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Review Article

Stem Cells: Novel Opportunities for Patients with Diabetes

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Abstract

Diabetes remains a major global health challenge, with current treatments primarily centered on insulin administration and glucose monitoring. Despite advancements in insulin analogs and continuous glucose monitoring, complications persist, highlighting the need for novel therapeutic approaches. Human pluripotent stem cells (hPSCs) have emerged as a promising avenue for diabetes therapy, offering the potential for insulin-producing beta-cell replacement. Early trials, such as ViaCyte's PEC-01 and Vertex Pharmaceuticals' VX-880, demonstrated the feasibility of stem cell-derived beta-cell transplantation but underscored challenges such as immune rejection, suboptimal engraftment, and the need for immunosuppression. Recent studies have explored chemically induced pluripotent stem cells (iPSC) and endometrial stem cells (EnSCs) for improved glycemic control and insulin independence, with promising preclinical and early clinical outcomes. Furthermore, allogeneic mesenchymal stem cells (MSCs) are being investigated for their immunomodulatory and regenerative properties, providing a complementary approach to beta-cell replacement by protecting residual beta-cell function. While autologous iPSC-derived beta cells offer a theoretically immunosuppression-free solution, the high cost, risk of tumorigenicity, and complex differentiation protocols remain significant hurdles. Conversely, allogeneic MSCs provide a scalable and standardized option, with advances in immune-evasive strategies enhancing therapeutic potential. The integration of bioengineered scaffolds, metabolic interventions, and immune tolerance induction is expected to further optimize stem cell-based diabetes therapies. Ongoing clinical trials continue to refine these approaches, paving the way for transformative treatments that may ultimately provide a functional cure for diabetes.

Introduction

While contemporary therapies for diabetes largely center on insulin administration and monitoring, a cure continues to elude scientists. Indeed, technology has significantly advanced the type of insulin delivered (i.e., genetically engineered insulin analogues,

with a much faster acting time (5-30 min), and blood glucose (BG) monitoring techniques (e.g. continuous glucose monitor (CGM)), complications are still frequent and adverse impacta quality of life and life expectancy. Further, although continued efforts to improve transplant therapies and accompanying immunosuppressive regimens, organ transplants have substantial drawbacks and limited candidates for the procedures. Nearly a half century after the first autogenic islet transplantation, and a quarter of a century since the group in Edmonton Canada published the Edmonton Protocol using cadaveric islets in diabetic patients [1], the huge barrier to the feasibility of this approach has not led to the anticipated "cure" of this disease. Thus, novel therapeutic approaches have continued to evolve [2].

Human Pluripotent Stem Cells (hPSCs) in Diabetes Therapy

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 [3]. 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. This discovery pivoted the focus towards utilizing human-induced pluripotent stem cells (hPSCs) to create insulin-producing beta cells as a potential cure. However, obstacles remained 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 [4-6].

The ViaCyte trial marked one of the earliest and most significant efforts in developing stem cell-based therapy. ViaCyte, a biotechnology company, 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 nutrient exchange while protecting the cells from immune attack. 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 [7] To address these limitations, ViaCyte advanced its 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) [8]. However, over the 1-year observation period, C-peptide levels remained at only ~1% of normal ranges, and no clear therapeutic effect was observed. Further, potent systemic immune suppression persisted.

This work laid the foundation for Vertex Pharmaceuticals' VX-880 trial, which took a different 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 a Phase 1 trial of VX-880 (*https://www.hsci.harvard.edu/news/new-therapy-treating-type-1-diabetes*). The trial utilized human pluripotent stem cells (hPSCs). The hPSCs were generated by reprogramming adult somatic cells back into a pluripotent state using specific transcription factors. in this trial, 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 treatment. 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 producing their own insulin *https://www.clinicaltrialsarena.com/news/vertex-type-1-diabetes-trial/*). 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://www.thejdca.org/publications/report-library/archived-reports/2024-reports/vertex-t1d-trial-moves-into-phase-iii.html*). While the long-term outcomes remain uncertain, these early results are highly encouraging.

In 2022, *Du, et al* generated islets from human chemically induced pluripotent stem cells (hCiPSC-islets) and infused them into diabetic non-human primates (macaques) [9]. 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* [10] utilized endometrial stem cells (EnSCs) derived from the endometrial lining for diabetes therapy. EnSCs exhibit strong regenerative and immunomodulatory properties, making them a promising candidate. They have a high proliferation rate, 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.

Due to the high cost and time required for autologous iPSC procedures, researchers are pursuing allogeneic iPSC transplantation with immunosuppression. A clinical trial beginning in 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 [11].

EnSCs offer immunomodulatory and regenerative benefits similar to MSCs but with potentially greater accessibility and expansion potential [12]. 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.

Induced Pluripotent Stem Cells (iPSCs) in Diabetes Therapy

In 2006, pluripotency genomic factors, coined "Yamanaka Factors," were discovered. These factors possess the capacity to reprogram mature somatic cells back to their embryonic, pluripotent form (iPSC). 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, offering a promise for personalized cell therapy since they can be derived from a patient's own cells, potentially avoiding immune suppression. iPSCs provide the unique advantage of generating patient-specific, fully differentiated insulin-producing beta cells, potentially offering a functional cure for T1D.

In late 2024, *Wang, et al*. [13] 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 β-cells. Preclinical trials in 244 immunodeficient mice showed no tumor formation. The patient, who had a history of liver and pancreas transplants, 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.

Despite continued advancements, major hurdles for iPSC-based therapy include the need for complex differentiation protocols, potential risks of tumor formation, and the requirement for immunosuppression if allogeneic iPSCs are used. While autologous iPSC-derived beta cells could eliminate the need for immunosuppression, the process remains expensive and time-consuming. Although considered, in earlier stages of clinical translation due to challenges in consistency and safety (e.g., risk of mutations from reprogramming), rapidly emerging data suggests differentiated islets from iPSCs have high potential for getting closer to a cure.

Allogenic Mesenchymal Stem Cells (MSCs) in Diabetes Therapy

Unlike iPSCs or hPSCs, MSCs primarily function by modulating the immune response and promoting tissue repair, rather than directly differentiating into insulin-producing beta cells.

Ghoneim, et al [14] transplanted allogeneic IPCs derived from hAT-MSCs into STZ-diabetic humanized mice (NOG-EXL mice, Taconic, Bioscience, Rensselaer, NY, USA). Collectively, the results confirmed that the transplantation of allogeneic hAT-MSCs into diabetic humanized mice normalized their blood sugar levels. An allogeneic immune response was not detected. Differentiated IPCs accounted for only ~ 20% of the transplanted cells, suggesting that the undifferentiated population exerted an immunomodulatory effect.

Accumulating experimental evidence shows that allogenic transplantation does not evoke an immune response presumably based on the immunomodulatory functions of the undifferentiated population. The immunomodulatory function of allogenic MSCs can be further enhanced to overcome autoimmune reactions

While both allogeneic and autologous stem cell therapies are being actively explored to restore insulin production and achieve long-term glycemic control, allogeneic MSCs, which are derived from donors and used in recipients, offer a promising approach for diabetes treatment, particularly in immunomodulation, beta-cell protection, and regeneration. In contrast to autologous approaches, which aim to enhance pancreatic regeneration while minimizing immune rejection, regenerative aspects of allogenic MSCs may reside both in differentiation potential and the paracrine effects on immunomodulation, reducing β-cell destruction, and improving metabolic function. Allogeneic therapies offer a more standardized and scalable solution, with advances in immune-evasive strategies, such as gene editing and encapsulation technologies, helping to protect transplanted cells from autoimmune attack, reducing the need for lifelong immunosuppression. Clinical trials are increasingly evaluating combination approaches, integrating bioengineered scaffolds, metabolic interventions, and immune tolerance induction to enhance engraftment and function. The therapeutic potential of MSCs may also be affected by the type of diabetes presented by the patient. Savio-Silva and colleagues [15] 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.

Summary

Stem cell-based therapies have emerged as a promising approach for diabetes treatment, particularly in restoring insulin production and modulating the immune response. Among the various stem cell types being explored, iPSCs and allogeneic mesenchymal stem cells (MSCs) stand out for their distinct mechanisms and therapeutic potential. iPSCs, generated by reprogramming adult somatic cells into a pluripotent state, offer the ability to differentiate into insulin-producing beta cells, providing a potential functional cure for diabetes. Autologous iPSC-derived beta cells could theoretically eliminate the need for immunosuppression, but challenges such as tumorigenicity, differentiation inefficiencies, and high production costs remain obstacles to clinical application. Conversely, allogeneic MSCs, derived from sources like bone marrow, adipose tissue, and umbilical cord, primarily function through paracrine signaling and immunomodulation, rather than directly replacing beta cells. MSCs have shown promise in preserving residual beta-cell function, reducing inflammation, and delaying disease progression. While iPSC-derived beta cells aim to replace lost insulin-producing cells, MSCs focus on protecting and enhancing endogenous beta-cell function, making them complementary approaches rather than direct alternatives. Ongoing research is exploring strategies such as immune evasion techniques, encapsulation technologies, and combination therapies to maximize the therapeutic potential of both cell types. The promising outcomes from recent clinical trials suggest that transplantation of iPSC- or allogenic MSC-derived islet cells could pave the way for more effective and broadly accessible treatment options.

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