American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article



# Diabetes in the Pediatric Population-can Stem Cell Therapy Overcome the Associated Burden Disease

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***To Cite This Article:*** *Jonathan RT Lakey*, Carolina Bluguermann, Ian Jenkins, Krista Casazza, Waldemar Lernhardt, et al. Diabetes in the Pediatric Population-can Stem Cell Therapy Overcome the Associated Burden Disease. Am J Biomed Sci & Res. 2025 27(1) AJBSR.MS.ID.003519,* **DOI:** 10.34297/AJBSR.2025.27.003519

**Received:** May 14, 2025; **Published:** May 19, 2025

## Abstract

Stem cell therapy represents a transformative frontier in the management of type 1 diabetes (T1D), particularly in pediatric populations, where early intervention can preserve residual β cell function and alter disease trajectory. Current strategies target both immune modulation and β cell regeneration using a variety of stem cell types. Mesenchymal stem cells (MSCs), known for their immunomodulatory and paracrine effects, have demonstrated potential in protecting β cells and improving glycemic control. Hematopoietic stem cells (HSCs) are explored for immune system "resetting," while induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) offer avenues for generating insulin-producing β -like cells. Advances in differentiation protocols now enable the production of functional islets from human pluripotent stem cells (hPSCs), marked by stage-specific transcription factors such as PDX1 and NKX6.1. Clinical trials conducted by ViaCyte and Vertex Pharmaceuticals have shown promising outcomes with ESC- and iPSC-derived islet transplants with achievment of partial and full insulin independence. Despite progress, challenges including immunogenicity, safety concerns (e.g., tumorigenesis), and integration issues still exist. Gene-editing tools including CRISPR/Cas9 further enhance the potential for personalized therapy, while innovative delivery methods such as encapsulation and site-specific implantation are improving efficacy. In pediatric trials, stem cell therapies have shown safety and potential for preserving β cell function. As these therapies move toward clinical maturity, optimizing cell source, immunologic compatibility, and delivery strategies remain critical. This review summarizes the evolving landscape, recent breakthroughs, and remaining challenges of stem cell-based therapies in pediatric diabetes and will highlight their potential to offer durable, disease-modifying interventions.

## Introduction

Type 1 diabetes (T1D) is a chronic autoimmune disease that typically develops in childhood, with the immune system attacking insulin-producing $\beta$ cells in the pancreas which leads to lifelong insulin dependence1. The prevalence of T1D in children has been rising globally, with an estimated 1.1 million children and adolescents affected worldwide, and incidence rates increasing by about 3% annually [1]. Current treatments rely primarily on insulin therapy, delivered via multiple daily injections or insulin pumps, in conjunction with continuous glucose monitoring (CGM) systems to assess and maintain blood sugar levels [2]. While these advances improve management, they do not cure the disease or prevent long-term complications such as cardiovascular disease, kidney failure, and neuropathy. Unmet needs in pediatric T1D care include the development of curative therapies, better glycemic control methods, and strategies to prevent or delay disease onset [3]. Challenges include the burden of daily disease management, risk of life-threatening hypoglycemia, and disparities in access to advanced diabetes technologies. Emerging research is focused on $\beta$ cell replacement through stem cell therapy, immunotherapies to halt autoimmune destruction, and artificial pancreas systems to automate insulin delivery [4]. Despite these advancements, achieving a durable cure remains an unmet challenge, emphasizing the need for continued innovation in pediatric diabetes research and care [5].

Recent advances have been made in the study of T1D, particularly within the field of pediatric diabetes. Current strategies aim to regenerate $\beta$ cells, modulate the immune response, or replace lost islet cells. Various types of stem cells are under investigation, including mesenchymal stem cells (MSCs) for their immunomodulatory effects, hematopoietic stem cells (HSCs) for immune resetting, and induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs) for generating functional $\beta$ -like cells [4].

In pediatrics, the focus is primarily on early intervention to preserve residual $\beta$ cell function and prevent disease progression. Current applications of stem cell therapy in diabetes center on both replacing lost pancreatic $\beta$ cells and modulating the immune system to preserve or restore insulin production. To date, five types of stem cells are under evaluation for these purposes, with the potential for differentiation and proliferation varying considerably among sources [1,3,4]. These include mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs), and umbilical cord stem cells (CB) [6].

i. MSCs are derived from various sources which include bone marrow, umbilical cord, and adipose tissue. MSCs are used primarily for their immunomodulatory and anti-inflammatory properties, aiding in the protection of existing $\beta$ cells from autoimmune attack. They also have paracrine effects promoting a regenerative environment in the pancreas. *Ammar, et al.,* [7]. evaluated the effectiveness of bone marrow-derived MSCs (BM-MSCs) and adipose-derived MSCs (AD-MSCs) in improving induced cardiac dysfunction in diabetic rats. They found that both types of MSCs were effective, primarily by enhancing angiogenesis, reducing immune cell infiltration, and minimizing collagen buildup. MSCs have been tested in clinical trials for both type 1 and type 2 diabetes, showing improvements in blood glucose control and reduction in insulin requirements [8].

ii. In newly diagnosed patients with type 1 diabetes, autologous HSC transplantation can be applied to “reboot” or “reset” the immune system to stop the autoimmune destruction of $\beta$ cells. Some trials have reported periods of insulin independence in treated patients [9].

iii. iPSCs are reprogrammed from adult somatic cells that can be differentiated into insulin-producing $\beta$ -like cells. Research is advancing toward using patient-derived iPSCs to create personalized cell therapies, reducing the risk of immune-rejection. iPSC-derived $\beta$ cells are being tested in preclinical and early clinical studies [10,11].

iv. ESCs can also be differentiated into functional pancreatic progenitors or mature $\beta$ cells. ViaCyte has developed ESC-derived insulin-producing cells encapsulated in protective devices to transplant into patients without the need for immunosuppression [11,12].

v. In the early stages of type 1 diabetes, the damaged islet $\beta$ cells stimulate the production of large quantities of antibodies and effector T cells against $\beta$ cells and insulin. This autoimmune response leads to further immune attack on islets. By interacting with IL-10 and CD14 monocytes, MSCs are capable of suppressing the proliferation and activation of T cells [9,13,1415].

Pancreatic organogenesis is a highly intricate process in which the pancreatic endoderm responds to specific temporal and spatial signals, eventually forming functional $\beta$ -cell mass16. The key stages of organ development and biomarkers associated with hPSCs have been mapped and specified. Typically, hPSCs, whether derived from iPSCs or ECSs can differentiate into definitive endoderm and then into pancreatic endoderm (PE). This differentiation is marked by PDX-1 expression. Upregulation of SOX9 and NKX6.1 promotes PE development into either alveolar progenitor cells or ductal/endocrine progenitor cells. These progenitor cells then transition into NGN-3$^{+}$ endocrine progenitors, which can ultimately be induced to become hormone-producing cells, including α cells, $\beta$ cells, $\delta$ cells, and $\gamma$ cells [14].

Widely used gene-editing technologies, such as the CRISPR/Cas system and zinc finger nucleases (ZFNs), can enable the creation of known diabetes-related mutations or the correction of mutations in hPSCs, which retain the specific genetic information and mutations

of the donor tissue, serving as a powerful tool for diabetes research. Maehr and colleagues [17] successfully generated hPSCs from patients with type 1 diabetes and differentiated them into $\beta$ -like cells reporting a response to glucose both *in vitro* and *in vivo*. The hPSCs were also sensitive to antidiabetic drugs such as sulfonylureas, GLP-1R agonists, and GCK activators and $\beta$ -like cells derived from diabetic patients did not show significant differences compared to those from non-diabetic individuals. Furthermore, transplantation of these T1D $\beta$ -like cells into immunodeficient mice effectively protected against streptozocin (STZ)-induced diabetes [18].

## Benefits of Stem Cell Therapy

Stem cells offer a revolutionary avenue for regenerative medicine, with the potential to repair or replace damaged tissues and treat degenerative diseases. Therapies using stem cells can be either allogeneic (donor-derived) or autologous (patient-derived), each with unique advantages and risks. Allogeneic cells offer immediate availability and scalability but carry risks including immune rejection and graft-versus-host disease, while autologous therapies eliminate rejection concerns but face challenges with cell quality and resource-intensitve processing. Induced iPSCs and MSCs are key players; iPSCs offer broad differentiation potential ideal for specialized cell replacement but carry tumorigenic risks, whereas MSCs are safer and mainly support tissue repair through immunomodulation [19-21].

## Safety Concerns

Stem cell therapy offers powerful therapeutic potential due to abilities in tissue repair and immunomodulation through mechanisms like direct cell communication, secretion of bioactive factors, and extracellular vesicle release. Ensuring the safety of stem cell-based therapies, however, requires careful consideration of cell source. Allogeneic MSCs undergo extensive donor screening, immune compatibility testing, and standardized manufacturing to mitigate risks, while autologous MSCs, though less regulated for immune compatibility, must be individually evaluated due to patient-specific factors like age or disease state that could impair cell function. Advances in reprogramming technologies have further enhanced the scalability and control of MSC generation, offering more consistent therapeutic products [22,23].

Clinical studies across diseases highlight the efficacy and safety differences between autologous and allogeneic MSCs. In diabetes, both autologous and allogeneic MSCs support $\beta$ -cell preservation, but variability in autologous cells from type 2 diabetes patients raises concerns about efficacy [24]. Similarly, for autoimmune diseases, autologous MSCs from patients may be compromised by systemic inflammation and senescence, potentially reducing therapeutic benefits or exacerbating disease. Consequently, strategies including the use of healthy donor-derived allogeneic MSCs or enhancement of MSC function through preconditioning or genetic modification are being explored to optimize safety and efficacy [25].

Despite the promise of stem cell therapies, significant risks persist, including tumor formation, immune complications, and poor cell integration [22]. Differentiated stem cells are safer for direct transplantation but limited in regenerative scope, while undifferentiated cells offer broader applications with higher risks. Moreover, improper processing and the rise of unregulated stem cell clinics have led to documented cases of serious harm and death. Thus, while stem cell-based treatments are advancing, careful consideration of disease context, stem cell type, and safety measures is critical to their successful and responsible clinical use [26].

## Current Implementation

Most applications currently remain experimental or in clinical trial phases, with no stem cell therapy yet approved as a standard treatment for diabetes. Research trends are moving toward combinations of regenerative, immunomodulatory, and protective strategies which use stem cells to achieve durable insulin independence with minimal side effects; this review summarizes the current knowledge, trends, and challenges in stem cell therapy for pediatric diabetes.

In 2012, the groundbreaking discovery that mature cells can be reprogrammed into a pluripotent state by Sir John B. Gurdon and Shinya Yamanaka, eliminated the need for embryonic tissue by demonstrating that adult dermal fibroblasts could be converted into stem cells [27]. This breakthrough significantly advanced research in personalized and autologous medicine, allowing the generation of patient-specific cells, potentially bypassing the requirement for lifelong immunosuppression after transplantation. These findings pivoted research focus toward utilizing hPSCs to create insulin-producing $\beta$ cells as a potential cure [28]. However, obstacles still remain with early methods not generating cells capable of secreting insulin in response to glucose at physiologically relevant levels. Researchers have since identified key developmental markers that enhance $\beta$ -cell-specific transcriptional pathways and proinsulin processing, leading to improved differentiation protocols [29].

In 2020, *Wu, et al.,* published a systematic review and meta-analysis [30] to evaluate the efficacy and safety of stem cells transplantation (SCT) in patients with T1D. Of twenty-nine studies (n=487 patients with T1D), only seven were conducted in pediatric populations. No substantial publication bias was apparent with studies demonstrating that SCT led to a significant decrease HbA1c and significantly improved C-peptide levels evaluated at 1 year follow-up. Significant improvement of metabolic outcomes were also observed in the subgroups of MSCs combined with HSCs, with a significant age effect illustrating that age was directly associated with the efficacy in HSCs subgroup. A higher glutamic acid decarboxylase antibody (GADA) positive rate before treatment was also significantly associated with the decrease of daily insulin requirement. The transient insulin independence rate at last follow-up was 9.6 per 100 person-years, with the mean length of insulin independence reported to be 15.6 months and mortality

associated with SCT was 3.4%. The authors concluded that SCT is an efficacious and safe method for treatment of T1D patients, especially in the subgroups of MSCs combined HSCs and HSCs30.

The ViaCyte trial marked one of the earliest and most significant landmarks in developing stem cell-based therapy. ViaCyte is a biotechnology company that pioneered the use of stem cell-derived pancreatic progenitor cells (PEC-01) encapsulated within a semi-permeable device (VC-01) that prevented vascularization but allowed for nutrient exchange while protecting the cells from immune attack [31]. The goal was to mature these cells into insulin-producing $\beta$ cells *in vivo* after transplantation. Early trials demonstrated partial engraftment and insulin production but faced challenges, including insufficient cell survival, suboptimal differentiation into functional $\beta$ cells, and a lingering immune response despite the encapsulation strategy. The surviving cells became sparse within 12 weeks in most cases, theoretically due to hypoxic conditions caused by multinucleated giant cells surrounding the device. To address these limitations, ViaCyte advanced their technology with VC-02, a non-encapsulated approach requiring immunosuppression to improve vascularization and engraftment, leading to better $\beta$ -cell function. However, while these trials validated the feasibility of stem cell-derived therapies, they underscored the need for more mature $\beta$ cells and improved delivery methods (NCT03163511) [32]. However, over the 1-year observation period, C-peptide levels remained at only ~1% of normal ranges, and no clear therapeutic effect was observed. This work laid the foundation for the Vertex Pharmaceutical VX-880 trial, which took an alternative approach by transplanting fully differentiated, stem cell-derived insulin-producing $\beta$ cells rather than pancreatic progenitors.

In 2021, Vertex Pharmaceuticals seeking to achieve insulin independence and prevent severe hypoglycemic episodes, conducted transplantation of stem cell-derived $\beta$ cells alongside an immunosuppressive regimen in the Phase 1 trial of VX-880; the trial utilized hPSCs. These were derived by reprogramming adult somatic cells back into a pluripotent state using specific transcription factors. In this trial, the hPSCs were derived from embryonic stem cell derived $\beta$ cells (hESC-derived), which to date have been more widely studied for $\beta$ -cell differentiation. Several participants achieved HbA1c levels < 7% without requiring exogenous insulin administration. This breakthrough marked a significant step toward a functional cure. While the need for lifelong immunosuppression remains a challenge, the trial demonstrated the feasibility of using stem cell-derived $\beta$ cells as a potential therapeutic treatment [4].

As the study advanced to Phase 2, findings presented at the 2022 ADA Scientific Sessions were encouraging, with all participants (n=12) exhibiting islet engraftment and production of their own insulin. On November 4, 2024, the company announced the expansion of the ongoing Phase 1/2 trial into a Phase 1/2/3 study, aiming to enroll 50 patients who will receive a single dose of VX-880 (*https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-positive-results-ongoing-phase-12-study-vx-880*). While the long-term outcomes remain uncertain, these early results are highly encouraging.

In an open, single-center, randomized pilot study, twenty adults ages 18-40 years diagnosed <3 weeks before enrollment and with a stimulated C-peptide level >0.1 nmol/L *Carlsson, et al.,* [33] evaluated the safety of autologous MSCs as treatment [34]. Residual $\beta$ -cell function was analyzed as C-peptide concentrations in blood in response to a mixed-meal tolerance test (MMTT) at the 1-year follow-up. C-peptide peak values and C-peptide when calculated as area under the curve during the 1st year were preserved or even increased in MSC treated compared to non-treated controls. No side effects of MSC treatment were observed suggesting a safe and promising strategy to intervene in disease progression and preserve $\beta$ -cell function. Similarly, in *Hu, et al.,* [35] randomized newly diagnosed patients to receive Wharton's Jelly (WJ)-MSCs or normal saline based on insulin intensive therapy. There were no reported acute or chronic side effects in either group. However, patients treated with WJ-HSC showed improved HbA1c and C peptide relative to pretherapy values and the control group, demonstrating safety and effectiveness. Dave and colleagues [36] reported on young adult and adolescent males aged 22 and 15 years, respectively, with T1DM since 6 and 11 years, on exogenous insulin therapy. They infused *in vitro* generated insulin-making cells trans-differentiated from donor adipose tissue derived MSCs and BM-MSCs in their abdominal subcutaneous tissue, portal and thymic circulation under non-myeloablative conditioning. Euglycemia was reported in both withHbA1c of 6.3% and 6.8% and insulin requirement dropping by 44 and34 IU/day, respectively.

In 2022, *Du, et al.,* [37] generated islets from human chemically induced pluripotent stem cells (hCiPSC-islets) and infused them into diabetic non-human primates (macaques). The one-time infusion restored endogenous insulin secretion and improved glycemic control. Fasting and average pre-prandial blood glucose levels significantly decreased in all macaques. In addition, there was an increase in C-peptide release and body weight. Long-term follow-up (n=4) showed an average decrease in HbA1c by over 2% compared with peak values. The average exogenous insulin requirement reduced by nearly 50%, 15 weeks after transplantation.

More recently, *Wu, et al.,* [38] utilized endometrial stem cells (EnSCs) derived from the endometrial lining for diabetes therapy. EnSCs exhibit strong regenerative and immunomodulatory properties, making them a promising therapeutic candidate. They exhibit high proliferation rates, low immunogenicity, and secrete growth factors that promote pancreatic $\beta$ -cell survival. The group conducted a clinical trial to investigate the autologous transplantation of EnSC-derived pancreatic cells in a type 2 diabetes patient with a prior kidney transplant. Despite residual insulin secretion, the patient achieved insulin independence 11 weeks post-transplant, with HbA1c dropping from 6.6% to a stable normal range for over a year.

In late 2024, *Wang, et al.,* [39]. reported on the feasibility of autologous transplantation of chemically induced pluripotent stem-cell-derived islets (CiPSC islets) beneath the abdominal anterior rectus sheath for type 1 diabetes treatment. The iPSCs were generated from a 25-year-old woman using a proprietary chemical reprogramming method and differentiated into islet cell clusters, containing approximately 60% insulin-producing $\beta$ -cells. Preclinical trials in 244 immunodeficient mice showed no tumor formation. The female patient had a history of liver and pancreas transplants and received the islet cells under the anterior rectus sheath with immunosuppressive therapy. Prior to transplantation, she required 43 units of insulin daily, but achieved insulin independence within 75 days, which lasted a year. Glycemic control significantly improved, with HbA1c dropping from 7.6% to below 5.7% and time-in-range glucose increasing to over 98%. No severe hypoglycemic events occurred post-transplantation. Imaging confirmed no abnormal graft growth or tumors, and adverse effects were minimal. This breakthrough demonstrates the potential of chemically produced iPSC-derived islet transplantation as a transformative approach to stem cell therapy.

*Ghoneim, et al.,* [40] transplanted allogeneic IPCs derived from hAT-MSCs into STZ-diabetic humanized mice (NOG-EXL mice, Taconic, Bioscience, Rensselaer, NY, USA). The findings from the study confirmed that the transplantation of allogeneic hAT-MSCs into diabetic humanized mice normalized their blood sugar levels. An allogeneic immune response was not detected and differentiated IPCs accounted for only ~20% of the transplanted cells, suggesting that the undifferentiated population exerted an immunomodulatory effect.

The long-term benefit of autologous BM-MSC transplantation stimulated with filgrastim, without immune suppression was reported by *Mesples, et al.,* [41]. Among patients with chronic type 1 diabetes average age 36 years (n=134; 65 female) marrow stem cell transplantation protocol. Post transplantation c peptide, HbA1C, pancreatic islets and GADA and insulin dose were assessed at 6, 12, 24 and 36 months. Diabetes related parameters begin to how improvement at six months, across variables, with no evidence of new pancreatic antibodies or adverse events. The results of the three years of follow-up demonstrated safety and importantly restoration of pancreatic function with a significant increase in C-peptide levels and by consequence, significant decrease in the daily dose of exogenous insulin needed without an increase in ICA and GADA.

Clinical trials increasingly evaluate combination approaches, integrating bioengineered scaffolds, metabolic interventions, and immune tolerance induction to enhance engraftment and function. Savio-Silva and colleagues [21] reported that autologous MSCs from individuals with type 1 diabetes exhibited preserved morphology, growth kinetics, multipotency, and proliferative, immunomodulatory, immunosuppressive, and migratory capacities, while those from individuals with type 2 diabetes exhibited greater senescence, lower viability, increased apoptosis, less proliferative potential associated with increased doubling time, and a reduction in angiogenic potential. As such, testing of autologous transplantation including the type of diabetes, time elapsed since the diagnosis due to cellular metabolic memory, and cell source, which may impair MSC functional properties may be essential. Packman and colleagues also demonstrated allogeneic BM-derived MSCs were safe and improved diabetic nephropathy complication after administration in a randomized and placebo-controlled clinical study.

## Pediatric Applications

While the adult trials cited above show promise, there is limited information on clinical trials specifically focusing on pediatric patients with type 1 diabetes. However, there are institutions currently engaged in stem cell research for applications within the pediatric population [19].

Pediatric patients present distinct physiological characteristics that necessitate tailored considerations in the design of clinical trials for stem cell therapy in diabetes. Children possess an immature immune system, which not only predisposes them to autoimmune conditions including T1D but also influences their response to immunomodulatory treatments. This immaturity can affect the efficacy and safety profiles of stem cell-based interventions, including MSC therapy. Few stem cell based therapies are under investigation for their potential to modulate immune responses in autoimmune diabetes [42]. Additionally, the metabolic demands of children differ from adults due to ongoing growth and development, influencing pharmacokinetics including drug absorption, distribution, metabolism, and excretion, and thus requiring age-specific dosing and monitoring in clinical trials [43]. Ethical considerations are paramount, as children cannot provide informed consent, necessitating parental permission and, when appropriate, the child's assent [44]. Recruitment for pediatric trials also poses challenges due to the lower prevalence of type 2 diabetes in children and potential socioeconomic barriers, particularly among underserved populations [45]. To address feasibility concerns, trial designs may incorporate broader eligibility criteria and leverage external control data to augment limited pediatric sample sizes [46]. Overall, the unique physiological, developmental, and ethical considerations in pediatric populations demand meticulous clinical trial design to ensure the safety and efficacy of stem cell therapies in treating diabetes among children.

*Mesples, et al.,* [47] recently reported on children ages 6 to 10 years (n=6) recently diagnosed with type 1 diabetes mellitus with the presence of islet cell antibodies (ICA), antibodies against islet antigen-related tyrosine phosphatase 2 (IA2), GADA, and anti-insulin antibodies (AIA). ICA, IA2, GAD, AIA and ketoacidosis. The children were treated with an ABMSC stimulated with Filgrastim, granulocyte colony-stimulating factor (G-CSF), 10 ug/kg/day for 4 days. Assessment of the antibodies and hemoglobin A1c (HbA1c) revealed a significant decline (to a negative vale from positive pre-treatment and a gradual, yet significant decrease in IA2 while AIA

remained high. A significant decrease in blood glucose and HbA1C levels was also observed with no complications. This small study demonstrated that autologous HSCT without immunoablation was safe and effective in significantly decreasing the production and effect of autoantibodies against ICA, GAD, and IA2, as well as decreasing blood sugar levels and HbA1c. The advancements and evolution of research presented herein may pave the way for future pediatric clinical trials. Parents and caregivers interested in enrolling their children in such studies should consult with pediatric endocrinologists and monitor clinical trial registries for emerging trial opportunities.

## Discussion

Stem cell -based approaches offer major therapeutic promise for diabetes due to their inherent regenerative abilities and immunomodulatory functions. These strategies aim to restore glucose metabolism and immune balance by leveraging the ability of stem cells to both regenerate insulin-producing cells and modulate immune responses. The regenerative potential of stem cells provides a renewable source of glucose-responsive insulin-secreting cells for transplantation, while their immunomodulatory effects may help halt $\beta$ -cell destruction, preserve remaining $\beta$ -cell mass, support endogenous $\beta$ -cell regeneration, reduce graft rejection, and prevent autoimmune relapse. Consequently, stem cells could be used alone or alongside $\beta$-cell replacement therapies to correct hyperglycemia in type 1 diabetes. Various sources of stem cells have been investigated for these purposes, including ESCs, iPSCs, HSCs, UCB-derived MSCs, adipose tissue-derived MSCs, pancreas-derived progenitor cells located in the ductal and exocrine tissue, as well as progenitor cells from the spleen, liver, endometrium, and neural tissues.

In 2006, pluripotency genomic factors, coined "Yamanaka Factors," were discovered. These factors possesses the capacity to reprogram mature somatic cells back to their iPSC [23]. The iPSCs can then be differentiated into specialized cell types, including islet cells. Today, iPSCs represent a valuable source for generating insulin producing $\beta$ cells. Patient-specific iPSCs can be created and thus offering a promise for personalized cell therapy since they can be derived from a patient's own cells which potentially avoids immune suppression [48]. The iPSCs provide the unique advantage of generating patient-specific, fully differentiated insulin-producing $\beta$ cells, potentially offering a functional cure for T1D. Despite continued advancements, major hurdles for iPSC-based therapy still exisit, including the need for complex differentiation protocols, the potential risk of tumor formation, and the requirement for immunosuppression when allogeneic iPSCs are used. While autologous iPSC-derived $\beta$ cells could eliminate the need for immunosuppression, the process remains expensive and time-consuming. While differentiated islets from iPSCs have high potential as therapeutic agents and even cures for T1D, there are challenges with iPSC consistency and possess safety risks associated with mutations accumulated during reprogramming.

EnSCs offer immunomodulatory and regenerative benefits similar to MSCs but with potentially greater accessibility and expansion potential. While they cannot directly replace $\beta$ cells like iPSCs, they could serve as an adjunct therapy to enhance $\beta$ -cell survival, reduce inflammation, and improve transplantation outcomes. Future research will be key in determining their optimal application in diabetes treatment, whether as a standalone therapy or in combination with $\beta$ -cell replacement strategies. Due to the high cost and time required for autologous iPSC procedures, researchers are pursuing allogeneic iPSC transplantation with immunosuppression. An interesting clinical trial scheduled to initiate during 2025 at Kyoto University Hospital will test OZTx-410, an islet cell sheet from clinical-grade iPSCs, in three high-risk type 1 diabetes patients [49].

## Summary and Future Directions

Stem cell therapy for diabetes is an emerging, experimental field with promising strides but there still is no approved standard treatments to date. A major advancement includes the reprogramming of adult somatic cells into hPSCs which enables personalized, autologous therapies. Early trials, including ViaCyte's encapsulated pancreatic progenitors and Vertex's VX-880 fully differentiated $\beta$ -cell transplants, demonstrated insulin production and glycemic control, though long-term immunosuppression remained a challenge. MSCs, both autologous and allogeneic, have shown safety and potential for preserving endogenous $\beta$ -cell function. Recent pediatric studies and trials involving chemically induced pluripotent stem cells highlight expanding therapeutic options. Despite varying efficacy, most trials report improved C-peptide levels, HbA1c reductions, and reduced insulin requirements, with minimal adverse effects. Future efforts will likely focus on optimizing $\beta$ -cell differentiation protocols, improving graft survival through vascularization and immune shielding, and developing off-the-shelf allogeneic iPSC-derived therapies. Pediatric-specific studies, combination strategies using bioengineered scaffolds, and immune tolerance induction represent the next critical steps. Stem cell therapies must also address regulatory issues, cost, and scalability challenges. Ultimately, the integration of regenerative, immunomodulatory, and personalized approaches may usher in a functional cure for T1D.

The establishment of iPSC banks and the concurrent advancement of human leukocyte antigen (HLA) matching strategies represent a pivotal shift toward the realization of scalable, "off-the-shelf" allogeneic cell therapies. iPSC banks aim to create a repository of well-characterized, clinically compliant cell lines derived from donors with homozygous HLA haplotypes, enabling a broad coverage of the population while minimizing the risk of immune rejection. In Japan, the CiRA initiative demonstrated that just 50 HLA homozygous iPSC lines could cover over 90% of the Japanese population [50,51], a strategy now emulated globally. Efforts in Europe and the United States have expanded upon this framework, with international consortia such as the Global Alliance

for iPSC Therapies (GAiT) promoting standardization and sharing of HLA-typed cell lines [52]. Advances in gene-editing technologies, particularly CRISPR-Cas9, have further enabled the engineering of "hypoimmunogenic" iPSCs by deleting or modulating HLA class I and II expression while preserving NK cell evasion markers, such as HLA-E or CD [47], to generate universal donor cells [53,54]. These developments collectively increase the feasibility of iPSC-derived therapies for broad, immediate application without the need for patient-specific derivation. However, the challenge remains to balance immune evasion with safety, particularly tumorigenicity and functional integration. Regulatory guidance and harmonized GMP-compliant production pipelines are critical as these iPSC banks transition from experimental infrastructure to therapeutic mainstays [55]. Overall, HLA-matched or engineered universal iPSC lines offer a promising pathway toward accessible and equitable T1D regenerative therapies.

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