tracing proof demonstrating the plasticity of ductal epithelial cells in creating endocrine progenitors.[111–114] Similarly, studies have shown that the activation of the Notch pathway can influence the differentiation of ductal cells into cells that produce insulin.[115,116] Furthermore, research has shown that while mature β-cells are capable of limited proliferation, this process is often followed by temporary dedifferentiation.[117,118] During this phase, there is a decrease in the expression of insulin and key genes associated with β-cell identity, such as pancreatic and duodenal homeobox 1 (Pdx1) and V-maf musculoaponeurotic fibrosarcoma oncogene homolog A.[119–121] These findings emphasize the challenges of relying only on the replication of mature β-cells to regain function in diabetes and instead support the therapeutic strategy of employing progenitor cell populations or neogenesis to create robust, functional β-cells.

Uncovering hidden stem cells: The potential of ductal epithelium in pancreatic regeneration

Studies show that the duct epithelium in adults can still produce all the cell types in the pancreas, offering a potential source for pancreatic stem and progenitor cells.[105,111–113,122] Researchers have successfully extracted potential intra-islet stem cells, marked by nestin, from both rat and human islets.[123,124] One alternative concept suggests the existence of facultative or functional stem cells.[125,126] This implies that a fully differentiated epithelial cell can momentarily behave like a stem cell by undergoing multiple divisions, despite not being an actual stem cell. Animal studies show that after partial pancreas removal, mature ductal cells in rats can replicate and become less differentiated, forming islet, acinar, or duct cells.[127,128] Similarly, transgenic mouse models with overproduced interferon (IFN)-γ regulated by the insulin promoter have been shown to enhance neogenesis in adulthood.[129,130] These experiments cause insulitis by promoting IFN γ expression through insulin, leading to continuous ductal cell growth and new islet formation.[131,132] Most importantly, the new islets extend toward the ductal lumen, suggesting that pancreatic progenitor cells exist in the duct.[133,134]

Building on these findings, later research has further strengthened the regenerative abilities of adult pancreatic ductal epithelium. For example, studies indicate that ductal cells can transform into functional β-cells under specific conditions, such as the activation of key signaling pathways like Notch and Wingless-related integration site (Wnt).[135–137] Importantly, research in transgenic mice revealed that stimulating these pathways can convert mature ductal cells into insulin-producing β-like cells, offering a possible treatment method for regenerating β-cells.[138,139] Later research has also examined the role of inflammation and stress in promoting the growth of ductal progenitor cells. Research has indicated that enhancing β-cell regeneration following injury can be achieved by blocking key elements that limit progenitor cell activation, such as the TGF-β signaling pathway.[140,141] Additionally, studies revealed that after partial pancreatic damage, ductal cells exhibit greater plasticity and can regenerate functional insulin-secreting cells.[142,143] Recently, it has been shown that metabolic stress, such as insulin resistance caused by a high-fat diet, can stimulate the proliferation of ductal progenitor cells and enhance β-cell regeneration in diabetic models.[144,145] Similarly, it was recently discov-

ered that altering the Hippo signaling pathway in adult mice enhanced the plasticity of ductal cells and prompted the neogenesis of β-cells after pancreatic damage.[146–148] These findings support the idea that the ductal epithelium serves as an essential source of progenitor cells for β-cell regeneration and suggest that adjusting specific signaling pathways might improve neogenesis and offer a possible therapy for T1D.

Unlocking pancreatic regeneration: The power of single-cell transcriptomics

Put together, while the therapeutic potential of pluripotent stem cell-derived β-like cells has been demonstrated, the existence of a dedicated endogenous pancreatic stem cell population in adult humans remains under investigation. Nevertheless, the search for such cells remains crucial, particularly in the context of T1D, where inflammation-driven β-cell loss highlights the need for regeneration and replacement strategies. A comprehensive identification of plausible cell types could ultimately lead to the discovery of true pancreatic progenitor stem cells. In this context, single-cell transcriptomics serves as an effective technology for in-depth analysis. By exploring the gene expression profiles of individual cells within the ductal epithelium and newly formed islets, single-cell RNA sequencing can effectively identify and isolate potential progenitor cells, even those exhibiting minor or transient characteristics.[149,150] This method could identify markers specific to progenitor states, differentiate pathways, and assess the process of dedifferentiation or transdifferentiation occurring in pancreatic tissues.[151,152] In addition, the single-cell RNA sequencing technique can deconvolute the variegated cell types existing in the ductal epithelium and help discover subgroups with stem-like properties or plasticity, especially when injury is present or inflammation is triggered in transgenic models.[153,154] This ability to distinguish progenitor populations by their gene expression provides an avenue for their isolation and further study.[155,156] In essence, single-cell transcriptomics helps uncover more about pancreatic progenitor cells and provides the foundation for advancing regenerative medicine.[157,158] Critically, to assist readers in navigating the diverse techniques commonly employed in pancreatic β-cell regeneration, Table 1 provides a comprehensive summary of advanced experimental and translational techniques designed for the regeneration and preservation of β-cells in a T1D setting.[38,149–152,157–185] Such information is crucial to the development of next-generation cell therapies for diabetes.[38,157–185]

What α-cells know: Lessons learned to safeguard β-cells in T1D

As previously stated, T1D is an autoimmune disorder that destroys the β-cells in the pancreas, whereas the α-cells that generate glucagon typically remain unharmed. The selective preservation of β- and α-cells during immune attacks is shaped by a variety of molecular, immunological, and physiological factors that contribute to the protection of α-cells. Gaining insight into these mechanisms is crucial for understanding the onset of T1D and investigating potential treatment alternatives. A primary cause for the specific destruction of β-cells is the diverse expression of autoantigens.[186,187] β-cells are responsible for producing insulin and other proteins such as glutamic acid decarboxylase and insulinoma-associated antigen-2, which are targeted by autoreactive T cells in T1D.[188,189] Cytotoxic T lymphocytes (CTLs) kill the β-cells upon being activated by stimulation from major histocompatibility complex molecules.[190] Notably, in contrast to the β-cells, the α-cells seem to express considerably less of these autoantigens and are, therefore, not recognizable by the immune system.[191] As a result, α-cells frequently manage to evade the harmful effects that are primarily directed at the β-cells.

α-cell resilience: A key to β-cell regeneration and protection in T1D

Immunological stresses are not confined to the expression of antigens; rather, they inhibit normal β-cell function.[192] In addition, activated T cells produce inflammatory cytokines like IFN-γ and tumor necrosis factor alpha during any autoimmune response or condition.[193,194] This eventually leads to the endoplasmic reticulum inability to withstand oxidative stresses and subsequent cell death.[195,196] Given their substantial metabolic needs and high levels of insulin production, β-cells face a greater risk.[197,198] In contrast, α-cells demonstrate greater resilience to these cytokines, largely due to their different gene expression profiles and reduced reliance on insulin production.[199] Additionally, α-cells boast a stronger anti-apoptotic signaling route that balances oxidative stress and lowers responses to endoplasmic reticulum stress, thereby allowing these cells to sustain the inflammatory atmosphere typical of T1D.[200] Under certain conditions, α-cells can transdifferentiate into β-cells, enabling them to adapt and compensate for the loss of β-cells.[201,202] Though presumably not to the extent found in humans, this points toward the relatively plastic characteristics of α-cells compared to the more inflexible nature of β-cells. Differences might also arise in the vascular system as well as in the microenvironment within pancreatic islets, affecting immune responses.[203,204] α-cells are generally located at the periphery of islets and may be exposed to different levels of cytokines and immune cells than β-cells, which are situated centrally and are more directly involved in glucose regulation, making them more susceptible to immune attacks.[205] It is possible that the entire immune system is directed against the β-cells, considering their important function, insulin, in overall glucose regulation. As a major hormone regulating various functions in the body, insulin has strong immunogenic properties, making β-cells apparent immunological targets.[206] Glucagon secreted by α-cells is also a regulator of glucose, although its effects are secondary to those of insulin, and thus immune responses against α-cells are toned down.[207] Additionally, research indicates that α-cells might influence immune reactions within the islet microenvironment, which could aid in their survival.[208]

Immune resistance in pancreatic β-cells could potentially be enhanced by adopting strategies employed by α-cells in T1D, which have evolved mechanisms to evade immune-mediated destruction. One option could be molecular mimicry: modifying β-cells to express the protective molecules expressed by α-cells, thereby decreasing their immunogenicity.[209–211] In addition, α-cells employ immune checkpoint regulators, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4), to shield themselves from T-cell attacks; therefore, encouraging similar regulatory molecules in β-like cells may fortify them against autoimmunity.[212,213] Recognizing and increasing the levels of anti-inflammatory cytokines like IL-10 and TGF-β could also enable β-cells to withstand immune challenges, akin to α-cells.[214,215] For instance, in the non-obese diabetic mouse model for T1D, it has been noted that IL-10 therapy reduces β-cell damage and the infiltration of immune cells into the pancreas.[216,217] Furthermore, IL-10 enhances the Treg response, which is crucial for maintaining immune tolerance.[218] Preclinical studies, particularly in non-obese diabetic mice, have shown that IL-10–mediated enhancement of Tregs can delay or prevent diabetes onset, under-

Table 1. Emerging techniques in β-cell regeneration and therapeutic applications in type 1 diabetes

Technique	Purpose	Description	Therapeutic implications
Single-cell RNA sequencing (scRNA-seq)	Identification of progenitor/ stem-like cells	Examines gene expression at the single-cell level to investigate rare or transient progenitor cell states within the pancreatic ductal epithelium[149–151]	Enables the identification and isolation of potential regenerative cell types, which is an essential step in advancing targeted cell-based therapies[157,158]
Cellular reprogramming	Regeneration of β-cells	Transforms non-β cells, such as α-cells or ductal cells, into insulin-secreting β-cells through the use of transcription factors and the modulation of signaling pathways[159,160]	Provides a method to restore missing β-cells without depending on external stem cell sources[161]
Transgenic animal models	Understanding neogenesis and immune mechanisms	Genetic modification, such as the overexpression of IFN-γ, causes damage or inflammation in the pancreas to investigate regeneration and immune reactions[162]	Replicates human diseases, facilitating the identification of regeneration pathways and immune regulators [163]
Epigenetic profiling	Studying chromatin states and immune resilience	Investigates DNA methylation, histone modifications, and chromatin accessibility to understand the mechanisms behind α-cells' resistance to immune attacks[164,165]	May assist in reprogramming β-cells to reduce their immunogenicity and enhance their resistance to immune destruction[166]
Molecular mimicry	β-cell protection via immune evasion	Engineered β-cells produce immune-protective molecules similar to those found in α-cells, thereby minimizing immune targeting[167,168]	Decreases autoimmunity and improves the survival of β-cells following transplantation or during endogenous regeneration[169]
Immune checkpoint modulation	Immunosuppression and β-cell protection	Introduction or activation of checkpoint inhibitors (e.g., PD-1, CTLA-4) on β-cells to prevent T-cell mediated killing[170,171]	It could enhance β-cell tolerance and prolong survival in autoimmune conditions[172]
Anti-inflammatory cytokine therapy	Modulating immune environment	Utilization of cytokines like IL-10 or TGF-β to mitigate localized inflammation and safeguard β-cells[173,174]	Creates a favorable niche for β-cell regeneration and survival in T1D[175]
Lineage tracing	Tracking cell origin and fate	Employs genetic labeling techniques to monitor the conversion of ductal or α-cells into β-cells *in vivo*. The labeled cells are then tracked over time *in vivo* to monitor their potential conversion into insulin-producing β-cells[176]	Verifies the origins of neogenesis; substantiates regenerative processes in living tissues[177]
Organoid culture systems	*In vitro* modeling of regeneration	Three-dimensional (3D) cultures developed from pancreatic tissue or stem cells to replicate the structural and functional characteristics of the pancreas[178,179]	Facilitates the evaluation of regeneration protocols and the screening of pharmaceuticals within a regulated setting[180]
Gene editing (e.g., CRISPR/Cas9)	Modulating gene expression in pancreatic cells	Employed to alter the expression of autoantigens, improve β-cell functionality, or replicate the protective characteristics of α-cells[181,182]	Enables the development of tailored therapies and the generation of immune-resistant β-cells[183]
Beta cell encapsulation	Encapsulation of β-cells or progenitors in a protective barrier to shield them from immune attack	Involves enclosing insulin-producing cells in a semi-permeable membrane to protect them from immune attack while allowing nutrient and insulin exchange[184,185]	Long-term β-cell protection in an immune-privileged environment[38]

CRISPR, clustered regularly interspaced short palindromic repeat; CTLA-4, cytotoxic t-lymphocyte–associated protein 4; IFN-γ, interferon gamma; IL-10, interleukin 10; PD-1, programmed cell death protein 1; T1D, type 1 diabetes; TGF-β, transforming growth factor beta.

scoring its potential as a therapeutic target for preserving β-cell function in T1D.[219,220] In contrast, a lack of IL-10 accelerates the onset of diabetes and alters intestinal immunity.[221]

Another promising avenue is the downregulation or modified presentation of major β-cell autoantigens, such as insulin or glutamic acid decarboxylase-65, to reduce their visibility to autoreactive T cells.[222,223] Furthermore, epigenetic profiling of α-cells has revealed a more compact and immune-inactive chromatin state around key inflammatory gene loci, which may underlie their reduced immunogenicity.[224–227] Understanding and recreating such epigenetic states in β-cells could serve as a strategy to reprogram their immune profile.[228,229] These are strategies that can be applied in principle but require large-scale experimental verification before being turned into clinical processes.

In summary, during T1D, α-cells resist immune stress based on a low autoantigen expression profile, higher resistance against inflammatory stimuli, and activation of pathways that inhibit cell death. The possibility that α-cells may transdifferentiate into β-cells could allow for certain regenerative strategies. Strategies such as immune checkpoint modulation, molecular mimicry, and the use of anti-inflammatory cytokines could help protect or restore β-cell function, though further research is required. The immune-mediated destruction of β-cells in T1D involves intricate interactions concerning antigen presentation, immune targeting, cellular stress, and renewal. In this context of autoimmunity, α-cells demonstrate resilience, presenting opportunities to minimize β-cell loss through their adaptability and informing future T1D therapies.

Reversing T1D: Transcriptional and NGN3 signaling pathways in β-cell regeneration

As mentioned earlier, although current T1D management includes insulin replacement, new regenerative therapies aim to replenish endogenous β-cell mass through cellular reprogramming. They rely on an accurate understanding of the molecular mechanisms that govern pancreatic development, lineage determination, and β-cell maturation. Key transcription factors, initially identified during embryonic development and currently utilized to guide stem or progenitor cells toward a β-cell identity, continue to be vital for the future of this area.[230,231] Simultaneously, pathways such as Wnt/β-catenin and Hippo/YAP provide crucial signals for the proliferation, survival, and differentiation of progenitor cells.[232,233] By adjusting these signaling and transcriptional networks, scientists aim to reprogram non-β-cell types or increase β-cell numbers, ultimately offering a route to insulin independence in T1D. In addition to the aforementioned transcription factors, Table 2 includes a comprehensive list of key transcription factors and signaling pathways that play a role in β-cell reprogramming and regeneration.[234–271] This table will serve as a reference throughout the article, highlighting their roles in promoting β-cell regeneration, protecting against β-cell impairment, and facilitating the conversion of non-β-cells into insulin-producing cells. These elements hold significant therapeutic potential for diabetes treatment. In essence, Table 2 outlines the essential transcription factors and pathways involved in this regenerative process, along with their therapeutic significance. This introduction lays the foundation for the subsequent discussion on key signaling pathways, including NGN3, Hippo/YAP, and GLP-1.

In principle, T1D reversal needs to be poised to undertake therapeutic intervention directed at the repair of pancreatic insulin-producing β-cells that were destroyed in T1D patients.[272] This notion forms an important part of current research attempting to understand the underlying mechanisms of T1D pathology, thereby offering hope for new therapeutic avenues and even a cure. The regeneration of β-cells is considered the ultimate objective of T1D therapy, which could transform the approach to managing the disease or possibly eliminate it altogether. Achieving β-cell regeneration presents significant possibilities for novel therapies.[273] If scientists succeed in finding ways to regenerate or substitute these lost cells, it could result in groundbreaking treatments for T1D. A noteworthy strategy for generating functional β-cells involves transforming pancreatic stem cells into insulin-producing cells.[274,275] Various crucial signaling pathways play a vital role in guiding these stem cells to differentiate into β-cells, providing researchers with several targets for therapeutic approaches.[266,276] NGN3 is one of the major signaling pathways involved in this process, and it is important in the development of pancreatic endocrine tissue.[277,278] NGN3 is a transcription factor that directs progenitor cells to differentiate into hormone-secreting cells, including β-cells. Pancreatic stem or progenitor cells are rendered insulin-secreting β-cells by NGN3 expression, which can bring about the restoration of insulin production in T1D patients.[236,237]

To further elaborate, recent studies have highlighted the essential function of NGN3 in reinstating endocrine differentiation in the adult pancreas during instances of injury or regenerative cues.[279,280] Models of pancreatic damage or diabetes suggest that brief activation of NGN3 in ductal or acinar cells can reactivate an endocrine differentiation pathway and produce insulin-secreting cells.[281,282] Induced NGN3 expression in pancreatic duct cells has been shown to lead to the formation of glucose-responsive β-like cells in mouse models.[283,284] Moreover, lineage-tracing investigations have confirmed that reactivated adult ductal epithelium serves as a source of endocrine progenitors when stimulated with NGN3.[285,286] Importantly, NGN3 has been integrated with other key transcription factors, such as Pdx1 and V-maf musculoaponeurotic fibrosarcoma oncogene homolog A, in reprogramming strategies to convert non-β pancreatic cells or even intestinal cells into functional β-cells.[287,288] Moreover, organoid and stem cell-derived pancreatic progenitor models have demonstrated that NGN3 induction is a vital step for committing to the endocrine lineage, and its appropriate expression significantly enhances the effectiveness of generating insulin-positive cells *in vitro*.[289,290] Collectively, this information highlights that NGN3 is essential not only in embryonic development but can also be utilized in adult regenerative contexts to restore β-cell mass and function, suggesting potential treatments for diabetes.

Importantly, the Wnt/β-catenin signaling pathway, along with NGN3, affects cell fate, growth, and differentiation levels throughout pancreatic development.[291,292] When activated, this pathway promotes the self-renewal and proliferation of pancreatic progenitor cells, resulting in a greater number of potential β-cell precursors. Furthermore, this pathway is essential for maintaining stem cells in a progenitor-like state, which is crucial for their transformation into β-cells.[293] Inducing Wnt signaling in β-cells is crucial for their continued proliferation and differentiation into functional β-cells, as it has been shown to be effective in promoting regeneration. Recent studies indicate that activating canonical Wnt/β-catenin signaling enhances the levels of key β-cell transcription factors such as Pdx1 and NK6 homeobox 1, which are vital for maintaining β-cell identity and facilitating insulin secretion.[294,295] Additionally, modifying Wnt signaling in pancreatic organoid cultures has significantly improved the effectiveness of endocrine lineage specification, indicating its potential therapeutic benefit in β-cell replacement therapy.[296,297]

Table 2. Key transcription factors and signaling pathways in β-cell reprogramming and regeneration

Transcription factor/ signaling pathway	Function in β-cell reprogramming/regeneration	Therapeutic implications
Pdx1 (pancreatic and duodenal homeobox 1)	Master regulator of β-cell differentiation and maintenance. Promotes insulin secretion and β-cell identity[234]	Potential therapeutic target for β-cell regeneration in T1D. Can enhance endogenous β-cell regeneration or reprogram non-β-cells into functional β-cells[235]
NGN3 (neurogenin 3)	Induces pancreatic endocrine differentiation and promotes β-cell lineage specification[236]	Targeting NGN3 could induce the generation of new β-cells from pancreatic progenitors or ductal cells, offering promising treatments for T1D[237]
MAFA (V-maf avian musculoaponeurotic fibrosarcoma oncogene homolog A)	Regulates insulin expression in β-cells and aids in maintaining their function. Important for maintaining β-cell function during stem cell differentiation[238]	Therapeutic application in augmenting insulin production or improving β-cell survival in diabetes[239]
NEUROD1 (neurogenic differentiation 1)	It is a basic helix-loop-helix (bHLH) transcription factor. Works downstream of NGN3; critical for terminal differentiation and functional maintenance of β-cells[240]	Utilization in cell-based therapies or reprogramming protocols may help restore β-cell mass in diabetes, especially when used in combination with Pdx1, MAFA, or NGN3[241]
PAX4 (paired box gene 4)	Promotes β-cell fate over α-cell fate during endocrine progenitor differentiation; supports β-cell survival[242]	Conversion of pancreatic stem cells or non-β-cells into insulin-producing β-cells: a potential strategy for β-cell restoration in T1D[244]
ARX (aristaless-related homeobox)	Antagonistic to PAX4; promotes α-cell fate—needs to be suppressed to favor β-cell lineage[244]	Downregulation or inhibition of ARX in pancreatic stem cells or progenitors can enhance β-cell differentiation by shifting the endocrine fate toward insulin-producing β-cells as opposed to glucagon-producing α-cells[245]
ISL1 (ISL LIM homeobox 1)	Supports pancreatic endocrine development and insulin gene transcription[246]	Promotes endocrine lineage commitment and β-cell maturation; has the potential to enhance functional β-cell generation from stem cells for T1D therapy[247]
FOXO1 (forkhead box O1)	A transcription factor that regulates β-cell fate by balancing proliferation, maintenance, and differentiation from progenitor or stem cells[248]	Modulating FOXO1 activity may enhance β-cell regeneration and function, offering a potential strategy for restoring β-cell mass in T1D[249]
Sox9 (SRY-box transcription factor 9)	Regulates pancreatic progenitor cell fate and is critical in ductal cell differentiation[250]	Targeting Sox9 could aid in reprogramming ductal cells into β-cells, a potential therapeutic approach for restoring β-cell mass in T1D[250,251]
GATA4	Critical for β-cell survival and differentiation, it contributes to maintaining β-cell identity[252]	Therapeutic modulation of GATA4 can potentially enhance stem cell-derived β-cell generation in T1D[253]
HNF1β & HNF4α (hepatocyte nuclear factors)	Key in early pancreas development and glucose regulation; mutations associated with maturity-onset diabetes of the young (MODY)[254]	Potential therapeutic modulation of HNF1β and HNF4α can promote β-cell neogenesis from stem cells by regulating pancreatic development and insulin expression[255]
YAP/TAZ (Yes-associated protein/ transcriptional coactivator with PDZ-binding motif)	Part of the Hippo signaling pathway, it regulates β-cell proliferation and regeneration[256]	Therapeutic modulation of YAP/TAZ signaling potentially promotes β-cell proliferation, regeneration, and differentiation from stem cells, offering a strategy for restoring β-cell mass in diabetes[257]

(continued)

Table 2. *(continued)*

Transcription factor/ signaling pathway	Function in β-cell reprogramming/regeneration	Therapeutic implications
Wnt (Wingless/Integrated)/β-catenin pathway	Regulates β-cell differentiation and proliferation. Important for the expansion of the β-cell population[258]	Therapeutic activation of Wnt/β-catenin signaling may enhance β-cell regeneration and promote stem cell differentiation into β-cells for T1D treatment[259]
Tcf7l2 (T-cell factor 7-like 2)	Involved in Wnt/β-catenin signaling and promotes β-cell proliferation and survival[260]	Activating Tcf7l2 signaling may offer potential for stimulating β-cell regeneration from stem cells in T1D therapy[261]
Notch signaling pathway	Modulates endocrine differentiation, influencing β-cell identity and function[262]	Manipulating Notch signaling could enhance β-cell regeneration and reprogramming of progenitor cells[263]
JAK/STAT (Janus kinase/signal transducer and activator of transcription) pathway	Involved in cell survival and immune response regulation. Plays a role in β-cell regeneration[264]	Targeting JAK/STAT could enhance β-cell survival and regeneration, particularly in inflammation-driven β-cell loss in T1D[265]
TGF-β (transforming growth factor beta) pathway	Inhibits β-cell proliferation and differentiation but also regulates their function[266]	TGF-β pathway inhibition may enhance the differentiation of pancreatic progenitor cells into β-cells, overcoming differentiation barriers[267]
SMAD pathway	Regulates β-cell differentiation and expansion. Plays a role in TGF-β signaling in β-cells[268]	Targeting SMAD signaling may overcome β-cell growth inhibition and enhance differentiation of pancreatic stem cells into functional β-cells for T1D therapy[269]
GLP-1 (Glucagon-like peptide-1)	Enhances β-cell proliferation, survival, and function[270]	Therapeutic GLP-1 analogs can promote β-cell regeneration and support stem cell-derived β-cell maturation in diabetes[271]

GATA4, GATA binding protein 4; T1D, type 1 diabetes.

Key pathways in β-cell regeneration: Hippo/YAP, GLP-1, growth differentiation factor 11 (GDF11), and beyond

Another important pathway in β-cell regeneration is the Hippo/YAP signaling pathway, which plays a crucial role in pancreatic tissue repair.[298,299] Typically, the Hippo pathway limits cell growth to maintain organ size. However, when this pathway is inhibited, it activates YAP, promoting the growth, survival, and advancement of β-cells.[298,300] The triggering of YAP via the inhibition of the Hippo pathway underlines the core aspect of pancreatic stem cell differentiation and maturation to β-cells for tissue repair and regeneration through accelerated development.[299,301] Hormones, in addition to these signaling pathways, also trigger β-cell regeneration. The action of GLP-1 not only augments the secretion of insulin from β-cells and favors their growth and survival,[302,303] it has been reported that GLP-1 is capable of increasing the mass and functionality of β-cells, particularly when those cells are under stress in the milieu of T1D.[304,305] For instance, numerous studies indicate that GLP-1 improves β-cell mass and functionality, especially in T1D situations where β-cells face immune-related damage.[306,307] The use of GLP-1 or GLP-1R agonists (GLP-1RAs) in T1D animal models has led to a significant increase in β-cell mass and improved insulin secretion, even with ongoing immune challenges.[308,309] Additionally, it has been shown that GLP-1 enhances β-cell survival in diabetes by reducing inflammation and oxidative stress, key factors behind β-cell impairment and loss in T1D.[310,311]

In addition to benefiting mature β-cells, GLP-1 stimulates pancreatic progenitor cells to develop into insulin-producing β-cells.[312] These regenerative processes are thought to be partly influenced by GLP-1's regulation of central signaling routes, such as the phosphatidylinositol 3-kinase/protein kinase B pathway, which is crucial for cell survival and proliferation.[313,314] The protective role of GLP-1 against β-cell apoptosis has been further substantiated by evidence showing that GLP-1RAs can counteract the negative effects of inflammatory cytokines commonly increased in the diabetic setting, such as tumor necrosis factor alpha and IL-1β, which are recognized as inducers of β-cell apoptosis.[315,316] Scientists are thus using GLP-1 or GLP-1RAs to aid in β-cell regeneration from stem cells, potentially leading to improved insulin secretion and the development of new β-cells.[317,318] Alongside these effects on β-cell growth and longevity, recent findings have also suggested that GLP-1 plays a role in enhancing the functional efficacy of β-cells, particularly under metabolic stress conditions. The administration of GLP-1 in animal models exhibiting insulin resistance has resulted in elevated insulin secretion and enhanced glucose tolerance, indicating that GLP-1 preserves β-cell function even during periods of metabolic stress on β-cells.[319,320] This is particularly significant in T1D, where β-cell function is often compromised due to autoimmune damage and where the regeneration or maintenance of functional β-cells is essential for reinstating normal glucose balance. Moreover, GLP-1's effect on β-cell regeneration extends beyond β-cell proliferation and survival to also enhance β-cell plasticity.[295,321] Studies have shown that GLP-1RAs can convert α-cells into insulin-producing β-like cells in diabetic mice, thereby reinforcing the therapeutic promise of GLP-1 in promoting the regeneration of β-cells in diabetes.[295] These findings suggest that GLP-1 could be a very potent therapeutic agent for increasing β-cell mass as well as improving the functional incorporation of newly generated β-cells into the pancreatic islet. In summary, these investigations highlight the multifaceted role of GLP-1 in enhancing β-cell regeneration and functionality, particularly in stressful environments such as T1D, and support its use as a potential treatment strategy for β-cell replacement and diabetes management.

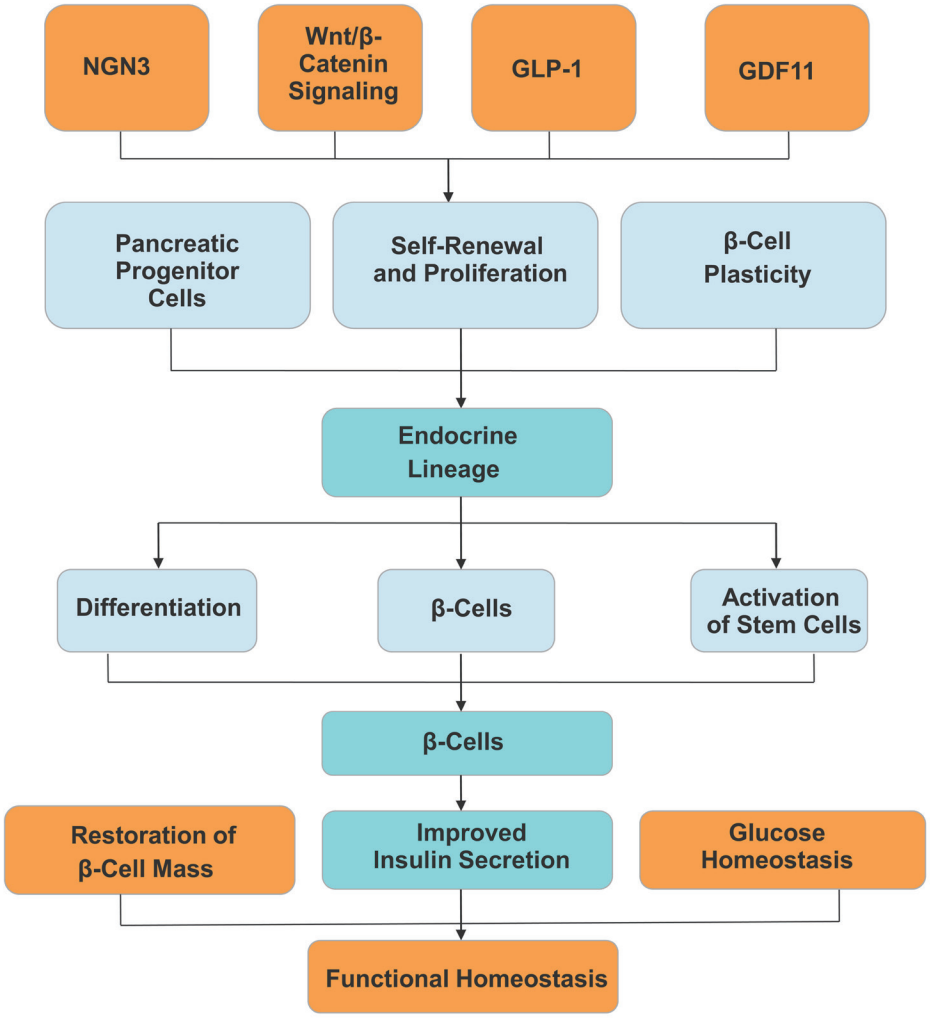

Fig. 1. Integrated signaling pathways governing pancreatic β-cell regeneration and functional homeostasis. Schematic representation of interconnected molecular pathways that control the regeneration of pancreatic beta (β)-cells and maintain functional balance. Orange boxes indicate significant upstream signaling molecules (neurogenin 3 (NGN3), Wingless/Integrated (Wnt)/β-catenin pathway, glucagon-like peptide-1 (GLP-1), and GDF11 (growth differentiation factor 11)) that function at distinct yet comparable stages in β-cell regeneration. NGN3 is a fundamental helix-loop-helix transcription factor well-known for determining endocrine lineage during pancreatic development and facilitating the activation of pancreatic progenitor cells. Wnt/β-catenin signaling is a well-preserved cell-cell communication pathway that manages self-renewal and the growth of endocrine progenitors. GLP-1 is released following nutrient intake and is an incretin hormone that aids in the proliferation and survival of β-cells; GDF11 contributes to maintaining functional β-cell plasticity. All these routes lead to the creation of an endocrine lineage (bright blue) that develops into functional β-cells. The supportive intermediate processes are illustrated as progenitor cell differentiation, new β-cell formation, and stem cell stimulation (light blue boxes). These mechanisms ultimately aid in the growth and development of β-cells. The functional maturity of the β-cell then yields physiological results from a rise in β-cell mass, improved insulin secretion, and preservation of glucose homeostasis (orange boxes), contributing to the restoration of functional homeostasis. Color labels also signify functional classifications: orange denotes upstream signals and downstream physiological endpoints; light blue boxes illustrate transitional cellular events, whereas bright blue indicates critical lineage transitions.

On the other hand, GDF11, a probable candidate for β-cell regeneration, is yet another TGF-β family member.[322] It stimulates pancreatic stem cells to become active β-cells.[323,273] Several studies have shown that GDF11 increased both β-cell mass and glucose regulation in animals, suggesting that it might have a role in therapy for T1D.[324] Furthermore, the tissue-rejuvenating properties of GDF11 may be especially advantageous for elderly individuals, as their capacity for pancreatic tissue regeneration usually declines with age.[325,326]

Together, these pathways, NGN3 activation, Wnt/β-catenin signaling, the Hippo/YAP pathway, GLP-1, and GDF11, create an important framework for regenerative medicine to reverse T1D effects. Figure 1 provides an overview of the integrated signaling pathways that regulate pancreatic β-cell regeneration and maintain their functional homeostasis. By manipulating these pathways, we may trigger β-cell regeneration in the pancreas and restore normal insulin production. These strategies offer hope for T1D patients and could change how diabetes is treated. However, alongside these regenerative approaches, it is essential to address the ongoing risk of autoimmune relapse, which remains an important obstacle. Various mechanisms have been proposed to either prevent or control such relapses, but this topic still requires more detailed

investigation, which is beyond the scope of this narrative review. These strategies include inducing immune tolerance, such as using antigen-specific therapies aimed at re-educating the immune system rather than suppressing it entirely, and immune modulation with agents like anti-CD3 monoclonal antibodies, CTLA-4-Ig, and anti-CD20 treatments that target autoreactive T cells or boost Treg activity.[327,328] Also, β-cell encapsulation techniques provide a physical barrier that shields transplanted β-cells from immune attack while allowing the exchange of nutrients and insulin.[329,330] Advances in β-cell genetic engineering, employing methods like clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (hereinafter referred to as Cas9) to modify genes, aim to reduce their immunogenicity or produce local immunomodulatory factors, offering hope for longer-lasting β-cell survival.[331,332] What's more, combining immune modulation and β-cell replacement therapies may offer the most promising approach to achieve a cure and prevent relapses, eventually leading to sustained remission from T1D.[333,334]

Finally, besides stem cell–based approaches for β-cell replacement, a novel and highly promising strategy is emerging that aims to stimulate endogenous pancreatic cell regeneration.[94,335] Therapies employing glucagon receptor (GCGR) monoclonal antibodies, such as evogliptin, leverage the glucagon signaling pathway—aligning with the classical view of diabetes as a bi-hormonal disease.[336–338] GCGR monoclonal antibodies exert their effects by inhibiting glucagon action, leading to physiological changes characterized by elevated circulating amino acids and increased levels of gut-derived hormones such as GLP-1.[339–341] These changes promote α-cell proliferation and facilitate the transdifferentiation of α-cells into insulin-producing β-like cells. Preclinical studies in rodent and non-human primate models have demonstrated substantial improvements in glycemic control and increases in functional β-cell mass, even in the absence of exogenous stem cell input.[342,343] Early-phase clinical trials in individuals with T1D have reported reduced insulin requirements and improved glycemic regulation following administration of GCGR monoclonal antibodies.[341] While further large-scale and long-term studies are necessary to confirm these findings, GCGR-targeted therapy represents a compelling endogenous regeneration strategy that could complement or potentially substitute for stem cell transplantation, particularly in patients retaining a functional α-cell population. Notably, Table 3 offers a comprehensive overview of current strategies for pancreatic β-cell regeneration, outlining their progression from basic research to clinical application.[122,341,344–360] It summarizes available approaches—such as stem cell-derived islet cells, autologous and allogeneic transplantation, endogenous regeneration, gene editing, and encapsulation technologies—and organizes them by source, developmental stage, significant clinical trials or references, main benefits, and key challenges. The goal is to help readers understand the full translational pipeline and the clinical potential and challenges of these therapies for the treatment of T1D.

Major technical hurdles hindering the clinical translation of stem cell therapy for T1D

Stem cell–based therapies represent a promising avenue for a long-term cure for T1D. However, their clinical translation faces several technical and biological hurdles. A major challenge lies in scaling up the production of insulin-producing beta-like cells from pluripotent stem cells.[361,362] This process requires complex, multi-step differentiation protocols that are difficult to standardize and scale under Good Manufacturing Practice conditions. Additional issues include batch-to-batch variability, high reagent costs, and the need for tightly controlled culture environments, all of which contribute to inconsistent outcomes and elevated production costs, ultimately impacting therapy accessibility and affordability.[363–365]

Another significant obstacle is immune rejection. Since T1D is an autoimmune disease, even autologous or human leukocyte antigen (HLA)-matched allogeneic cells may be susceptible to immune attack.[366,367] Encapsulation strategies have been developed to offer immunoprotection. Microencapsulation uses semi-permeable biomaterials such as alginate, chitosan hydrogel, or agarose to allow the exchange of essential molecules while preventing immune cell infiltration.[61,368] However, inconsistencies in biomaterial composition can affect their mechanical properties and stability, leading to variable foreign body responses and potential graft failure.[369,370] Macroencapsulation devices like the PEC-Direct enable direct vascularization, supporting graft survival and functional integration, but they do not provide immune shielding, necessitating lifelong immunosuppression.[329,371] Moreover, macroencapsulation is associated with limited nutrient and oxygen diffusion, risk of cell aggregation and central necrosis, and suboptimal vascularization, all of which impair islet viability and function.[372,373] Gene-editing strategies such as CRISPR have also been explored to reduce immune recognition by deleting HLA molecules or immune-activating surface proteins.[374,375] While promising, these approaches raise valid concerns about off-target effects and long-term genomic stability.

Importantly, a persistent limitation in the field is the functional immaturity of stem cell–derived beta-like cells.[376,377] These cells often exhibit fetal-like phenotypes characterized by poor glucose responsiveness and inadequate insulin secretion. Contributing factors may include incomplete differentiation, altered ion channel expression, and insufficient vascularization at transplantation sites, particularly ectopic locations lacking the appropriate pancreatic microenvironment.[378,379] This suboptimal glucose-stimulated insulin secretion limits their ability to tightly regulate glycemia, undermining their therapeutic efficacy.[380,381]

Furthermore, differentiation protocols often generate heterogeneous cell populations, including off-target or incompletely differentiated cells. These may express markers of non-β-cell pancreatic or extrapancreatic lineages, raising concerns about ectopic hormone production, inappropriate signaling, or unintended paracrine interactions.[382,383] Residual undifferentiated pluripotent stem cells within the graft pose a significant tumorigenic risk, such as teratoma formation, especially in long-term applications.[384,385] These concerns highlight the necessity for rigorous purification and safety validation protocols before clinical use.

Although the study of immune checkpoint pathways, such as PD-1 and CTLA-4 ligands, offers promising avenues for immunomodulation in T1D, a critical appraisal reveals that their clinical translation is considerably more complex than initially anticipated. These pathways have been extensively studied in the context of cancer immunotherapy, primarily to reinvigorate exhausted T cells.[386,387] However, in T1D, they may be more appropriately applied to restrain autoreactive immune responses targeting pancreatic β-cells. Despite this potential, checkpoint blockade carries significant risks, including off-target immune activation and systemic immune dysregulation, which could exacerbate existing autoimmunity or precipitate immune-related adverse events in other organ systems.[388,389] Moreover, their efficacy in preserving or restoring endogenous β-cell mass in T1D remains unproven, particularly when used in isolation.

Parallel investigations into β-cell regeneration have focused on

Table 3. Bench-to-bedside strategies for pancreatic β-cell regeneration

Strategy	Approach/cell source	Development stage	Pivotal trials/references	Key advantages	Major challenges
Stem cell–derived β-cells	Differentiation from hESCs/iPSCs (e.g., VX-880)	Phase 1/2 Clinical Trials	The FORWARD study (VX-880) accomplished insulin independence within a year, with many participants experiencing a reduction in severe hypoglycemia[344,345]	Unlimited availability; expandable; significant glucose regulation	Immune rejection: transplantation requires immunosuppression
Islet allotransplantation	Donor-derived islets (Donislecel/Lantidra)	FDA-approved since June 2023	Donislecel received FDA approval with 21 out of 30 patients insulin independent for over a year; serious adverse events occurred in about 90%[346,347]	Immediate glycemic restoration; no cell engineering needed	Limited donors, necessity for continuous immunosuppression, and adverse events
Autologous iPSC-derived β-cells	Patient-derived iPSCs to β-cells	Preclinical / Early clinical	Proof-of-concept studies are ongoing; it is not yet in late-stage trials[348,349]	Personalized; lower immune rejection risk	High cost, time-consuming, and QC and maturation challenges
Endogenous regeneration (drug-induced)	GCGR (glucagon receptor antagonist) mAb (volagidemab), GLP-1 analogs, GABA (gamma-aminobutyric acid)	Phase 1/2 Clinical Trials	Volagidemab Phase 2 study: Decrease in HbA1c, reduced insulin usage, yet primary endpoint not achieved[341]	Non-invasive; stimulates α-to-β conversion	Effects limited; safety issues with off-target outcomes; primary goals not achieved
Direct lineage reprogramming	α-cells/ductal cells → β-cells via TFs	Preclinical	Classic studies[122,350]	Uses endogenous plasticity	*In vivo* efficiency low; off-target reprogramming
MSC/HSC therapies	Immunomodulation, β-cell mass preservation	Phase 1/2 Clinical Trials	MSC trials in new-onset T1D show immune regulation[351,352]	Delay autoimmune degradation	Limited β-cell regeneration
Encapsulation technologies	Immune-shielding of transplanted β-cells	Clinical Trials (ViaCyte PEC-Encap)	NCT02239354 trials are ongoing[353,354]	Protects grafts without global immunosuppression	Fibrosis, diffusion limits, vascularization
Gene editing (CRISPR/Cas9)	β-cells engineered for hypoimmunity	Preclinical / Early trials	VCTX210 for universal stem-cell islets[355,356]	Precision modifications; potential to avoid rejection	Regulatory and ethical challenges
Organoids & 3D bioprinting	Scaffold-based islet cluster constructs	Preclinical	Studies by Sun Lab and Kaminiski Lab[357,358]	Improved maturation and insulin response	Complex fabrication; vascularization issues
Combined β-cell + immunotherapy	β-cell therapy plus immunomodulators	Preclinical / Early trials	Ongoing combo trials like Teplizumab + islet therapy[359,360]	Targets regeneration and autoimmunity	Risk of immune adverse events

CRISPR, clustered regularly interspaced short palindromic repeats; FDA, Food and Drug Administration; GLP-1, glucagon-like peptide 1; HESC, human embryonic stem cell; HSC, hematopoietic stem cell; iPSCs, induced pluripotent stem cells; MSC, mesenchymal stem cell; PEC, pancreatic endocrine cell; QC, quality control; T1D, type 1 diabetes.

transcription factors such as NGN3, a key regulator of endocrine lineage specification during pancreatic development. Reactivation of NGN3 in adult pancreatic tissue holds theoretical promise for the de novo generation of insulin-producing cells.[51,390] However, the therapeutic modulation of NGN3 and associated pathways (e.g., Notch, Wnt/β-catenin) is inherently challenging. NGN3 expression is tightly regulated in both temporal and spatial dimensions, and its ectopic or sustained activation can lead to aberrant differentiation or tumorigenesis.[391,392] Additionally, successful regeneration requires a careful balance between progenitor cell proliferation and proper β-cell maturation and function, an outcome not yet reliably achieved by current approaches.[393,394] Therefore, while these signaling pathways represent compelling therapeutic targets, their clinical implementation must prioritize safety and necessitate a nuanced understanding of their context-dependent activity in the diabetic pancreas.

Taken together, these intersecting biological, engineering, and regulatory challenges underscore the complexity of translating stem cell–based therapies into safe, scalable, and effective treatments for T1D.[395,396] Addressing these issues will require sustained interdisciplinary innovation across both research and clinical practice.

Limitations

While advancements in regenerative medicine for T1D have led to some beneficial therapeutic solutions, there are still challenges in translating recent progress into clinical practice. A significant challenge is that β-like cells derived from stem cells continue to show functional immaturity; they typically display a fetal-like characteristic with restricted glucose responsiveness and compromised insulin secretion. Producing these cells on a large scale while adhering to Good Manufacturing Practice standards is technically challenging, frequently hindered by inconsistencies in differentiation efficiency, elevated costs, and prolonged protocols. Immune rejection continues to be a significant obstacle—autologous or HLA-matched cells can still face the risk of autoimmune reactivation. Although encapsulation technologies and gene-editing strategies have demonstrated potential, they bring about further complications, including limited nutrient diffusion, fibrotic overgrowth, and unintended genetic consequences. Additionally, existing differentiation protocols tend to result in mixed cell populations, which raises the likelihood of inappropriate hormone release and the potential for tumor formation. Reprogramming approaches encounter challenges related to stability, effectiveness, and safety, as excessive expression of lineage-defining transcription factors may result in partial conversion or oncogenic transformation. Immunotherapy techniques, like checkpoint blockade, are limited by their systemic immune system effects and their restricted ability to prevent recurrent β-cell autoimmunity. Additionally, one of the most significant obstacles is the insufficient integration of transplanted or reprogrammed β-like cells within the host pancreatic environment. Adequate vascularization, nerve supply, and cell-to-cell communication are vital for the long-term survival and functionality of these cells, yet these features are not adequately replicated in existing models.

Future directions

In the future, strategies aimed at regeneration for T1D will need to move beyond traditional models by embracing a more comprehensive, systems-level approach that integrates stem cell biology, immunoengineering, developmental endocrinology, and tissue bioengineering. A key aim in these regenerative efforts will be to elucidate the processes through which immature β-like cells develop into glucose-responsive, functionally effective insulin-producing cells. The developmental environment can be mimicked using biomimetic scaffolds alone, ECM hydrogels by themselves, or possibly through vascularized organ-on-chip systems, which may provide the necessary biochemical and mechanical cues for proper islet development and functionality.[397,398] These culture systems might also have the capability to facilitate the co-differentiation of supporting islet-resident cell types, such as endothelial cells, pericytes, or pancreatic stellate cells, which play essential supportive roles by providing angiocrine signals, paracrine signals, and immune modulation.[399,400]

Concurrently, studies that utilize single-cell multi-omics and spatial transcriptomics for lineage tracing and fate mapping are necessary to gain a clearer understanding of the identity, plasticity, and differentiation capacity of adult pancreatic progenitor and non-β-cell lineages. This is important for developing more informed in situ regenerative therapy strategies, such as activating dormant progenitor-like states or orchestrating transdifferentiation pathways of either α-, δ-, or acinar cells into insulin-secreting cells through the application of transcription factor combinations or epigenetic modifiers. Moreover, reprogramming techniques should not only achieve lineage conversion but also guarantee that they encourage lasting phenotypic stability and controlled growth, as any improper growth could lead to hyperplasia or neoplasia.[399,400]

Understanding these strategies within the realm of immunology by combining tolerogenic and regenerative elements will be essential. There are emerging possibilities with tissue-engineered islets that are encapsulated with immunoregulatory ligands, local administration of checkpoint modulator-based methods to promote antigen-specific tolerance, and hybrid encapsulation systems that can release immunosuppressive cytokines or utilize agents like TGF-β or immune checkpoint agonists such as CTLA-4-Ig in optimal spatiotemporal release patterns. Furthermore, using neo-self signaling pathways to reprogram designed β-cells can help them evade immune recognition by showcasing “don’t-eat-me” signals like CD47 or create synthetic immunomodulatory networks to promote immune effector evasion, while simultaneously allowing host surveillance to overpower foreign pathogens.[401,402]

A critical yet underutilized area of research is the neuroendocrine regulation of regenerated β-cells.[403,404] Successful biofunctionality requires the secretion of insulin triggered by hyperglycemia, along with autonomic nerve input and endocrine coordination with systemic hormones.[405,406] There is an urgent need for research focused on the reorganization of neurovascular networks and how this may influence β-cell function and longevity. Similarly, it is essential to develop closed-loop systems that integrate biosensors to facilitate the smart delivery of various trophic and immunomodulatory factors capable of promoting regeneration in response to mechanical stimulation.[407,408]

Moreover, predictive modeling driven by artificial intelligence and based on individualized immunogenetic, transcriptomic, and metabolic information can be employed to categorize patients, anticipate the reactivation of autoimmunity, and customize regenerative strategies to improve their effectiveness and safety.[409,410] Gene-editing technologies like base editors or prime editors could allow for precise modifications of loci associated with autoimmune susceptibility or even changes to β-cell immunogenicity while minimizing the risk of genotoxic effects.[411,412] It will also be essential for ethical and regulatory frameworks to evolve in order to ensure

that the ramifications of these personalized and potentially heritable treatments are safe, fair, and monitored for long-term safety.

Ultimately, future clinical trials need to implement adaptive and decentralized designs that allow for real-time biomarker analysis, immune profiling, and comprehensive multi-omics evaluations focusing not only on glycemic control but also on immune compatibility, graft integration, and the β-cell stress response.[413,414] Collaborative global consortia and partnerships between the public and private sectors will be crucial for standardizing differentiation methods, potency evaluations, and long-term safety outcomes, which will help transition the field from a proof-of-concept stage to large-scale and equitable treatments. In conclusion, the path ahead necessitates collaboration among bioengineering, immunology, systems biology, and patient-centered precision medicine to create effective, safe, and sustainable cures for T1D.

Conclusions

Regenerative medicine aims to transform conventional T1D treatment by enabling the restoration of functional insulin-secreting β-cells. A particularly promising therapeutic strategy involves cellular reprogramming, which seeks to convert adult non-β pancreatic cells—such as α-cells or ductal epithelial cells—into insulin-producing β-like cells, potentially bypassing the need for exogenous stem cell sources. This approach leverages the inherent plasticity of pancreatic cell lineages and is driven by key developmental signaling pathways, including NGN3, Wnt/β-catenin, and Hippo/YAP. Recent advances, such as single-cell RNA sequencing and lineage tracing technologies, are critical for identifying rare progenitor subsets, mapping dynamic cell fate transitions, and confirming the fidelity and functionality of reprogrammed cells. Additionally, 3D pancreatic organoid models provide physiologically relevant platforms for assessing reprogramming efficiency, β-cell maturation, and disease modeling. Another major opportunity lies in engineering β-cells with immune-evasive properties, inspired by the natural immune privilege of α-cells. Epigenetic profiling has uncovered protective chromatin configurations and methylation landscapes in α-cells, which may be recapitulated in β-cells using CRISPR/Cas9 genome editing to downregulate autoantigen expression and enhance cell survival. Concurrently, immunemodulatory approaches, such as PD-1/CTLA-4 immune checkpoint inhibition and administration of anti-inflammatory cytokines (e.g., IL-10, TGF-β), are being developed to promote a localized immune-tolerant microenvironment. Nonetheless, several critical knowledge gaps impede clinical translation, including incomplete understanding of the molecular determinants of stable β-cell identity post-reprogramming; the long-term functionality and glucose responsiveness of reprogrammed cells under physiological stress; the mechanisms of immune escape; and the integration of engineered cells within native islet architecture, innervation, and vasculature. Moreover, issues of scalability, ethical considerations, and regulatory complexity must be systematically addressed to advance these innovations toward durable, clinically viable therapies for T1D.

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Conflict of interest

The authors have nothing to declare.

Author contributions

Conceptualization, formal analysis, original draft preparation, project supervision, project administration, funding acquisition (SKC), and writing—review and editing (SKC, DC). Both authors have approved the final version and publication of the manuscript.

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