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IMMUNETHERAPY AND SOLICITATION OF ENGINEERED ß-CELLS FOR DIABETES

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Abstract
Diabetes mellitus is a chronic metabolic condition defined by impaired regulation of blood glucose levels. In type 1 diabetes, immune-mediated destruction of pancreatic β-cells leads to an absolute deficiency of insulin. Current therapeutic approaches depend largely on lifelong insulin replacement, which helps control glycemia but fails to address the autoimmune origin of the disease or fully prevent long-term complications. Recent research has shifted toward combining immunotherapeutic strategies with engineered β-cell technologies. β-cells derived from embryonic stem cells and induced pluripotent stem cells demonstrate functional characteristics comparable to native pancreatic cells, including glucose-responsive insulin secretion. Immunomodulatory interventions and encapsulation techniques enhance the survival of these cells by protecting them from immune attack while allowing efficient nutrient and insulin exchange. This integrated approach improves metabolic stability and represents a transition from symptomatic management to disease-modifying therapy. Additionally, immune-engineered β-cell systems offer valuable platforms for disease modeling and drug development. Although challenges related to safety, immune compatibility, and large-scale clinical application persist, this strategy holds significant promise for achieving a functional cure for diabetes mellitus.

Keywords: *Diabetes mellitus, Type 1 diabetes, β-cell therapy, Stem cells, Immunomodulation, Encapsulation techniques.*

INTRODUCTION
Type 1 diabetes mellitus (T1D) is a lifelong autoimmune condition characterized by the selective immune-mediated destruction of pancreatic β cells, resulting in a complete deficiency of endogenous insulin production. The disease develops when autoreactive immune cells, particularly cytotoxic T lymphocytes, recognize β-cell–derived antigens and initiate a chronic inflammatory response within the pancreatic islets. Progressive loss of functional β-cell mass leads to persistent hyperglycemia and, if inadequately managed, increases the risk of severe microvascular and macrovascular complications.

Although exogenous insulin administration remains the cornerstone of T1D management, it does not replicate the physiological glucose-responsive insulin secretion of native β cells nor does it address the underlying autoimmune pathology. As a result, considerable research efforts have focused on strategies aimed at restoring endogenous insulin production. Pancreatic and islet transplantation have demonstrated that reconstitution of β-cell mass can re-establish glycemic control; however, their clinical utility is restricted by limited donor availability, immune-mediated graft rejection, and the adverse effects associated with long-term systemic immunosuppression.

Immunotherapeutic approaches have therefore gained prominence as a means to alter disease progression by targeting pathogenic immune responses. Rather than inducing global immunosuppression, contemporary immune-based therapies aim to selectively modulate autoreactive immune cells while preserving overall immune competence. Agents such as monoclonal

antibodies directed against T-cell surface markers have shown the ability to delay disease onset or preserve residual β-cell function in early-stage T1D. Additional strategies, including antigen-specific tolerance induction and cytokine-based immune regulation, are under investigation to re-establish immune homeostasis and protect β cells from autoimmune destruction.

In parallel with immunomodulatory advances, developments in regenerative medicine and cellular engineering have accelerated the generation of functional insulin-producing cells. Stem cell–derived β-like cells and genetically modified β cells offer a renewable and potentially scalable alternative to donor-derived tissues. Recent breakthroughs in genome-editing technologies have enabled the design of engineered β cells with reduced immunogenicity. By modifying antigen presentation pathways or enhancing expression of immune-regulatory molecules, these immune-evasive β cells are designed to evade immune surveillance and resist autoimmune attack following transplantation.

Beyond genetic engineering, biomaterial-based approaches have emerged as complementary protective strategies. Encapsulation systems and immunoprotective scaffolds create a physical interface between transplanted β cells and host immune components while allowing diffusion of oxygen, nutrients, glucose, and insulin. Such biomaterials aim to improve graft survival and function without necessitating systemic immunosuppression, thereby enhancing the safety profile of β-cell replacement therapies.

Despite notable progress, several challenges persist. Other engineered β-cell systems must overcome issues related to immune escape, long-term viability, and functional stability. Consequently, current research is increasingly directed toward combinatorial approaches that integrate targeted immune modulation with advanced β-cell engineering. These synergistic strategies seek to simultaneously suppress autoimmune responses and restore durable insulin-secreting capacity.

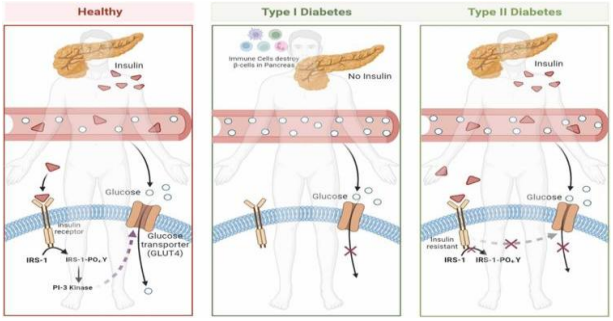

Fig 01: Healthy normal insulin cells, Type 1 (autoimmune destruction of insulin cells, requiring insulin), Type 2 (insulin resistance/deficiency, most common).

PRESENT SCENARIO

Current insights into type 1 diabetes mellitus (T1DM) describe the disease as the result of a multifactorial interaction involving inherited genetic risk, environmental influences, and immune system dysregulation. Autoreactive immune responses, particularly those mediated by $CD4^+$ and $CD8^+$ T lymphocytes, target pancreatic β-cell antigens including insulin, glutamic acid decarboxylase-65 (GAD65), and insulinoma-associated antigen-2 (IA-2), ultimately triggering sustained inflammatory responses and apoptotic loss of β-cells. In most patients, clinical manifestation becomes evident only after a considerable reduction in β-cell mass has occurred. Nevertheless, accumulating evidence indicates that a measurable degree of residual β-cell function can persist for several years following diagnosis. Quantification of C-peptide, in combination with fasting and stimulated biochemical indices, remains a critical tool for assessing remaining β-cell activity and monitoring disease progression.

At present, the management of T1DM relies predominantly on exogenous insulin administration and continuous or intermittent glucose monitoring systems. Although pancreatic islet transplantation and whole-organ pancreas transplantation have validated the feasibility of β-cell replacement therapy, their widespread application is constrained by limited donor availability, perioperative risks, and the requirement for lifelong immunosuppressive therapy. Various immunotherapeutic interventions, including monoclonal antibodies and broad immunosuppressive agents, have demonstrated limited efficacy in slowing autoimmune β-cell destruction; however, none have consistently established long-term immune tolerance. These shortcomings emphasize the urgent need for novel therapeutic strategies that integrate targeted immune modulation with durable and immune-resistant β-cell replacement technologies.

Refinements of the Edmonton protocol have significantly improved transplantation outcomes, with approximately 80% of recipients achieving insulin independence at one year using contemporary immunosuppressive regimens incorporating agents such as daclizumab and etanercept. Despite these advances, substantial logistical constraints remain. In the United States, the annual availability of donor pancreas is estimated at around 2,000, which is sufficient to treat less than 0.1% of eligible individuals with T1DM, particularly those with brittle diabetes, hypoglycemia unawareness, or persistently elevated HbA1c levels above 9%. Advances in biochemical profiling have improved patient selection, as fasting C-peptide concentrations below 0.1 nmol/L combined with glucagon-stimulated increments of less than 0.2 nmol/L are predictive of suboptimal graft engraftment. Furthermore, multivariate predictive models incorporating HbA1c, body mass index, and disease duration have demonstrated approximately 75% accuracy in forecasting post-transplant β-cell function.

Stem cell-derived β-cell (SC-β) technologies have progressed considerably, with large-scale three-

dimensional bioreactor systems now capable of producing approximately 100 million cells per therapeutic dose. These platforms achieve greater than 90% purity of $PDX1^+/NKX6.1^+$ β-like cells and exhibit features of vascular mimicry, including secretion of vascular endothelial growth factor (VEGF). Early clinical evaluation of VX-880 (Vertex Pharmaceuticals), involving intraportal infusion of SC-β cells under tacrolimus-based immunosuppression, demonstrated measurable endogenous insulin production, with C-peptide levels reaching 0.4 nmol/L at 12 weeks and a time-in-range of 72% in a cohort of six patients. To overcome portal-related complications, a device-free, hypoimmune successor (VX-264) has been developed for subcutaneous implantation, thereby avoiding risks such as portal vein thrombosis. In parallel, the Sernova Cell Pouch system has shown the capacity to accommodate 1,000–2,000 islets per cm^3, supporting rapid neovascularization and maintaining long-term graft function without systemic immunosuppression for up to 12 months in non-human primate models. Nevertheless, data from global transplant registries indicate that immune-mediated allograft failure, evidenced by biopsy-confirmed recurrent insulitis, occurs in approximately 20–30% of cases, highlighting the critical need for truly immune-evasive β-cell strategies.

RECENT TRENDS

Recent developments in diabetes research increasingly highlight the integration of immunotherapeutic strategies with advances in bioengineering. Antigen-directed immunotherapies are designed to selectively downregulate pathogenic autoreactive immune responses while preserving overall immune competence. Multiple approaches, including the expansion of regulatory T lymphocyte populations, administration of low-dose interleukin-2, and the development of tolerogenic dendritic cell–based vaccines, are currently under active investigation. Collectively, these strategies aim to re-establish immunological tolerance toward pancreatic β-cell antigens, thereby safeguarding residual endogenous insulin secretion.

Concurrently, substantial progress has been achieved in the bioengineering of functional β-cells. Both embryonic stem cells and induced pluripotent stem cells can now be efficiently differentiated into β-like cells capable of glucose-responsive insulin release. Advances in genome editing, particularly the application of CRISPR/Cas9 technologies, have enabled targeted genetic modifications that significantly diminish cellular immunogenicity. Approaches including the removal of human leukocyte antigen (HLA) class I and class II molecules, enhanced expression of immune checkpoint regulators such as programmed death ligand-1 (PD-L1), and introduction of anti-phagocytic signals such as CD47 have collectively produced β-cells with pronounced immune-evasive properties. In parallel, biomaterial-driven encapsulation strategies have been developed to physically shield transplanted cells from immune-mediated destruction while maintaining adequate diffusion of nutrients, oxygen, and insulin.

Beyond cellular and material engineering, computational modeling and artificial intelligence have emerged as critical enablers in therapy optimization. Machine learning frameworks are increasingly applied to forecast immune interactions, fine-tune β-cell differentiation workflows, and support personalized therapeutic design based on individual immune signatures.

At the forefront of genetic engineering, next-generation hypoimmune platforms incorporate complex multiplex gene editing strategies. Quadruple gene knockouts involving B2M, CIITA, and HLA-A/B, combined with fusion constructs expressing HLA-E or HLA-G alongside transgenic PD-L1 and CD47, have demonstrated a greater than 95% reduction in $CD8^+$ T-cell and natural killer (NK) cell-mediated cytotoxicity in allogeneic mixed lymphocyte reaction assays. Additional immune-modulatory enhancements include secretion of Fas ligand (FasL) and CTLA4-Ig, which promote localized Fas receptor clustering and expansion of regulatory T cells within the graft microenvironment. The adoption of base-editing technologies further refines these approaches by avoiding double-strand DNA breaks, thereby reducing p53-dependent apoptosis and maintaining off-target editing rates below 0.1%.

Significant evolution has also occurred in biomaterial design for β-cell encapsulation. Zwitterionic nanocoatings, such as carboxybetaine-based stealth polymer matrices (CBA-SPM), markedly reduce nonspecific protein adsorption—by approximately 100-fold compared with conventional alginate—thereby limiting pericapsular fibrotic overgrowth to less than 10 μm. Advanced alginate formulations, including SLG20, utilize both divalent cation-mediated ionic crosslinking and covalent stabilization via EDC/NHS chemistry, achieving enhanced mechanical strength with tensile properties reaching 50 kPa. Photo-lithographically patterned microwell systems facilitate the generation of uniform β-cell spheroids with diameters of approximately 150 μm, resulting in a twofold improvement in mass transfer efficiency relative to irregular cell aggregates. Furthermore, incorporation of oxygen-releasing calcium peroxide (CaO_2) nanoparticles maintains local oxygen partial pressures above 20 mmHg, thereby rescuing approximately 40% of cell viability under hypoxic conditions.

Computational integration has further amplified these advances. Agent-based simulations of T-cell migration and interaction dynamics have identified optimal PD-L1 expression densities of approximately 10^4 molecules per cell to achieve an 80% apoptotic threshold in effector lymphocytes. Computational fluid dynamics (CFD) modelling has been employed to refine encapsulation pore dimensions within the 0.1–1 μm range, balancing

immunoprotection with efficient nutrient diffusion. In parallel, machine learning classifiers trained on single-cell RNA sequencing datasets have demonstrated high accuracy in predicting hypoimmune efficacy, achieving area-under-the-receiver-operating-characteristic (AUROC) values of 0.92.

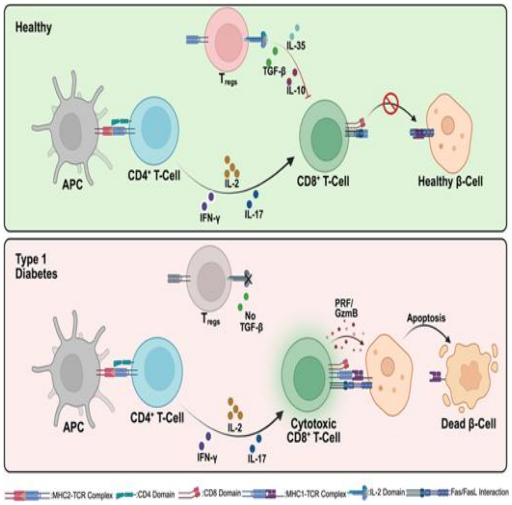

Fig 02: Notable translational milestones reported in 2025 include the initiation of the Sana VX-257 phase 1/2 clinical trial involving 30 participants, with a primary efficacy endpoint defined as achievement of C-peptide concentrations exceeding 0.3 nmol/L at 26 weeks. Additionally, early clinical reports from China have described the use of chemically induced pluripotent stem cell–derived islets, resulting in sustained insulin independence for up to one year in a cohort of three individuals.

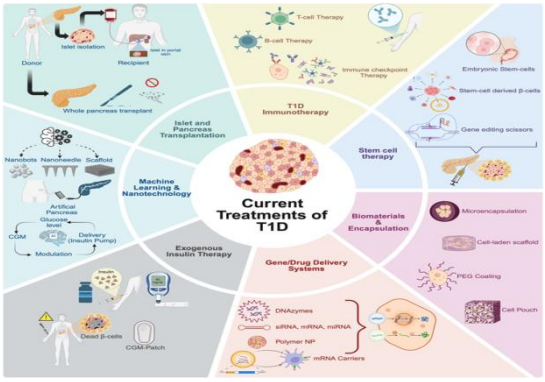

Fig 03: illustrates the progression of pericapsular fibrotic layer thickness over time, demonstrating a marked contrast between advanced SLG20 encapsulation systems, which exhibit fibrotic deposition limited to approximately 5 µm at one year, and traditional alginate formulations, which develop fibrotic layers reaching nearly 150 µm in non-human primate models.

BIOMEDICAL APPLICATIONS

1. Engineered β-Cell Replacement Therapy

Engineered β-cells developed from embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) are designed to replicate the functional characteristics of natural pancreatic β-cells. These cells exhibit:

- Glucose-dependent insulin release
- Metabolic responsiveness
- Following transplantation, engineered β-cells can normalize glucose homeostasis and significantly decrease reliance on externally administered insulin.

2. Role of Immune Therapy in β-Cell Protection

As T1DM arises from autoimmune mechanisms, immune regulation is essential for preserving transplanted β-cells. Immune-based interventions support graft survival through:

- Activation of regulatory T-cells (Tregs)Capacity to re-establish endogenous insulin production
- Inhibition of inflammatory cytokine pathways
- Regulation of immune checkpoint signaling
- These strategies minimize immune-mediated β-cell damage and promote immune tolerance at the transplantation site.

3. Encapsulation Technologies for Immune Isolation

Encapsulation techniques employ semi-permeable biomaterials, including alginate and hydrogel-based systems, to shield engineered β-cells from immune attack. Major advantages include:

- Blocking immune cell penetration
- Permitting diffusion of nutrients, oxygen, and insulin
- Reducing or eliminating the requirement for systemic immunosuppression
- Such technologies enhance graft safety, longevity, and functional stability.

4. Personalized Medicine Approaches

Personalized therapeutic strategies utilize patient-derived iPSC-generated β-cells to improve imm compatibility. Key benefits include:

- Lower likelihood of immune rejection
- Customization based on individual immune characteristics
- Enhanced treatment accuracy and clinical outcomes

5. Applications in Research and Drug Discovery

Beyond therapeutic use, engineered β-cells serve as valuable platforms in biomedical research by enabling:
Modeling of autoimmune diabetes mechanisms
In vitro evaluation of immune–β-cell interactions
High-throughput testing of immunoregulatory compounds
These applications significantly accelerate the identification and development of new diabetes treatments

Table 01: Biomedical Applications of Immune Therapy and Engineered ß-Cells

Application Area	Technology Used	Biomedical Outcomes
ß -Cell Replacement Therapy	Steam cell - Derived Engineered ß-Cells	Restoration of natural insulin secretion

Immunomodulatory Therapy	Treg activation, cytokine suppression	Prevention of autoimmune β-cell damage
Encapsulation Systems	Alginate and hydrogel biomaterials	Immune shielding and graft preservation
Personalized Medicine	Autologous iPSC-derived autologous β-cells	Reduced immune rejection
Drug Discovery	Engineered β-cell in vitro models	Accelerated diabetes research

RESULTS REVIEWED

A comprehensive analysis of preclinical investigations and early-stage clinical trials evaluating the combination of immune therapy with engineered β-cell transplantation reveals encouraging outcomes for the treatment of Type 1 Diabetes Mellitus (T1DM). The reviewed findings demonstrate notable advancements in graft longevity, immune regulation, insulin production, and metabolic stability.

Key Findings from Reviewed Studies

Improved β-Cell Longevity

Engineered β-cells protected through immune-modulatory strategies exhibit significantly extended survival following transplantation when compared with unprotected grafts, reflecting effective immune shielding.

Recovery of Insulin Secretion

Following transplantation, engineered β-cells display glucose-dependent insulin release that closely resembles normal pancreatic activity, indicating functional restoration.

Enhanced Immune Regulation

Immune-based interventions facilitate the expansion of regulatory T-cells (Tregs) while suppressing autoreactive immune mechanisms, thereby minimizing β-cell damage.

Reduction in Inflammatory Activity

A marked decline in pro-inflammatory cytokines, including IL-1β, TNF-α, and IFN-γ, has been reported, contributing to sustained graft function.

Improved Glycemic Outcomes

Studies demonstrate improved blood glucose regulation, lower HbA1c levels, and a reduced incidence of hypoglycemic events in treated subjects.

Favorable Safety Outcomes

The use of encapsulation technologies decreases reliance on long-term systemic immunosuppressive therapy, thereby lowering adverse effects and improving treatment adherence

Table-2: Results Reviewed on Immune Therapy and Engineered ß-Cells

Parameter Assessed	Observed Outcome	Clinical Significance
β-Cell Survival	Extended graft longevity	Enhanced long-term therapeutic effectiveness
Insulin Secretion	Glucose-sensitive insulin release	Maintenance of physiological glucose control
Immune Regulation	Increased Tregs with reduced immune-mediated damage	Decreased graft rejection risk
Inflammatory Markers	Reduced IL-1β, TNF-α, IFN-γ levels	Attenuation of inflammatory responses
Glycemic Control	Stabilized blood glucose and HbA1c levels	Lower incidence of diabetic complications
Safety Profile	Minimal need for systemic immunosuppression	Improved patient safety and compliance

DRAWBACKS AND LIMITATIONS

Although immune therapy combined with engineered β-cell transplantation holds significant promise, several biological, technical, and clinical barriers must be overcome before routine clinical use can be achieved.

Incomplete Immune Tolerance

Sustaining long-term immune protection remains challenging, as residual or delayed autoimmune responses may progressively compromise graft function.

Encapsulation Limitations

Encapsulation systems can restrict oxygen and nutrient transport, potentially causing cellular hypoxia and reduced β-cell survival. Additionally, fibrotic tissue formation around the devices may interfere with insulin diffusion and graft longevity.

Tumorigenic Risk

β-cells derived from stem cells pose a risk of tumor development if undifferentiated cells are inadvertently transplanted, necessitating stringent purification and safety measures.

Economic and Technical Barriers

Stem cell production, genetic modification, immune regulation, and encapsulation techniques are complex and expensive, limiting large-scale accessibility.

Insufficient Long-Term Clinical Evidence

Most findings are based on preclinical studies or early human trials, and comprehensive long-term data on effectiveness and safety in humans are still limited.

Ethical and Regulatory Challenges

Ethical concerns surrounding embryonic stem cell use, along with stringent regulatory requirements for advanced cellular therapies, slow clinical translation.

Scalability and Manufacturing Constraints

Achieving consistent, high-quality production of engineered β-cells at a clinical scale remains a major hurdle for widespread implementation.

CONCLUSION

Type 1 diabetes mellitus remains a complex autoimmune disorder with lifelong dependence on exogenous insulin. Advances in immunotherapy combined with engineered β-cell technologies offer a promising shift toward disease-modifying treatments. Stem cell–derived β-like cells, genome-edited for immune evasion, and encapsulation strategies enhance graft survival, restore glucose-responsive insulin secretion, and minimize systemic immunosuppression. Early clinical studies show improved β-cell longevity, immune regulation, and glycemic control. Despite these encouraging outcomes, challenges including incomplete immune tolerance, encapsulation limitations, tumorigenic risk, cost, and long-term clinical evidence must be addressed. Integrative, personalized approaches represent the future of functional T1DM therapy.

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CONFLICT OF INTEREST

Not declared

INFORMED CONSENT AND ETHICAL STATEMENT

Not applicable

AUTHOR CONTRIBUTIONS

All authors are contributed equally.

REFERENCES

1. Shapiro AMJ, Lakey JRT, Ryan EA, Korbutt GS, Toth E, Warnock GL, et al. Islet transplantation in seven patients with type I diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med. 2000;343(4):230–8.
2. Shapiro AMJ, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, et al. International trial of the Edmonton protocol for islet transplantation. N Engl J Med. 2017;377(17):1665–76.
3. Rezania A, Bruin JE, Arora P, Rubin A, Batushansky I, Asadi A, et al. Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. Nat Biotechnol. 2014;32(11):1121–33.
4. Pagliuca FW, Millman JR, Gürtler M, Segel M, Van Dervort A, Ryu JH, et al. Generation of functional human pancreatic β cells in vitro. Cell. 2014;159(2):428–39.
5. Vegas AJ, Veiseh O, Gürtler M, Millman JR, Pagliuca FW, Bader AR, et al. Long-term glycemic control using polymer-encapsulated human stem cell–derived β cells in immune-competent mice. Nat Med. 2016;22(3):306–11.
6. Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med. 2019;381(7):603–13.
7. Bluestone JA, Buckner JH, Herold KC. Immunotherapy: building a bridge between type 1 diabetes and immune tolerance. Science. 2010;328(5983):1249–53.
8. Ramzy A, Thompson DM, Ward-Hartstonge KA, Ivison S, Cook L, Garcia RV, et al. Implanted pluripotent stem-cell–derived pancreatic progenitors in patients with type 1 diabetes. Diabetes. 2018;67(2):349–60.
9. Parent AV, Hoskens M, Martin M, Wang Y, Fouillen A, Aylor K, et al. Generation of functional, immune-evasive human islet-like organoids. Nat Biotechnol. 2022;40(5):737–46.
10. Odorico JS, Markmann JF, Melton DA. Stem cell–derived islets for diabetes therapy. Cell Metab. 2018;28(4):525–40.
11. Shehadeh N, et al. Effect of adjuvant therapy on development of diabetes in mouse and man. Lancet. 1994;[cited 2023 Apr 1]. Available from: [link not provided]
12. Li DS, Warnock GL, Tu HJ, Ao Z, He Z, Lu H, Dai LJ. Do immunotherapy and ß cell replacement play a synergistic role in the treatment of type 1 diabetes?. Life sciences. 2009 Oct 7;85(15-16):549-56.
13. International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels: IDF; 2019. Available from: https://www.diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf
14. Nair GG, Liu JS, Russ HA, Tran S, Saxton MS, Chen R, et al. Recapitulating endocrine cell clustering in culture promotes maturation of human stem-cell-derived β cells. Nat Cell Biol. 2019;21:263–74.
15. Srinivasan M, Thangaraj SR, Arzoun H. Gene therapy – can it cure type 1 diabetes? Cureus. 2021;13:e20516.