Therapeutic Strategies for Pancreatic β cell Regeneration in Type 1 Diabetes

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***Abstract*—Type 1 diabetes mellitus (T1D) is a chronic autoimmune disorder characterized by the selective destruction of pancreatic β-cells, leading to absolute insulin deficiency and lifelong dependence on exogenous insulin therapy. Despite advances in glucose monitoring and insulin delivery, these approaches fail to restore endogenous β-cell mass or address disease progression. Consequently, regenerative strategies aimed at preserving, replacing, or regenerating functional β-cells have emerged as promising therapeutic alternatives. This review comprehensively discusses current and emerging therapeutic strategies for pancreatic β-cell regeneration in T1D. Key mechanisms of β-cell regeneration, including β-cell proliferation, neogenesis, transdifferentiation of non-β cells, and redifferentiation of dedifferentiated β-cells, are explored in detail. Pharmacological approaches targeting immune modulation, β-cell proliferation, survival, senescence, and incretin signaling are highlighted, along with advances in targeted drug delivery and combination therapies. In addition, stem cell–based strategies involving mesenchymal, pluripotent, hematopoietic stem cells, and stem cell-derived exosomes are examined for their regenerative and immunomodulatory potential. Gene therapy and gene-editing technologies, including CRISPR/Cas9-based approaches, are discussed as innovative tools for reprogramming non-β cells, enhancing β-cell survival, and correcting genetic defects. Finally, the review addresses current challenges and future directions, emphasizing the need to overcome autoimmune destruction, improve functional maturation, ensure long-term graft survival, and enhance clinical scalability.**

***Index Terms*—Type 1 diabetes mellitus, β-cell regeneration, Neogenesis, Transdifferentiation, Redifferentiation, Therapeutic Strategies.**

I. Introduction

The body's immune system targets and kills pancreatic β cells, resulting in type 1 diabetes, a chronic disease [1]. The vital internal organ processes of blood glucose control and food digesting are supplied by the pancreas endocrine and exocrine compartments. Acinar cells produce different digesting enzymes, and ductal cells carry them to the duodenum, forming the exocrine compartment. Five different types of hormone-secreting cells make up the endocrine compartment: β cells, which are produced by insulin (Ins), α cells, which are produced by glucagon (Gcg), δ cells, which are produced by somatostatin (Sst), PP cells, which are produced by pancreatic polypeptide (Ppy), and ε cells, which are produced by ghrelin (Ghrl) [2]. It performs regulatory functions and monitors variations in blood glucose. There are two methods to regenerate pancreatic β cells[3]. The first is preventing β cell loss, which includes preventing apoptosis/necrosis and β cell dedifferentiation. Endogenous regeneration (which stimulates β cell proliferation, induces transdifferentiation and transdetermination of other cells to β cells, reactivates pancreatic endocrine progenitors, and facilitates differentiation into β cells in vivo) and exogenous supplementation (which promotes stem cell differentiation into β cells, induces mature cell reprogramming into β cells in vitro, and then transplants the obtained cells to diabetic patients) are the second strategy for supporting newborn cells [4-6]. A new strategy for managing insulin insufficiency in diabetes, in addition to traditional

treatments, is the proliferation of preexisting β-cells [7-8]. The growth and repair of β-cells can aid in controlling type 1 diabetes . A mechanism controls the renewal of β-cells. Functional β-cell regeneration depends on an understanding of the diversity and development of β-cell populations [9–10].

II. Mechanism of β cell regeneration

Neogenesis - β-cell neogenesis refers to the process of generating new insulin-producing pancreatic β-cells. It is considered a promising therapeutic strategy for diabetes mellitus, where β-cell failure plays a central role [11]. Neogenesis can occur through several mechanisms: the proliferation of existing β-cells, the differentiation of stem cells, the trans-differentiation of non-β cells, and the re-differentiation of dedifferentiated β-cells [12]. Stimulating β-cell proliferation is one of the most direct approaches, where signaling pathways such as AKT, ERK/MAPK, and mTORC1 regulate cell cycle proteins to promote expansion of β-cell mass; for example, osteocalcin and inhibition of microRNA-7a have been shown to enhance proliferation and insulin secretion [13].

Proliferation - The division of preexisting pancreatic β-cells to increase their numbers is referred to as proliferation of β-cells.Increasing the mass of pancreatic β-cells has the potential to restore insulin production in both type 1 and type 2 diabetes, making it a promising therapeutic path [14]. β-cells reproduce aggressively in their early years but become mostly inactive as they get older, with replication rates falling to around 0.1%. Cell cycle machinery, such as cyclin-dependent kinases (CDKs) and their cyclin partners, which trigger cell division when activated, strictly controls proliferation [15]. Numerous pharmacological methods for inducing proliferation have been uncovered via research. Compounds like harmine, for instance, block DYRK1A, which increases calcineurin/NFAT signaling and β-cell multiplication. β-cell proliferation has also been linked to other kinase targets, including glucokinase, adenosine kinase, and salt-inducible kinases (SIKs) [16]. Moreover, growth factors and hormones like prolactin, insulin, GLP-1 receptor agonists, epidermal growth factor (EGF), and liver-secreted proteins like SerpinB1 have demonstrated the capacity to stimulate β-cell proliferation [17].

Transdifferentiation - One possible method for β-cell regeneration in diabetes is transdifferentiation, also known as lineage reprogramming, which is the conversion of one mature cell type into another [18]. Since they share a developmental origin with β-cells, non-β-cell types such hepatocytes, biliary cells, gastrointestinal cells, and pancreatic α, δ, acinar, and ductal cells are excellent candidates for reprogramming . Usually, the expression of important transcription factors like as Pdx1, MafA, Ngn3, NeuroD1, and Pax4 or therapies with small molecules, growth factors (e.g., EGF, GLP-1, gastrin, TGF-α), and medications like GABA or artemisinins are used to induce transdifferentiation. Hepatocytes and biliary epithelial cells can be forced toward a β-cell phenotype by activating Wnt signaling and overexpressing Pdx1 and NeuroD1, while pancreatic α-cells can become β-cells when Arx is inhibited or Pax4 is overexpressed [19]. Similar to this, Pdx1, MafA, and Ngn3 can reprogrammed intestinal and gastric cells into β-like cells, however their phenotypes are frequently unstable and lacking. Efficiency reports range from 10–20% for pancreatic ductal cells to up to 70% for acinar cells, 30% for gastrointestinal cells, 5–20% for biliary cells, and 10–30% for hepatocytes [20].

Re-Differentiation - It is possible to redifferentiate dedifferentiated human β-cell-derived (BCD) cells in vitro by focusing on the signaling pathways that cause them to lose their identity [21]. The use of shRNAs to inhibit important mediators of the NOTCH, WNT, TGFβ, and ZEB1 pathways resulted in a mesenchymal-to-epithelial transition (MET), reactivation of β-cell gene expression, and cell growth halt. The re-establishment of β-cell identity is supported by the downregulation of AKT and MYC, activation of FOXO1, microRNAs like miR-200c and miR-375, and cell cycle inhibitors (p21, p27, and p57) that were present during this process [22]. A soluble factor mixture known as the Redifferentiation Cocktail (RC), which included high glucose, nicotinamide, activin A, and

exendin-4, further accelerated redifferentiation by promoting insulin gene expression and glucose-responsive insulin secretion. The insulin content of these cells remained around 10% of that of normal β-cells, even though up to 60% of cells could be made to redifferentiate [23]. Crucially, in diabetic mice, these redifferentiated cells were able to reverse hyperglycemia, indicating potential for treatment. Inhibition of ARX further improved the efficiency of insulin-producing cell formation. Additionally, some dedifferentiated cells activated progenitor-like transcription factors (e.g., SOX9, NGN3, FOXA2, PAX4, ARX), indicating a transitory progenitor state during redifferentiation [24].

Figure 1

Therapeutic strategy

1. **Pharmacological approach**
   Table 1

2. **Stem cell approach**
   The ability of stem cells to self-renew and differentiate into various cell types is one of their unique characteristics. Various stem cells have the ability to enhance insulin sensitivity, decrease inflammation, enhance endothelial functions, and raise pancreatic β-cell activity. Different stem cell involved in β cell regeneration in type 1 diabetes [34].
   Mesenchymal stem cells (MSCs)- mesenchyme stem \ stromal cells (MSCs) have shown great promise in β cell regeneration in diabetes because of their special blend of immunomodulatory, paracrine, and differentiational characteristics [35]. Although their efficiency is usually lower than that of native β-cells, MSCs, which can be derived from bone marrow, adipose tissue, and umbilical cord, can differentiate into cells that produce insulin under certain culture conditions and express important pancreatic transcription factors like Pdx1, Ngn3, and MafA [36]. In addition to direct differentiation, MSCs have strong paracrine effects through the release of growth factors, cytokines, and exosomes, such as VEGF, HGF, IGF-1, and miRNAs, which promote vascularization of the islets and improve β-cell survival, proliferation, and insulin secretion. By inhibiting T-cell, B-cell, and NK-cell activity and encouraging anti-inflammatory macrophage polarization, MSCs regulate immunological responses in the setting of autoimmune diabetes, shielding β-cells from immune-mediated death [37-38]. Furthermore, MSCs have the ability to promote the growth of pre-existing endogenous β-cells, which aids in the restoration of β-cell mass. Both differentiation and paracrine pathways are responsible for the effects of MSC transplantation, which have been shown in preclinical investigations in diabetic animal models to improve blood glucose control, increase β-cell mass, and enhance insulin secretion [39]. Although there are still issues with standardizing MSC sources, optimizing dosage, guaranteeing long-term engraftment, and reducing potential risks like immune rejection or tumorigenicity, early-phase clinical trials have similarly reported improvements in C-peptide levels, decreased insulin requirements, and overall safety [40]. MSCs are a strong contender for new diabetes treatments because, when used together, they enhance β-cell regeneration mainly by establishing a regenerative milieu that encourages the survival, proliferation, and functional recovery of β-cells rather than completely replacing them [41].
   Pluripotent stem cells -A possible method for restoring β-cell mass in Type 1 Diabetes (T1DM) is the differentiation of pluripotent stem cells, such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), into insulin-producing β-like cells [42]. These cells can successfully replace missing β-cells by secreting insulin that is sensitive to glucose [43]. Transplanting ESC-derived β-cells has been shown in recent clinical developments, such as Vertex Pharmaceuticals' VX-880, to restore endogenous insulin production, as indicated by measurable C-peptide levels [44]. In certain cases, this can allow patients to reduce or stop using exogenous insulin. Early research on autologous iPSC-derived islet transplantation has also demonstrated long-term insulin independence, underscoring the promise of customized cell treatment [45]. Encapsulation techniques have been investigated to enhance graft longevity and function by shielding transplanted cells from immune-mediated destruction. Even with these developments, there

are still obstacles to overcome, such as getting β-like cells to fully mature functionally, avoiding immunological rejection, guaranteeing long-term survival, and increasing production for clinical use [46]. All things considered, pluripotent stem cell-derived β-cells offer a viable path toward β-cell regeneration in type 1 diabetes, with continued research aimed at maximizing durability, safety, and efficacy [47].

Hematopoietic stem cells (HSCs)- The potential therapeutic use of hematopoietic stem cells (HSCs) for β-cell regeneration has been studied, especially in autoimmune diabetes (Type 1 Diabetes, T1D). The primary purpose of HSCs, which are obtained from bone marrow or peripheral blood, is to replace blood cell lineages [48]. However, they also have immunomodulatory and paracrine actions that can support and shield pancreatic β-cells. Autologous HSC transplantation has been demonstrated to revitalize the immune system, inhibit autoreactive T-cells, and maintain residual β-cell function in T1D, where autoimmune destruction hinders insulin production [49]. This can occasionally result in decreased insulin needs or temporary insulin independence. HSC transplantation enhances glycemic control and promotes β-cell survival by secreting cytokines and growth factors such IL-10, TGF-β, and VEGF, according to preclinical research in diabetic animal models[50] . While it is uncommon for HSCs to directly differentiate into β-cells that produce insulin, their ability to regulate immunological responses and encourage the growth of endogenous β-cells helps to restore β-cell bulk . There are still issues despite encouraging outcomes, such as patient response variability, myeloablation hazards, and the requirement for long-term efficacy studies [51-52]. Thus, the immunological reset and supportive milieu are the main reasons that HSC-based therapies are valued, and current research is looking into gene editing or combinatory techniques using mesenchymal stem cells to improve β-cell regeneration [53].

Exosome-based therapy The paracrine actions of stem cells can be used to promote β-cell regeneration in diabetics without the risks associated with direct cell transplantation. Small extracellular vesicles called exosomes are secreted by cells such as mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs) [54]. Lipids, proteins, mRNAs, and microRNAs (miRNAs), which facilitate intercellular communication, are examples of bioactive materials [55]. It has been shown in preclinical studies that MSC-derived exosomes carry protective miRNAs like miR-21 and miR-26a as well as crucial transcription factors like Pdx1, MafA, and Nkx6.1, which enhance glucose-stimulated insulin secretion, raise β-cell survival, and promote proliferation. By decreasing autoreactive T-cell activity and enhancing regulatory T-cell function, exosomes also alter the immunological environment, shielding β-cells from autoimmune destruction [56-57]. When it comes to Type 1 Diabetes, this is very crucial. By means of VEGF, HGF, and FGF, exosomal cargo also promotes angiogenesis, which improves islet vascularization and creates an environment that is conducive to β-cell regeneration [58]. Customized delivery, the ability to transport therapeutic chemicals, and a decreased risk of tumor growth or immunological rejection are some advantages of exosomes over conventional stem cell therapy [59]. However, a number of challenges still exist, including the need for long-term safety evaluation and scalable production, the need to optimize dosage and administration techniques, and the variation in exosomes based on the cell source. By itself or in combination with other regeneration methods, exosome-based therapy offers a versatile and promising approach to β-cell survival, proliferation, and function [60].

Table 2.

3. Gene Therapy approach

A possible method for rebuilding pancreatic β-cells—which are in charge of manufacturing insulin and preserving blood glucose homeostasis—is gene therapy. Chronic hyperglycemia is caused by the destruction or malfunction of β-cells in diabetes, especially type 1 diabetes. Conventional therapies like islet transplantation or insulin shots only offer short-term or incomplete fixes. However, gene therapy uses the patient's own body to regenerate or reprogram β-cells in order to restore endogenous insulin production [65].

Reprogramming Non β cells into β cells

One of most promising strategies in β-cell regeneration is the Reprogramming of non β cells into insulin producing β-like cells through gene therapy. The approach utilizes the delivery of specific transcription factors or signaling molecules capable of altering the gene expression profile of other pancreatic or hepatic cell types thereby inducing them to acquire- β cell like functionality. The transcription factors MAFA (v-Maf Avian Musculoaponeurotic Fibrosarcoma Oncogene Homolog A), NGN3 (Neurogenin 3), and PDX1 (Pancreatic and Duodenal Homeobox 1) are essential to this reprogramming process. NGN3 controls endocrine cell differentiation, PDX1 is critical for pancreatic development and β-cell identity, and MAFA is involved in insulin transcription and β-cell maturation [66]. In order to transfer these genetic factors into target cells, such as α-cells (which typically produce glucagon), ductal cells, acinar cells, and even hepatocytes in the liver because they share an endodermal origin with pancreatic cells, gene therapy uses viral vectors like adeno-associated viruses (AAV) or adenoviruses. Interestingly, preclinical research has shown that adenoviral delivery of PDX1, NGN3, and MAFA into pancreatic exocrine cells in mice effectively transformed these cells into functional β-like cells that produce insulin. The therapeutic promise of cellular reprogramming for diabetes management is further demonstrated by the fact that treatments employing AAV-mediated delivery of PDX1 and MAFA have been demonstrated to restore glycemic control in diabetic animal models [67].

Promoting β-cell proliferation or survival

Encouraging the growth of already-existing β-cells or improving their survival through gene therapy is another crucial pathway in β-cell regeneration. Mature β-cells have a limited capacity for regeneration under normal physiological conditions, but some genes can be targeted to stop apoptosis or reactivate cell-cycle machinery. It has been demonstrated that the overexpression of cell-cycle regulators like Cyclin D2, CDK4, and c-MYC increases the mass of β-cells and promotes their proliferation. In parallel, β-cells can be shielded from oxidative stress, inflammatory cytokines, and autoimmune destruction by activating pro-survival and anti-apoptotic pathways via genes like BCL-2, IGF-1, and AKT [68]. Additionally, gene delivery of incretin hormones like GIP (Gastric Inhibitory Polypeptide) and GLP-1 (Glucagon-Like Peptide-1) can improve metabolic function, increase insulin secretion, and improve β-cell viability. When combined, these genetic treatments seek to preserve the long-term function of β-cells in diabetic conditions in addition to restoring their numbers [69].

Immune modulation for autoimmunity

Encouraging the growth of already-existing β-cells or improving their survival through gene therapy is another crucial pathway in β-cell regeneration. Under normal physiological conditions, mature β-cells have a limited capacity for regeneration; however, certain genes can be targeted to stop apoptosis or reactivate cell-cycle machinery [70]. Overexpression of cell-cycle regulators such as Cyclin D2, CDK4, and c-MYC has been shown to increase the mass of β-cells and stimulate their proliferation. Genes such as BCL-2, IGF-1, and AKT can activate pro-survival and anti-apoptotic pathways, protecting β-cells from oxidative stress, inflammatory cytokines, and autoimmune destruction [71]. Furthermore, gene delivery of incretin hormones such as GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory polypeptide) can enhance β-cell viability, boost insulin secretion, and improve metabolic function. Together, these genetic therapies aim to both restore the number of β-cells and maintain their long-term function in diabetic conditions [72].

4. Gene editing technology

Advances in gene editing technologies, particularly CRISPR/Cas9 and base editing tools, have revolutionized the area of β-cell regeneration by providing precise and efficient genetic modifications [73]. These technologies allow for the correction of monogenic mutations associated with forms of diabetes caused by anomalies in genes such as INS (Insulin), GCK (Glucokinase), and HNF1A (Hepatocyte Nuclear Factor 1 Alpha), therefore restoring normal β-cell function. Additionally, gene editing can be applied to stem cells, such as induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs), to introduce transcription factors like PDX1, MAFA, and NKX6.1, driving their differentiation into mature, insulin-secreting β-like cells suitable for transplantation [74]. Moreover, CRISPR technology facilitates the improvement of β-cell resilience

by targeting stress-response pathways or eliminating genes that predispose cells to death or immune attack. Collectively, these cutting-edge gene editing technologies show significant potential for producing patient-specific, functionally robust, and immune-compatible β-cells, paving the path for curative therapy for type 1 diabetes [75].

Future direction and challenge

The development of precision regenerative therapies (e.g., small-molecule drugs that stimulate β-cell proliferation or neogenesis, or gene-editing approaches to enhance β-cell survival), stem cell-derived β-cell replacement (using human embryonic or induced-pluripotent stem cells), and bioengineering platforms (e.g., encapsulation or 3D scaffolds) to deliver and protect new β-cells.However, there are still significant obstacles to overcome [76]. The autoimmune destruction that underlies T1D must be addressed in order to prevent the destruction of regenerated or transplanted β-cells, the scalability, functional maturity, and long-term survival of newly generated β-cells in humans are still uncertain, donor scarcity or manufacturing limitations persist, and immunoprotection (avoiding lifelong immunosuppression), vascularization, engraftment, and safety (e.g., risk of dedifferentiation or tumorigenesis [77]. In short, although the area has progressed from inconceivable to feasible, coordinated advancements in immunology, stem cell biology, biomaterials, and translational medicine are necessary to reach a therapeutic therapy that is broadly applicable [78].

Figures and Tables

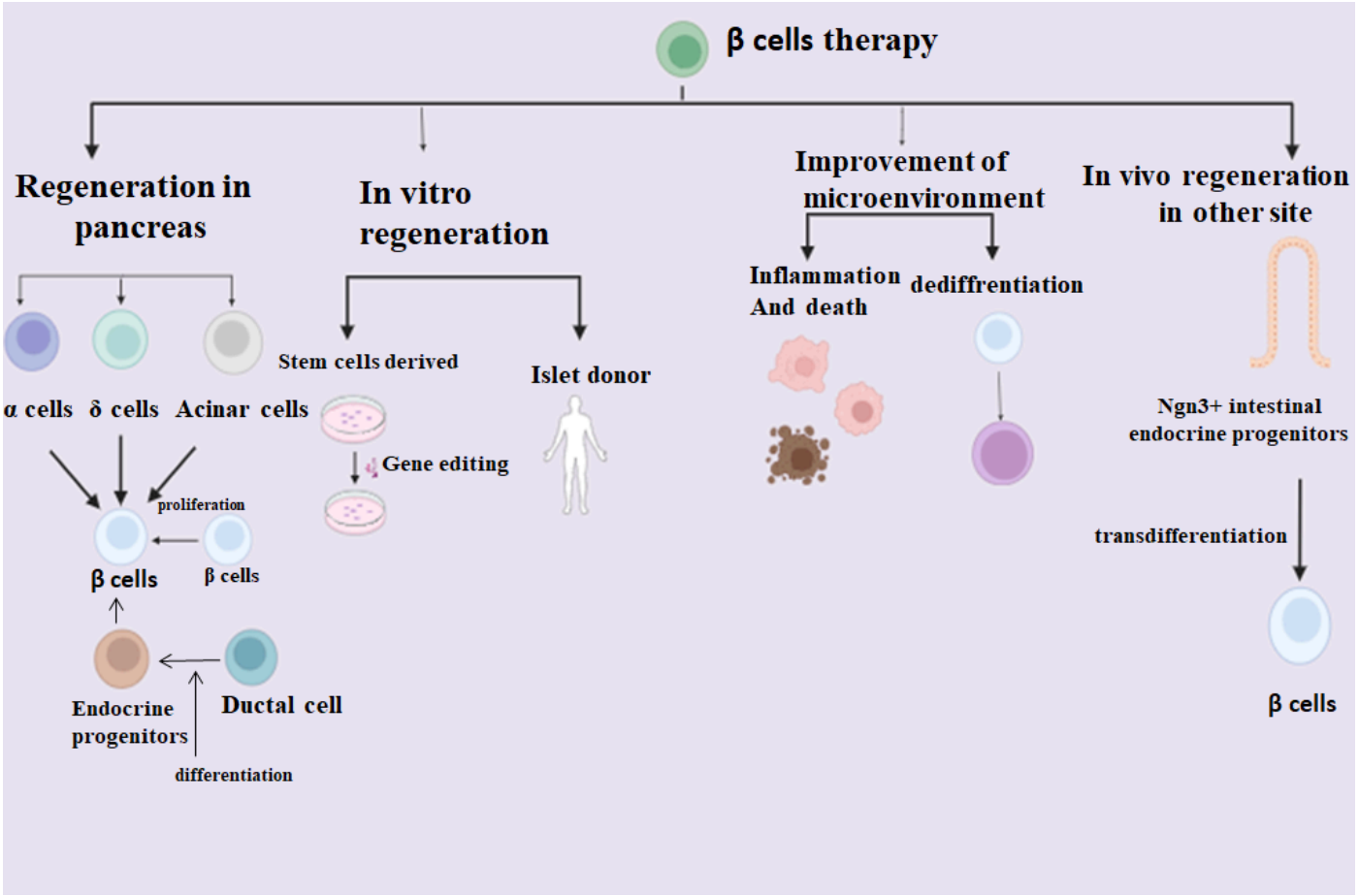

Fig.1 Mechanism involved in therapeutic Strategies for β cell regeneration [25]

Table 1- Pharmacological approach for β cell regeneration

Class of drug\ strategy	Mechanism of action	Example	Status	References
Immune modulation(protect β-cell)	Prevents autoimmune destruction, protects the surviving β-cells, and opens the window for regeneration.	Teplizumab (anti-CD3 mAB), antigen specific vaccines (GAD), Treg therapies	Teplizumab has been shown to delay the onset of T1D and preserve C-peptide in at-risk or recently diagnosed persons (FDA-approved for delay).	26
DYRK1A Inhibitor	Inhibit DYRK1A, trigger NFAT signaling, and promote β-cell proliferation.	Harmine , 5-IT	β-cells replicate well in animal and in vitro models; safety and targeting barriers prevent human application at this time.	27
Protective repurposed agents	Decrease β-cell stress and apoptosis through AMPK activation, TXNIP inhibition, and other.	Verapamil	Juvenile RCTs showed that verapamil retained C-peptide, while preclinical T1D and T2D showed β-cell protection.	28
Incretine based therapy	Improve the function, survival, and production of insulin by β-cells	**GLP-1receptor agonists(Liraglutide, Semaglutide) DPP-4 inhibitors (**Vildagliptin)	Extensively utilized in T2D; preclinical T1D research show β-cell protecting and regenerative properties; little clinical evidence points to a supporting role.	29
GABA based therapy	Potential α→β reprogramming, anti-inflammatory, and Immunomodulatory	GABA, GABA+ GAD-Alum vaccine	Mixed effects on C-peptide; safe in small RCTs; continuing trials	30
Senolytic \Senomorphics	Senescence-associated secretory phenotype (SASP) suppression and senescent β-cell elimination	Dasatinib+ Quercetin	In preclinical (mouse) T1D models, demonstrate improved β-cell activity and decreased inflammation; human T1D has not yet been tested.	31
Target delivery \ Nano medicine	Improved local impact, decreased systemic toxicity, and direct medication delivery to islets	Encapsulation systems, nanoparticles, and ligand-conjugates (such as islet-targeted prodrugs and GLP-1-conjugated nanoparticles)	Shown in preclinical proof-of-concept research; no human trials have been conducted yet, but it is essential for safe clinical translation.	32

Combination of small molecule	Synergistic pathway inhibition for stronger proliferation	DYRK1A + TGF-β\SMAD inhibiter, DYRK1A + GLP-Analogues	Ex vivo research in human islets demonstrates synergistic proliferation; in vivo investigations reveal increased β-cell mass; translation is constrained by safety issues and off-target consequences.	33

Fig. 2 – Differentiation Between Stem cell approach for β cell regeneration

Stem cell approach	Source	Action	Preclinical evidence	Risk	reference
Pluripotent stem cell (ESCs & iPSCs)	iPSCs & ESCs differentiated into insulinproducing cells	Produce functioning cells that produce insulin to replace destroyed β-cells.	Vertex's VX-880 trial: restored C-peptide, some patients reduced or stopped insulin	immunosuppression, tumorigenesis risk,long-term survival.	61
Mesenchymal stem cell (MSCs)	Bone marrow ,adipose, umbicalcord etc	Immunomodulation: pro-inflammatory cytokines, Tregs, and β-cell protection and regeneration	clinical studies: ↓HbA1c, ↑C-peptide, fewer hypoglycemic events, reduced insulin needs (esp. newly diagnosed	Variability in source/dose, heterogeneity, transient effect	62
Hematopoietic stem cell HSCs	Bone marrow	Reset or rebuild immune system to reduce autoimmune β –cells distruction	Some trials: partial remission, reduced insulin requirements	infection risk, conditioning regimen toxicity, limited safety	63
Exosome \ Extracellular vesicle based therapies	Vesicle from MSCs or other cell	Boost β-cell survival, adjust immunology, and increase insulin sensitivity	Preclinical: improved glucose tolerance, insulin sensitivity, β-cell protection; "educated EVs" induced insulin & C-peptide expression	Not standardized, durability unclear, early research stage	64

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It is not applicable

Consent to publish

It is not applicable

Consent for publication

It is not applicable.

Availability of data and materials

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Author contributions

Dr. Priya Pathak: Conceptualized the work, reviewed and edited the manuscript, and acquired funding. Ram Saran Kashyap: Writing Original Draft.

Competing interests

The authors declare no potential conflicts of interest concerning this article's research, authorship, and/or publication.

References

[1] Quattrin T, Mastrandrea LD, Walker LS. Type 1 diabetes. The Lancet. 2023 Jun 24;401(10394):2149-62.
[2] Yu XX, Xu CR. Understanding generation and regeneration of pancreatic β cells from a single-cell perspective. Development. 2020 Apr 1;147(7):dev179051.
[3] Robertson, M.A.; Padgett, L.R.; Fine, J.A.; Chopra, G.; Mastracci, T.L. Targeting polyamine biosynthesis to stimulate beta cell regeneration in zebrafish. Islets 2020, 12, 99–107.
[4] Zhong F, Jiang Y. Endogenous pancreatic β cell regeneration: a potential strategy for the recovery of β cell deficiency in diabetes. Frontiers in endocrinology. 2019 Feb 20;10:101.
[5] Efrat S. Beta-cell dedifferentiation in type 2 diabetes: concise review. Stem Cells. 2019 Oct 1;37(10):1267-72.
[6] Chernysheva MB, Ruchko ES, Karimova MV, Vorotelyak EA, Vasiliev AV. Development, regeneration, and physiological expansion of functional β-cells: Cellular sources and regulators. Frontiers in Cell and Developmental Biology. 2024 Jul 9;12:1424278.
[7] Robertson, M.A.; Padgett, L.R.; Fine, J.A.; Chopra, G.; Mastracci, T.L. Targeting polyamine biosynthesis to stimulate beta cell regeneration in zebrafish. Islets 2020, 12, 99–107.
[8] Bonner-Weir S. New evidence for adult beta cell neogenesis. Cell Stem Cell. 2021 Nov

4;28(11):1889
[9] Niu F, Liu W, Ren Y, Tian Y, Shi W, Li M, Li Y, Xiong Y, Qian L. β-cell neogenesis: A rising star to rescue diabetes mellitus. Journal of advanced research. 2024 Aug 1;62:71- 89.
[10] Sharma RB, Landa-Galván HV, Alonso LC. Living dangerously: protective and harmful ER stress responses in pancreatic β-cells. Diabetes. 2021 Nov 1;70(11):2431-43.
[11] Ikegami H, Babaya N, Noso S. b-Cell failure in diabetes: Common susceptibility and mechanisms shared between type 1 and type 2 diabetes. J Diabetes Invest 2021.
[12] Guney MA, Lorberbaum DS, Sussel L. Pancreatic β cell regeneration: to β or not to β. Current opinion in physiology 2020.
[13] Zhao H, Lui KO, Zhou B. Pancreatic beta cell neogenesis: debates and updates. Cell Metabolism. 2021 Nov 2;33(11):2105-7.
[14] Kalwat MA, Cobb MH. Mechanisms of the amplifying pathway of insulin secretion in the β cell. Pharmacology & therapeutics. 2017 Nov 1;179:17-30.
[15] Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Centers for Disease Control and Prevention, US Dept of Health and Human Services [Internet]. 2020
[16] Dotta F, Censini S, van Halteren AG, Marselli L, Masini M, Dionisi S, Mosca F, Boggi U, Muda AO, Prato SD, Elliott JF. Coxsackie B4 virus infection of β cells and natural killer cell insulitis in recent-onset type 1 diabetic patients. Proceedings of the National Academy of Sciences. 2007 Mar 20;104(12):5115-2
[17] Roep BO, Thomaidou S, Van Tienhoven R, Zaldumbide A. Type 1 diabetes mellitus as a disease of the β-cell (do not blame the immune system?). Nature Reviews Endocrinology. 2021 Mar;17(3):150-61.
[18] Wang W, Zhang C. Targeting β-cell dedifferentiation and transdifferentiation: opportunities and challenges. Endocrine Connections. 2021 Aug 1;10(8):R213-28.
[19] Spezani R, Reis-Barbosa PH, Mandarim-de-Lacerda CA. Update on the transdifferentiation of pancreatic cells into functional beta cells for treating diabetes. Life sciences. 2024 Jun 1;346:122645.
[20] Sachdeva MM, Claiborn KC, Khoo C, Yang J, Groff DN, Mirmira RG & Stoffers DA. Pdx1 (MODY4) regulates pancreatic beta cell susceptibility to ER stress. PNAS 2009 106 19090–19095.
[21] Efrat S. Mechanisms of adult human β‐cell in vitro dedifferentiation and redifferentiation. Diabetes, Obesity and Metabolism. 2016 Sep;18:97-101.
[22] Aguayo-Mazzucato C, Bonner-Weir S. Pancreatic β cell regeneration as a possible therapy for diabetes. Cell metabolism. 2018 Jan 9;27(1):57-67.
[23] Sintov E, Nathan G, Knoller S, Pasmanik-Chor M, Russ HA, Efrat S. Inhibition of ZEB1 expression induces redifferentiation of adult human β cells expanded in vitro. Scientific reports. 2015 Aug 12;5(1):13024.
[24] Efrat S. Mechanisms of adult human β‐cell in vitro dedifferentiation and redifferentiation. Diabetes, Obesity and Metabolism. 2016 Sep;18:97-101.
[25] Niu F, Liu W, Ren Y, Tian Y, Shi W, Li M, Li Y, Xiong Y, Qian L. β-cell neogenesis: a rising star to rescue diabetes mellitus. Journal of advanced research. 2024 Aug 1;62:71-89.
[26] Ramos EL, Dayan CM, Chatenoud L, Sumnik Z, Simmons KM, Szypowska A, Gitelman SE, Knecht LA, Niemoeller E, Tian W, Herold KC. Teplizumab and β-cell function in newly diagnosed type 1 diabetes. New England Journal of Medicine. 2023 Dec 7;389(23):2151-61.
[27] Wang P, Karakose E, Choleva L, Kumar K, DeVita RJ, Garcia-Ocaña A, Stewart AF. Human beta cell regenerative drug therapy for diabetes: past achievements and future challenges. Frontiers in Endocrinology. 2021 Jul 16;12:671946.
[28] Forlenza GP, Schamberger MS, Buckingham BA. Verapamil and Pancreatic Beta Cell Function in Pediatric Type 1 Diabetes—Reply. Jama. 2023 Jul 25;330(4):380.
[29] Wang KL, Tao M, Wei TJ, Wei R. Pancreatic β cell regeneration induced by clinical and preclinical agents. World Journal of Stem Cells. 2021 Jan 26;13(1):64.
[30] Ramdass PV, Rea N. GLP-1 receptor agonists and pancreatic beta cell apoptosis in diabetes

mellitus: a systematic review and meta-analysis of preclinical studies. Frontiers in Clinical Diabetes and Healthcare. 2025 Aug 27;6:1579961.

[31] Choat HM, Martin A, Mick GJ, Heath KE, Tse HM, McGwin Jr G, McCormick KL. Effect of gamma aminobutyric acid (GABA) or GABA with glutamic acid decarboxylase (GAD) on the progression of type 1 diabetes mellitus in children: Trial design and methodology. Contemporary Clinical Trials. 2019 Jul 1;82:93-100.

[32] Thompson PJ, Shah A, Ntranos V, Van Gool F, Atkinson M, Bhushan A. Targeted elimination of senescent beta cells prevents type 1 diabetes. Cell metabolism. 2019 May 7;29(5):1045-60.

[33] Bourgeois S, Coenen S, Degroote L, Willems L, Van Mulders A, Pierreux J, Heremans Y, De Leu N, Staels W. Harnessing beta cell regeneration biology for diabetes therapy. Trends in Endocrinology & Metabolism. 2024 Nov 1;35(11):951-66.

[34] Wang P, Karakose E, Liu H, Swartz E, Ackeifi C, Zlatanic V, Wilson J, González BJ, Bender A, Takane KK, Ye L. Combined inhibition of DYRK1A, SMAD, and trithorax pathways synergizes to induce robust replication in adult human beta cells. Cell metabolism. 2019 Mar 5;29(3):638-52.

[35] Wan XX, Zhang DY, Khan MA, Zheng SY, Hu XM, Zhang Q, Yang RH, Xiong K. Stem cell transplantation in the treatment of type 1 diabetes mellitus: from insulin replacement to beta-cell replacement. Frontiers in endocrinology. 2022 Mar 18;13:859638.

[36] Azarpira N, Kaviani M, Salehi S. The role of mesenchymal stem cells in diabetes mellitus. Int J Stem Cell Res Ther. 2015;2(2):1-5.

[37] Zhang T, Wang H, Wang T, Wei C, Jiang H, Jiang S, Yang J, Shao J, Ma L. Pax4 synergistically acts with Pdx1, Ngn3 and MafA to induce HuMSCs to differentiate into functional pancreatic β-cells. Experimental and therapeutic medicine. 2019 Oct;18(4):2592-8.

[38] Maacha S, Sidahmed H, Jacob S, Gentilcore G, Calzone R, Grivel JC, Cugno C. Paracrine mechanisms of mesenchymal stromal cells in angiogenesis. Stem cells international. 2020;2020(1):4356359.

[39] Song N, Scholtemeijer M, Shah K. Mesenchymal stem cell immunomodulation: mechanisms and therapeutic potential. Trends in pharmacological sciences. 2020 Sep 1;41(9):653-64.

[40] Zeinhom A, Fadallah SA, Mahmoud M. Human mesenchymal stem/stromal cell based-therapy in diabetes mellitus: experimental and clinical perspectives. Stem Cell Research & Therapy. 2024 Oct 29;15(1):384.

[41] De Klerk E, Hebrok M. Stem cell-based clinical trials for diabetes mellitus. Frontiers in endocrinology. 2021 Feb 26;12:631463.

[42] Wan XX, Zhang DY, Khan MA, Zheng SY, Hu XM, Zhang Q, Yang RH, Xiong K. Stem cell transplantation in the treatment of type 1 diabetes mellitus: from insulin replacement to beta-cell replacement. Frontiers in endocrinology. 2022 Mar 18;13:859638.

[43] Fujikura J, Anazawa T, Toyoda T, Ito R, Kimura Y, Yabe D. Toward a cure for diabetes: iPSC and ESC‐derived islet cell transplantation trials. Journal of Diabetes Investigation. 2025 Mar;16(3):384-8.

[44] Griffo A. Insulin independence from stem-cell-derived islets. Nature Biomedical Engineering. 2024 Dec;8(12):1507.

[45] Reichman TW, Ricordi CA, Naji AL, Markmann JF, Perkins BA, Wijkstrom MA, Paraskevas S, Bruinsma BO, Marigowda G, Shih JL, Wang CH. 836-P: glucose-dependent insulin production and insulin-independence in type 1 diabetes from stem cell–derived, fully differentiated islet cells—Updated data from the VX-880 clinical trial. Diabetes. 2023 Jun 23;72(Supplement_1):836-P

[46] Chu SN, Stock PG, Gardner JM. Implantation of autologous induced pluripotent stem cell-derived islets provides long-term insulin independence in a patient with type 1 diabetes. American Journal of Transplantation. 2024 Dec 1;24(12):2144-5.

[47] Kioulaphides S, García AJ. Encapsulation and immune protection for type 1 diabetes cell

therapy. Advanced drug delivery reviews. 2024 Apr 1;207:115205.

[48] Jeyagaran A, Lu CE, Zbinden A, Birkenfeld AL, Brucker SY, Layland SL. Type 1 diabetes and engineering enhanced islet transplantation. Advanced drug delivery reviews. 2022 Oct 1;189:114481.

[49] Pastore I, Assi E, Ben Nasr M, Bolla AM, Maestroni A, Usuelli V, Loretelli C, Seelam AJ, Abdelsalam A, Zuccotti GV, D'Addio F. Hematopoietic stem cells in type 1 diabetes. Frontiers in immunology. 2021 Jul 9;12:694118.

[50] D'Addio F, Valderrama Vasquez A, Ben Nasr M, Franek E, Zhu D, Li L, Ning G, Snarski E, Fiorina P. Autologous nonmyeloablative hematopoietic stem cell transplantation in new-onset type 1 diabetes: a multicenter analysis. Diabetes. 2014 Sep 1;63(9):3041-6.

[51] Hassanpour M, Salybkov AA, Kobayashi S, Asahara T. Anti-inflammatory Prowess of endothelial progenitor cells in the realm of biology and medicine. npj Regenerative Medicine. 2024 Sep 30;9(1):27.

[52] Voltarelli JC, Couri CE, Stracieri AB, Oliveira MC, Moraes DA, Pieroni F, Coutinho M, Malmegrim KC, Foss-Freitas MC, Simoes BP, Foss MC. Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. Jama. 2007 Apr 11;297(14):1568-76.

[53] Abou Zaki R, El-Osta A. Advancing type 1 diabetes therapy: autologous islet transplant breakthrough. Signal Transduction and Targeted Therapy. 2024 Dec 23;9(1):366.

[54] Wang L, Jiang X, Zhao F, Duan P, Li Z, Luo Y. A review of adipose-derived mesenchymal stem cells 'impacts and challenges: metabolic regulation, tumor modulation, immunomodulation, regenerative medicine and genetic engineering therapies. Frontiers in Endocrinology. 2025 May 29;16:1606847.

[55] Kim JE, Lee JW, Cha GD, Yoon JK. The Potential of Mesenchymal Stem Cell-Derived Exosomes to Treat Diabetes Mellitus. Biomimetics. 2025 Jan 14;10(1):49.

[56] Ghoneim MA, Gabr MM, El-Halawani SM, Refaie AF. Current status of stem cell therapy for type 1 diabetes: a critique and a prospective consideration. Stem cell research & therapy. 2024 Jan 29;15(1):23.

[57] Chidester S, Livinski AA, Fish AF, Joseph PV. The role of extracellular vesicles in β-cell function and viability: A scoping review. Frontiers in Endocrinology. 2020 Jun 11;11:375

[58] Chen J, Chen J, Cheng Y, Fu Y, Zhao H, Tang M, Zhao H, Lin N, Shi X, Lei Y, Wang S. Mesenchymal stem cell-derived exosomes protect beta cells against hypoxia-induced apoptosis via miR-21 by alleviating ER stress and inhibiting p38 MAPK phosphorylation. Stem cell research & therapy. 2020 Mar 4;11(1):97.

[59] Sun F, Sun Y, Wu F, Xu W, Qian H. Mesenchymal stem cell-derived extracellular vesicles: a potential therapy for diabetes mellitus and diabetic complications. Pharmaceutics. 2022 Oct 17;14(10):2208.

[60] Kou M, Huang L, Yang J, Chiang Z, Chen S, Liu J, Guo L, Zhang X, Zhou X, Xu X, Yan X. Mesenchymal stem cell-derived extracellular vesicles for immunomodulation and regeneration: a next generation therapeutic tool?. Cell Death & Disease. 2022 Jul 4;13(7):580.

[61] Yang M, Chen J, Chen L. The roles of mesenchymal stem cell-derived exosomes in diabetes mellitus and its related complications. Frontiers in endocrinology. 2022 Oct 21;13:1027686.

[62] Raoufinia R, Rahimi HR, Saburi E, Moghbeli M. Advances and challenges of the cell-based therapies among diabetic patients. Journal of Translational Medicine. 2024 May 8;22(1):435.

[63] Kashbour M, Abdelmalik A, Yassin MN, Abed M, Aldieb E, Abdullah DM, Elmozugi T, Isawi Y, Hassan E, Almuzghi F. Mesenchymal stem cell-based therapy for type 1 & 2 diabetes mellitus patients: a systematic review and meta-analysis of randomized controlled trials. Diabetology & Metabolic Syndrome. 2025 Jun 3;17(1):189.

[64] Ghoneim MA, Gabr MM, El-Halawani SM, Refaie AF. Current status of stem cell therapy for

type 1 diabetes: a critique and a prospective consideration. Stem cell research & therapy. 2024 Jan 29;15(1):23.

[65] Gabr MM, El-Halawani SM, Refaie AF, Khater SM, Ismail AM, Karras MS, Magar RW, Sayed SE, Kloc M, Uosef A, Sabek OM. Modulation of naïve mesenchymal stromal cells by extracellular vesicles derived from insulin-producing cells: an in vitro study. Scientific Reports. 2024 Aug 1;14(1):17844.

[66] So WY, Han W. Gene therapy targeting key beta cell regulators as a potential intervention for diabetes. EMBO Molecular Medicine. 2024 Jul 15;16(7):1490-4.

[67] Akinci E, Banga A, Greder LV, Dutton JR, Slack JM. Reprogramming of pancreatic exocrine cells towards a beta (β) cell character using Pdx1, Ngn3 and MafA. Biochemical Journal. 2012 Mar 15;442(3):539-50.

[68] Baeyens L, Lemper M, Leuckx G, De Groef S, Bonfanti P, Stangé G, Shemer R, Nord C, Scheel DW, Pan FC, Ahlgren U. Transient cytokine treatment induces acinar cell reprogramming and regenerates functional beta cell mass in diabetic mice. Nature biotechnology. 2014 Jan;32(1):76-83.

[69] Tschen SI, Zeng C, Field L, Dhawan S, Bhushan A, Georgia S. Cyclin D2 is sufficient to drive β cell self-renewal and regeneration. Cell cycle. 2017 Nov 17;16(22):2183-91.

[70] Chon S, Gautier JF. An update on the effect of incretin-based therapies on β-cell function and mass. Diabetes & metabolism journal. 2016 Apr;40(2):99-114.

[71] Stamateris RE, Landa-Galvan HV, Sharma RB, Darko C, Redmond D, Rane SG, Alonso LC. Noncanonical CDK4 signaling rescues diabetes in a mouse model by promoting β cell differentiation. The Journal of Clinical Investigation. 2023 Dec 20;133(18).

[72] Fatrai S, Elghazi L, Balcazar N, Cras-Méneur C, Krits I, Kiyokawa H, Bernal-Mizrachi E. Akt induces β-cell proliferation by regulating cyclin D1, cyclin D2, and p21 levels and cyclin-dependent kinase-4 activity. Diabetes. 2006 Feb 1;55(2):318-25.

[73] Tonne JM, Sakuma T, Deeds MC, Munoz-Gomez M, Barry MA, Kudva YC, Ikeda Y. Global gene expression profiling of pancreatic islets in mice during streptozotocin-induced β-cell damage and pancreatic Glp-1 gene therapy. Disease models & mechanisms. 2013 Sep 1;6(5):1236-45.

[74] Ma S, Viola R, Sui L, Cherubini V, Barbetti F, Egli D. β cell replacement after gene editing of a neonatal diabetes-causing mutation at the insulin locus. Stem cell reports. 2018 Dec 11;11(6):1407-15.

[75] Lotfi M, Butler AE, Sukhorukov VN, Sahebkar A. Application of CRISPR‐Cas9 technology in diabetes research. Diabetic Medicine. 2024 Jan;41(1):e15240.

[76] Aigha II, Abdelalim EM. NKX6. 1 transcription factor: a crucial regulator of pancreatic β cell development, identity, and proliferation. Stem cell research & therapy. 2020 Oct 29;11(1):459.

[77] Wang P, Karakose E, Choleva L, Kumar K, DeVita RJ, Garcia-Ocaña A, Stewart AF. Human beta cell regenerative drug therapy for diabetes: past achievements and future challenges. Frontiers in Endocrinology. 2021 Jul 16;12:671946.

[78] Rech Tondin A, Lanzoni G. Islet Cell Replacement and Regeneration for Type 1 Diabetes: Current Developments and Future Prospects: AR Tondin, G. Lanzoni. BioDrugs. 2025 Mar;39(2):261-80.

[79] Afelik S, Rovira M. Pancreatic β-cell regeneration: advances in understanding the genes and signaling pathways involved. Genome medicine. 2017 May 16;9(1):42.