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COMMENTARY

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Stem cell-derived islets — significant progress amidst ongoing challenges for type 1 diabetes

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The recent publication of the VX-880-101 FORWARD trial in the *New England Journal of Medicine* documents a significant advance in pursuing a functional cure for type 1 diabetes (T1D).[1] Vertex Pharmaceuticals' allogeneic human pluripotent stem cells(hPSCs)-derived islet therapy, zimislecel, shows robust efficacy in restoring physiologic insulin production as well as glycemic control. These encouraging results reveal therapeutic promise of stem cell approaches, while also identifying potential translational barriers or risks which we must overcome in the future.

This phase 1-2 study shows consistent engraftment and physiologic function with the stem cell-based strategy. All 14 participants, who had undetectable C-peptide at baseline, achieved restored islet function following zimislecel infusion into the portal vein. Efficacy data for the 12 full-dose recipients are particularly promising: 100% achieved freedom from severe hypoglycemia (days 90-365) and maintained HbA1c levels below 7%. Notably, 83% (10/12) achieved insulin independence at day 365, with >70% time-in-range (70-180 mg/dL). This efficacy profile substantially surpasses current T1D management strategies, targeting the restoration of insulin secretion at a physiologic level. Because the transplanted cells are fully differentiated islets, their effect takes place much faster than the clinical experiments using pancreatic endoderm,[2-3] which require about six months to detect glucose-responsive C-peptide.

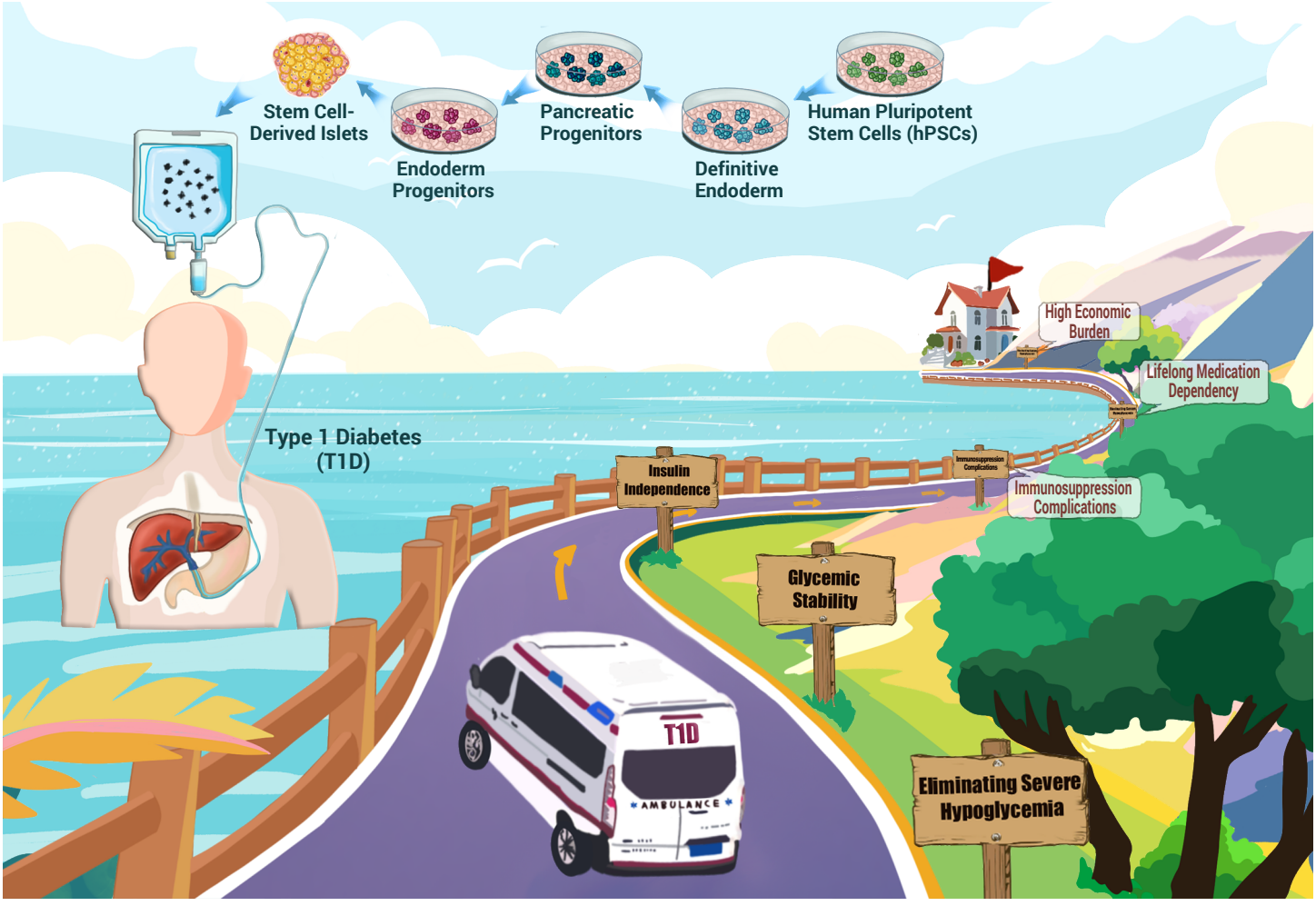

Figure 1. Therapeutic journey of stem cell-derived islets for type 1 diabetes An ambulance labeled "T1D" advances along a coastal highway toward a destination house representing functional cure. Wooden signposts physically mark six critical therapeutic milestones: Insulin Independence; Glycemic Stability; Eliminating Severe Hypoglycemia; Immunosuppression Complications; Lifelong Medication Dependency; High Economic Burden; Spatial positioning reflects clinical achievement status—the first three milestones are provisionally attained, while distant milestones signify persistent translational barriers. *(Inset, top left)* Stem Cell Differentiation and Transplantation: Human pluripotent stem cells undergo stepwise differentiation into glucose-responsive islets, followed by clinical delivery via portal vein.

Zimislecel addresses donor scarcity through standardized islet production from a master stem cell bank, providing theoretically unlimited islet supply. The achievement of insulin independence in 83% of full-dose recipients at one year even surpasses early outcomes from cadaveric islet trials using the "Edmonton protocol", further verifying the potency of this stem cell product.

In the study, all participants received immunosuppressive therapy to protect the donor cells, revealing associated management challenges. Notable adverse events such as neutropenia were observed in three participants. Moreover, two fatalities occurred during the study. One death resulted from cryptococcal meningitis, a recognized risk associated with immunosuppressive regimens. The other death was attributed to severe dementia with agitation due to progression of pre-existing neurocognitive impairment. These events emphasize the need for ongoing optimization of the accompanying immunosuppressive strategy, and enhanced neurocognitive monitoring. The FORWARD regimen—combining broad T-cell depletion via anti-thymocyte globulin (Thymoglobulin®; ATG) and dual-pathway inhibition of T-cell activation (calcineurin & mTOR blockade by tacrolimus/sirolimus)—effectively prevents graft rejection but concurrently induces two vulnerability cascades: (i) Infection susceptibility: Profound CD4+ lymphopenia from ATG impairs pathogen surveillance, permitting opportunistic pathogens; (ii) Neurotoxicity amplification: Tacrolimus disrupts blood-brain barrier integrity via endothelial nitric oxide synthase suppression, while sirolimus exacerbates pre-existing neurodegeneration by inhibiting microglial autophagy-dependent clearance of toxic proteins. Future protocols may explore cytokine-targeted agents (e.g., anti-IL-21) or local immunomodulation to decouple efficacy from systemic vulnerability.

Despite promising results, the study faces inherent limitations: the small cohort size (n=14) and relatively short follow-up (12 months) require longer observation. Participant selection might favor individuals stable enough to tolerate the procedure and immunosuppression, limiting generalizability. The persistent dependency on chronic immunosuppression remains a primary challenge for clinical implementation. Beyond these biological constraints, prohibitive cost-accessibility barriers threaten real-world translation. Current projections indicate stem cell-islet therapy expenses exceed multiple fold the lifetime cost of insulin therapy, primarily due to complex GMP manufacturing, specialized transplantation procedures, and indefinite immunosuppression management. While innovative payment models (e.g., outcome-based reimbursement) may improve near-term adoption, sustainable accessibility requires industrialized production platforms—encompassing closed automated bioreactors, xeno-free differentiation matrices, and decentralized manufacturing networks—to align pricing with global healthcare economics.

The FORWARD trial provides strong support for continued investigation of stem cell-derived islets for T1D. Prioritized next steps include larger phase 3 trials verifying long-term durability and safety, with particular attention to immunosuppression-related outcomes. Developing immunosuppression-reduction strategies—such as encapsulation technologies, genetic engineering for immune evasion (such as hypoimmunogenic cells), localized immunomodulation, or tolerance induction—could be crucial. Parallel efforts toward scalable, cost-effective manufacturing will be equally vital to ensure broad accessibility of these therapies. The complex interplay of therapeutic achievements and persisting challenges is summarized in Figure 1.

Globally, complementary approaches are emerging. Wang S. et al reported a novel strategy for diabetes treatment based on chemical reprogramming technology and alternative transplantation site:[4] using chemical molecule cocktails to reprogram patient somatic cells into induced pluripotent stem cells (CiPSCs), which are then differentiated into functional islet cells, providing a new approach for personalized diabetes therapy. In their 2024 *Cell* publication detailing the first clinical case, a T1D patient with an 11-year disease history achieved complete insulin independence within 75 days after receiving autologous CiPSCs-derived islet transplantation. The patient's glycated hemoglobin declined to levels comparable to non-diabetic individuals. Critically, the patient maintained insulin-free status for over 1 year without transplantation-related adverse events. This approach utilized an innovative transplantation site beneath the rectus abdominis sheath—avoiding the portal vein—which significantly reduced early cell loss from instant blood-mediated inflammatory reactions (IBMIR), enabled real-time graft monitoring, and positioned the graft away from critical abdominal organs for potential minimally invasive removal. Since autologous cells were used, this strategy potentially avoids immunosuppression requirements for T1D patients with non-autoimmune etiology. However, for the majority of T1D cases, which are primarily due to autoimmune attacks, this approach would still require the use of immunosuppression.

Besides T1D, stem cell-derived islets also show preliminary promise for advanced type 2 diabetes (T2D).[5] Wu J. et al established endoderm stem cells (EnSCs) from patient-derived induced pluripotent stem cells, generating functional islets that were transplanted into the liver via portal vein infusion in patients with long-standing, insulin-dependent T2D. This approach achieved a sustained insulin-free remission, with one patient maintaining complete insulin independence for over 3 years. Given that to date only one reported case of sustained insulin-free remission in T2D using this approach has been formally documented, larger cohorts are needed to demonstrate the general applicability of stem cell-derived islets for treating advanced T2D. While both T1D and advanced insulin-dependent T2D may benefit from stem cell-derived islet therapy, their pathological distinctions dictate divergent suitability. In T1D, autoimmune-mediated β-cell destruction creates an ideal niche for cell replacement, provided autoimmunity is controlled. Conversely, T2D primarily involves insulin resistance and metabolic dysfunction; stem cell therapy is thus reserved for late-stage patients with profound β-cell failure, where insulin secretion deficit—not resistance—dominates pathophysiology.

In conclusion, these findings demonstrate a pivotal advance, demonstrating the potential of stem cell-derived islets to restore physiologic insulin secretion and transform the management of T1D. The achievement of insulin independence and glycemic control is encouraging. However, the current necessity for lifelong immunosuppression for most T1D and the associated management complexities demand systematic resolution. To translate this breakthrough into widely accessible cures, we recommend prioritizing three pillars: (i) Development of safer immunosuppression regimens (e.g., targeted T-cell modulation) or immune-evasive grafts via hypoimmunogenic engineering; (ii) Further validation of ectopic transplantation sites and encapsulation devices to enable graft monitoring/retrieval; and (iii) Cost-optimized scalable manufacturing through automated bioreactors and decentralized production.

REFERENCES

1. Reichman T.W., Markmann J.F., Odorico J., et al. (2025). Stem cell-derived, fully differentiated islets for type 1 diabetes. *N. Engl. J. Med.* Online ahead of print. DOI:10.1056/NEJMoa2506549
2. Ramzy A., Thompson D.M., Ward-Hartstonge K.A., et al. (2021). Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes. *Cell Stem Cell* **28**:2047–2061.e5. DOI:10.1016/j.stem.2021.10.003
3. Keymeulen, B., De Groot, K., Jacobs-Tulleneers-Thevissen, D., et al. (2024). Encapsulated stem cell-derived beta cells exert glucose control in patients with type 1 diabetes. *Nat. Biotechnol.* **42**:1507–1514. DOI:10.1038/s41587-023-02055-5
4. Wang S., Du Y., Zhang B., et al. (2024). Transplantation of chemically induced pluripotent stem-cell-derived islets under abdominal anterior rectus sheath in a type 1 diabetes patient. *Cell* **187**:6152–6164.e18. DOI:10.1016/j.cell.2024.09.004
5. Wu J., Li T., Guo M., et al. (2024). Treating a type 2 diabetic patient with impaired pancreatic islet function by personalized endoderm stem cell-derived islet tissue. *Cell Discov.* **10**:45. DOI:10.1038/s41421-024-00662-3

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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