iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 13 **Issue:** IV **Month of publication:** April 2025

DOI: https://doi.org/10.22214/ijraset.2025.69209

www.ijraset.com

Call: 08813907089 | E-mail ID: ijraset@gmail.com

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 13 Issue IV Apr 2025- Available at www.ijraset.com

Innovative Therapies for Type 1 Diabetes: Immunotherapy and Beta-Cell Regeneration

Miss Renuka Raut[1], Miss Sakshi Rathod[2], Mr. Rohit Sajjanshette[3], Mrs. Reshma Dhakate[4], Mr Rahul Sanap[5], Mr. Vishwajeet Rohom[6]

Abstract: ***Diabetes is a chronic condition that disrupts glucose metabolism in the body. As there is no clinical cure available, the condition is managed through medications, insulin therapy, dietary changes, exercise, and other lifestyle adjustments. However, traditional treatments are often limited by their lifelong dependence and reduced effectiveness over time, hindering the patient's full recovery. This limitation has led to a shift in focus, prompting research into alternative strategies. Since Type 1 diabetes (T1D) is an autoimmune disorder, approaches that target the immune system to either stimulate or suppress its activity have shown promise in reducing beta cell destruction and improving insulin response to high blood sugar. Additionally, the use of nanoparticles to deliver immunomodulators, insulin, or vaccines to immune cells is being explored as a potential therapeutic option. This method of nanoparticle-based targeting offers significant promise for improving T1D care. This review summarizes the current understanding of T1D's causes, clinical challenges, and the emerging role of nanoparticle-based therapies. We also evaluate the feasibility of bringing these approaches into clinical practice.***

Furthermore, stem cell therapy shows potential to restore ß-cell function and reduce reliance on insulin therapy, though its clinical application is still in early stages. Significant progress has been made in preclinical studies, but more research is needed to ensure the safety and effectiveness of stem cell treatments and to prevent immune rejection. This review also examines ongoing research into cellular therapies, including stem cell treatments, gene therapy, immunotherapy, artificial pancreas systems, and cell encapsulation, as well as their potential for clinical use in treating T1D.

Immunotherapy-based strategies have recently been integrated into the existing treatments for Type 1 diabetes (T1D) to block T-cell responses against beta cell antigens, which are commonly involved in the onset and progression of T1D. However, achieving complete preservation of beta cell mass and insulin independence remains an unresolved challenge. As a result, no immunotherapy for T1D has yet been developed to replace the need for standard insulin therapy. Currently, several innovative therapeutic approaches are being explored to protect beta cells and achieve normal blood sugar levels. This review examines the current progress in immunotherapy for T1D, highlights key studies in the field, and discusses potential future strategies for treating the condition. *[1,2,28,29]*

Keywords: type 1 diabetes, autoimmunity, regulatory T cell, immunosuppression, transplantation immunology

I. INTRODUCTION

Diabetes mellitus is an endocrine disorder primarily characterized by elevated blood glucose levels (hyperglycemia). This condition leads to a lack of glucose in tissues and organs, which can cause damage, and if left untreated, may result in tissue destruction, necrosis, and even death. The disease is divided into two main types: Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM). T1DM is mainly autoimmune in nature and typically develops in individuals under 20-30 years of age, often referred to as juvenile-onset diabetes. On the other hand, T2DM is a chronic metabolic condition primarily caused by genetic factors and insulin resistance, which means the body's tissues do not effectively respond to insulin, leading to poor glucose absorption. Several mechanisms, including glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum stress, and amyloid deposits, are thought to contribute to the development of T2DM. T2DM has also been subdivided into three distinct subtypes.

Diabetes, particularly T1D and T2D, is a major global health concern, marked by abnormally high blood glucose levels due to inadequate insulin production in T1D and insulin resistance in T2D. According to the 2019 International Diabetes Federation (IDF) Atlas, 1.52 million of the 8.75 million individuals with T1D worldwide are under the age of 20, highlighting the lack of sufficient research data for adult populations. Pediatric T1D is on the rise and can lead to diabetic ketoacidosis, which can be fatal without early diagnosis and treatment. T1D occurs when the immune system attacks and destroys insulin-producing beta cells in the pancreas, impairing insulin production and leading to symptoms like excessive thirst, frequent urination, unexplained weight loss, fatigue, blurred vision, and increased hunger. Due to the complete lack of endogenous insulin, individuals with T1D require daily insulin injections, making it known as insulin-dependent diabetes.

The diagnosis of T1D involves measuring blood glucose levels through tests such as fasting blood glucose, oral glucose tolerance, and random blood glucose tests. Managing T1D involves insulin therapy to regulate blood sugar, either via injections or insulin pumps, with careful monitoring to prevent episodes of hypoglycemia or hyperglycemia. In addition to insulin, lifestyle changes, such as maintaining a healthy diet and exercising regularly, can help manage blood glucose levels. If left uncontrolled, T1D can lead to severe complications like cardiovascular disease, neuropathy, retinopathy, and kidney disease, significantly affecting quality of life. Regular monitoring and management of blood glucose are essential to avoid these complications. [3,4,5,30,31]

II. IMMUNE ETIOLOGY OF T1DM

Type 1 diabetes mellitus (T1DM) is believed to be caused by an autoimmune response (Figure 1A), although the exact mechanisms by which the immune system targets the pancreas remain unclear. It is generally understood that the body becomes self-reactive to various pancreatic autoantigens, leading to insulitis (Figure 1B), an inflammation in the Islets of Langerhans. These islets contain α-cells (producing glucagon), β-cells (producing insulin), γ-cells (producing pancreatic polypeptide), δ-cells (producing somatostatin), and ε-cells (producing ghrelin). The coordinated function of these cells, primarily through the secretion of peptide hormones, maintains normal islet structure and function (1–3).

The specific causes of β-cell loss in T1DM can vary, but evidence suggests that acute infections (8, 9) or sterile trauma (10) can trigger it, with genetic predisposition playing a role . Two main reasons are proposed for these mechanisms. First, infections or trauma can lead to heightened immune activation, increasing the number of primed lymphocytes that may cross-react with self-antigens. Second, elevated levels of cytokines, adhesion molecules, and co-stimulatory molecules on antigen-presenting cells (APCs) and parenchymal cells can sustain the activation of these cross-reactive lymphocytes.

Currently, T1DM is managed through regular monitoring of blood glucose levels and injections of long-acting insulin (e.g., Lantus, Levemir) and short-acting insulins for meals (e.g., Humalog, Novolog). In contrast, T2DM hyperglycemia is treated with insulin and oral medications that either enhance insulin sensitivity (e.g., metformin) or promote the excretion of excess glucose (e.g., canagliflozin) . However, both treatments rely on small molecule drugs that lack selectivity for target cells , making them temporary solutions that patients must continue indefinitely once the disease develops.

Type 1 diabetes (T1D) is a chronic autoimmune condition characterized by the destruction of insulin-producing beta cells in the pancreatic islets. This immune-mediated destruction leads to a lack of insulin production, requiring individuals to depend on external insulin sources for survival. Both genetic and environmental factors play a role in the development of T1D. Genetic predispositions are often linked to polymorphisms in genes associated with the human leukocyte antigen (HLA), insulin gene promoter, and cytotoxic T lymphocyte antigen-4. These genetic factors account for 55–65% of T1D cases. In most cases, the disease is marked by the presence of various pancreatic autoantibodies, including those targeting insulin (IAA), islet cell cytoplasmic antigens (ICA), insulinoma-associated 2 or protein tyrosine phosphatase antibodies (IA-2), zinc transporter 8 (ZnT8), and glutamic acid decarboxylase (GAD65). The quantity and presence of these autoantibodies are directly linked to the likelihood of developing T1D. These autoantibodies stimulate CD4+ and CD8+ T cells to enter the pancreatic islets, triggering inflammation (insulitis). As these immune cells infiltrate the islets, they multiply and attack the beta cells, halting insulin production and disrupting blood sugar regulation. The resulting lack of insulin prevents the suppression of lipolysis, leading to uncontrolled fat breakdown and the accumulation of ketone bodies in the blood. The buildup of ketones like acetoacetate and β-hydroxybutyrate causes ketoacidosis, which, if left unchecked, can lead to loss of consciousness, brain swelling, confusion, coma, or even death.[5,6,7]

A. Potential Therapy Approaches for Type 1 Diabetes (T1D)

Currently, insulin replacement is the only standard treatment for T1D as there is no cure. However, researchers are actively investigating new therapeutic strategies that could potentially prevent or reverse the autoimmune process and restore β-cell function. Some of the latest advancements in T1D therapies include:

B. Immunotherapy

Immunotherapy involves using drugs or other treatments to regulate the immune system and prevent the destruction of insulin-producing β-cells in the pancreas. These treatments may include immune modulators or biologics that selectively target specific immune cells or pathways. The aim of immunotherapy is to manipulate the immune system to prevent or reverse β-cell destruction. A pioneering study by Herald and colleagues tested the use of an anti-CD-3 antibody to target and deactivate T-cells that attack β-cells, finding that it helped preserve β-cell function in newly diagnosed T1D patients.

In a randomized clinical trial, newly diagnosed T1D patients were treated with autologous T-cells genetically modified to express a proinsulin peptide, which preserved β-cell function and reduced the deterioration of insulin secretion over two years. Additionally, low-dose interleukin-2 (IL-2) therapy has been shown to increase the number of regulatory T-cells (Tregs), which suppress the autoimmune response, thus improving β-cell function in patients with new-onset T1D.

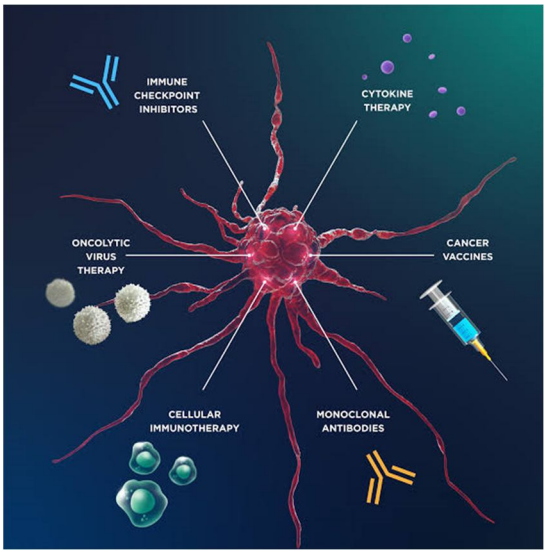


Fig .No 1 –Immunotherapy

Moreover, transplantation of engineered islet cells that can evade immune attack is being explored as a potential treatment. Modifying the surface of islet/β-cells with anticoagulant enzymes such as urokinase (UK) and thrombomodulin (TM), or by biotinylating the islet membrane to conjugate streptavidin-Fas-ligand (SA-FasL) proteins, has shown promise in protecting transplanted cells from immune attack in T1D patients. Other immunomodulatory proteins, such as A20 and PD-L1/CTLA4, have been used to protect islets from post-transplantation immune attack. These studies suggest that local immunomodulation plays a critical role in enhancing immunotherapy outcomes for T1D.[32,33,34,8,9]

C. Cell-Based Therapy

Cell-based therapies for T1D involve the transplantation of pancreatic islet cells or β-cells. Islet transplantation, which involves transferring islet cells from a healthy donor's pancreas into a T1D patient, has been shown to improve glucose control and reduce the risk of severe hypoglycemia. However, challenges such as the need for large numbers of donor cells and a limited supply of donors remain. To address these challenges, researchers are also exploring combinational cell therapies, including gene therapy and cell encapsulation, as promising diabetes treatments.

D. Gene Therapy

Gene therapy involves inserting genes into cells to correct genetic abnormalities or enhance their function. In T1D, gene therapy aims to promote β-cell growth and survival or to suppress genes that contribute to β-cell destruction. For example, introducing the pancreatic transcription factor Pdx-1 gene into pancreatic cells of diabetic mice has restored glucose homeostasis and insulin production. Another approach uses glucokinase, a key enzyme in glucose metabolism. A preclinical study demonstrated that gene therapy with glucokinase improved glucose regulation and prevented diabetes in mice. Since inflammation plays a significant role in T1D, gene therapy using anti-inflammatory cytokines like interleukin-10 (IL-10) has shown promise in preventing the onset of diabetes. Additionally, gene therapy with regulatory T-cells (Tregs) has been shown to suppress the autoimmune response and prevent β-cell destruction, thus improving glucose control in diabetic mice. Gene therapy using insulin-producing cells, derived from human embryonic stem cells, has also shown potential in preventing diabetes and improving glucose regulation mm +in preclinical studies. These advanced therapeutic strategies hold promise for improving T1D treatment and may ultimately provide new ways to manage or even cure the disease.

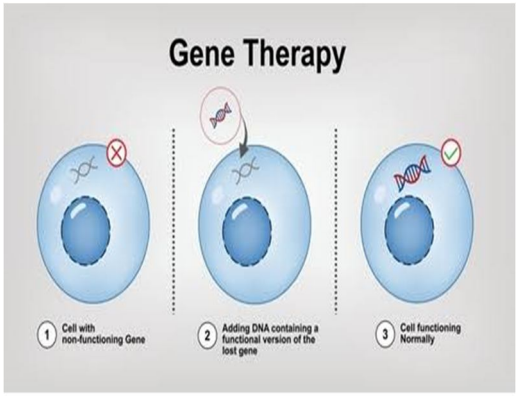


Fig.no 2.Gene Therapy

E. Stem Cell Therapy

Stem cell therapy is a rapidly advancing area of research in the context of T1D, aiming to regenerate β-cells in the pancreas using stem cells that can differentiate into various cell types. Researchers are exploring different types of stem cells, including induced pluripotent stem cells (iPSCs), adult stem cells, and embryonic stem cells, to achieve this goal. While early-stage clinical trials have shown promising results, further research is needed to fully evaluate the safety and efficacy of stem cell therapy .

F. Types of Stem Cells

Stem cells are undifferentiated cells with the unique ability to develop into specialized cell types and self-renew Several types of stem cells exist, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult stem cells. Stem cells hold great promise in regenerative medicine and as a therapeutic tool for various diseases. ESCs are derived from the inner cell mass of early embryos (blastocysts) and can differentiate into any body cell, making them useful for studying diseases. However, their use is controversial due to ethical concerns surrounding embryo use On the other hand, iPSCs are adult cells reprogrammed to a pluripotent state, similar to ESCs, typically through the introduction of specific genes using viral vectors or other techniques. iPSCs are valuable for disease modeling and drug discovery because of their ability to differentiate into any cell type Adult stem cells, found in specific tissues, can differentiate into cell types of the tissue in which they reside. For instance, hematopoietic stem cells in bone marrow can become different types of blood cells and are used in therapies like bone marrow transplants for leukemia and other blood diseases . Totipotent stem cells can differentiate into all cell types, including both embryonic and extra-embryonic tissues. In humans, totipotent stem cells are present only in the zygote (fertilized egg) and the earliest stages of development . In contrast, unipotent stem cells can differentiate into just one cell type but can self-renew. [10,11,12,13,14,35]

G. β Cell-Based Therapy

Type 1 Diabetes (T1D) is associated with the loss of tolerance by autoreactive β cells, which are involved in the autoimmune attack on pancreatic beta-cells. B lymphocytes, along with T lymphocytes, are key components of the adaptive immune system and contribute to both cellular and humoral defense against infections and tumors. However, to prevent autoimmunity, β cells must be either suppressed, restored, or eliminated. There is a correlation between the presence of CD20+ β cells and the decline in pancreatic beta-cell function. Despite insulin therapy being the standard treatment for T1D, it is not a cure, and there is a need for effective immunotherapies. In studies using non-obese mouse models, β cells were shown to halt disease progression at the preinsulitis stage, suggesting that β cell-targeted immunotherapy could be a promising treatment for T1D.

Monoclonal antibodies are being used to target β cells by identifying specific surface antigens involved in their maturation, differentiation, and survival. These antibodies work by inducing cell death through mechanisms like complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and apoptosis. Rituximab (RTX) is one such antibody used in β cell therapy, but it has shown limited efficacy due to side effects from β cell depletion, the rapid return of autoreactive β cells after treatment, and the depletion of regulatory cells as a side effect. Additionally, pancreas-localized β cells may resist RTX-mediated deletion due to reduced expression of the CD20+ surface marker. Manipulating RTX dosage and treatment duration has proven difficult, limiting the treatment's effectiveness.

Another approach is combination therapy, where antigens and antibodies are used together to enhance the therapeutic effect. For example, combining oral insulin with anti-CD20 antibodies has shown limited success in reversing T1D, but it has been moderately effective in preventing the disease. Overall, combination therapy has shown some potential for preventing T1D, but it has limited effectiveness in reversing the disease.

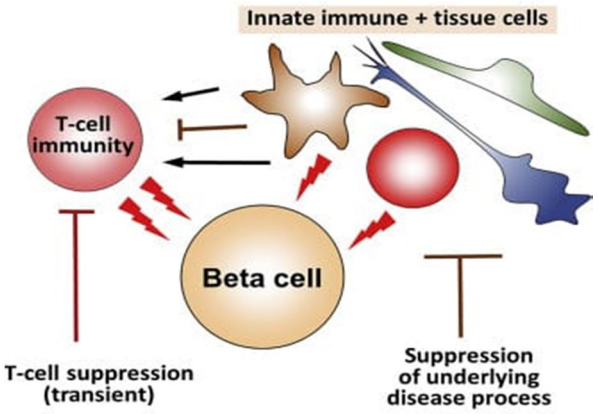


Fig. No. 3 Cell Based Therapy

H. Replacement Therapies: Edmonton Protcol

The Edmonton Protocol has demonstrated the effectiveness of islet transplantation in managing insulin regulation in Type 1 Diabetes (T1D) patients. In this protocol, pancreatic islets from deceased donors are infused into T1D patients who are immunosuppressed. Earlier trials, conducted before 1990 with single islet infusions, showed partial success, resulting in reduced insulin requirements and increased C-peptide levels. However, these trials did not take additional steps to enhance the islet mass.

The Edmonton Protocol, introduced in 2000, transformed islet transplantation into a promising therapy for T1D, as it remains the only method capable of achieving glycemic control without the need for insulin. Compared to whole pancreas transplants, islet transplantation offers several advantages, such as a less invasive surgical procedure, lower morbidity and mortality rates, and significantly lower costs. A key benefit of islet transplantation over traditional insulin therapy is that transplanted islets regulate blood glucose more efficiently without causing excess insulin production, which can lead to hypoglycemic episodes.

Modifications to the Edmonton Protocol, particularly in the immunosuppressive regimen, have eliminated the need for corticosteroids and enabled the use of a combination therapy involving anti-interleukin-2 receptor antibodies, sirolimus, and tacrolimus. This combination reduces beta cell toxicity, enhancing the therapy's effectiveness. Islet transplantation has shown some success in achieving insulin independence in both the short and long term. However, variability in results is influenced by factors related to both the donor and the recipient. Despite its benefits, there are challenges in standardizing the protocol, including the need for a large number of islets for transplantation and the potential adverse effects of immunosuppressive treatments. One solution could be the use of stem cells, which, with the appropriate differentiation protocols, can be made to produce glucose-sensitive insulin-producing cells.[15,16,17,18,19,20,37]

I. Beta-Cell Regeneration Strategies

Gastrin and GLP-1 work together to promote the regeneration and differentiation of beta cells. In the NOD mouse model, combining both molecules led to an increase in beta-cell mass. Additionally, combination therapy using DPP-4 inhibitors (to raise GLP-1 levels) and proton pump inhibitors (PPIs; to boost gastrin levels) resulted in higher C-peptide levels, enhanced insulin secretion, and restored normal blood glucose levels in NOD mice. In humans, the REPAIR-T1D study tested a similar one-year treatment using sitagliptin (a DPP-4 inhibitor) and lansoprazole (a PPI) in T1D patients. However, no significant differences in C-peptide levels were found between the treatment and placebo groups. The researchers suggested that the low increases in gastrin and GLP-1 levels were responsible for the ineffective treatment. Further clinical trials are needed to assess the potential of gastrin and GLP-1 combination therapy.[21,22,23]

III. IMMUNE INVOLVEMENT IN DISEASE ONSET AND PROGRESSION

T and B lymphocytes recognize antigens in different ways: B cells bind antigens directly, while T cells only recognize antigens that are presented on MHCI (for CD8 T cells) or MHCII (for CD4 T cells) molecules on the surface of antigen-presenting cells (APCs). Dendritic cells (DCs) are the most effective APCs and can activate naïve T cells, while macrophages and B cells are less potent but help sustain the activation and differentiation of already activated T cells. In certain stressful conditions, non-hematopoietic cells can also express MHCII and influence lymphocyte differentiation. The clusters of receptors that sense antigens on lymphocytes are called B cell receptors (BCRs) and T cell receptors (TCRs), with their signaling referred to as immune signal 1. This signal is essential for lymphocyte activation. However, for full activation and differentiation, signal 1 needs to be combined with co-stimulatory signal 2 (e.g., CD28, TNFRs, TLRs) and growth and differentiation signal 3 (e.g., IL-2 for T cells and IL-4 for B cells). Polarization, or signal 4, is shaped by various cytokines and other factors. T and B cells also need additional signals from membrane proteins and soluble factors to avoid autoimmune attacks. CD28 is the primary co-stimulatory protein in T cells, and after T cell division, IL-2 helps sustain clonal expansion. CTLA-4, which binds to CD80 and CD86 with higher affinity than CD28, downregulates T cell activation, but it may also function via regulatory T cells (Tregs) without interfering with the initial activation. Other receptors, such as those in the TNFR superfamily (e.g., CD134, CD137, and CD357), can modulate T cell responses, especially in peripheral tissues. The polarization signal determines the subtype of immune cells, such as Th1, Th2, Th17, and Tregs for CD4 T cells, and TC1, TC2, and Tregs for CD8 T cells. These subtypes play a role in immunity and inflammation, with Th2 skewing macrophages toward a less destructive M2 phenotype, while Th17 contributes to more aggressive inflammation. IL-21, produced mainly by activated CD4 T cells and natural killer cells, plays a key role in both T and B cell function. IL-21 promotes B cell activation, differentiation, and even cell death during immune responses. Excessive IL-21 production can contribute to autoimmune diseases and exacerbate inflammation.

IL-21 can inhibit TGFβ, which is necessary for the expression of Foxp3 in T cells, causing a shift in differentiation from Tregs to Th17 cells. Blocking IL-21 reduces immune cell infiltration into islets, and CD8 T cell-mediated rejection of islet grafts has been shown to depend on IL-21. Mice lacking the IL-21 receptor (Il21r−/−) in a non-obese diabetic (NOD) model are protected from type 1 diabetes (T1DM) and do not develop insulitis.[24,25,]

IV. NOVEL STRATEGIES

In recent years, chimeric antigen receptor (CAR) T-cell therapy, which involves engineering T-cells to express CARs targeting CD19, has emerged as a significant breakthrough in the treatment of CD19+ B-cell leukemia. CARs are complex molecules made up of several

components, including: (1) an antigen-specific recognition domain, often a single-chain variable region (scFv) from a monoclonal antibody; (2) a hinge region, derived from the Fc portion of human immunoglobulin (IgG1 or IgG4) or from CD8a or CD28 hinge domains; (3) a transmembrane domain; and (4) an intracellular signaling domain based on tyrosine residues. The signaling domain is the critical component, typically derived from CD3ζ, which is the key signaling chain of the T-cell receptor (TCR) complex. The main advantage of CAR-T cells is that their antigen recognition is independent of the major histocompatibility complex (MHC), but still activates TCR and co-stimulatory signaling pathways essential for T-cell activation and expansion.

V. CAR-T CELLS AND T1D

Inspired by CAR-based cancer therapies and the growing interest in Tregs as potential treatment for Type 1 diabetes (T1D), it is reasonable to hypothesize that equipping Tregs with β-cell-specific CARs could enhance their migration to the pancreas and pancreatic lymph nodes, offering protection to islet cells from autoimmune destruction. Several recent studies indicate that CAR-Treg therapy holds considerable promise in treating autoimmune diseases and preventing allograft rejection. For example, Fransson and colleagues explored CAR-Treg therapy in an experimental autoimmune encephalomyelitis (EAE) mouse model. In their study, CD4+ T-cells were engineered to express a CAR targeting myelin oligodendrocyte glycoprotein (MOG35-55) and a murine Foxp3 gene to drive Treg differentiation. Administering these CAR-Tregs intranasally successfully delivered them to the central nervous system (CNS), suppressed inflammation efficiently, and led to complete recovery from disease symptoms. Other research suggests CAR-Tregs could help prevent transplant rejection by generating HLA-A2-specific CAR-Tregs isolated from the host, which retained high Foxp3 expression and maintained their suppressive function without significant cytolytic activity. While further studies are needed to confirm the stability, purity, and long-term survival of these Tregs after transfer, this strategy is promising for promoting graft-specific tolerance and preventing transplant rejection. CAR-Tregs have also been tested in Hemophilia A, where mutations in the F8 gene affect Factor VIII (FVIII) production.

In patients with severe hemophilia, immune reactions to exogenous FVIII are common. Notably, FVIII-specific human CAR-Tregs were able to suppress antibody production in both in vitro and in vivo mouse models of Hemophilia A. However, since FVIII is a soluble protein, the exact mechanism of suppression remains unclear.

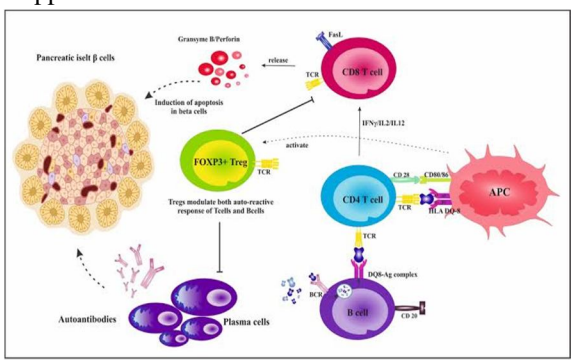


Fig No.4- CAR-T

A. *Challenges*

Despite the significant potential of CAR-Tregs therapies, there is no clear strategy yet for using this promising technology to treat Type 1 Diabetes (T1D). One of the major challenges is the absence of β cell-specific antibodies that could be utilized to create islet-protective CAR-Tregs. A potential solution is to employ human islet-specific TCR gene transfer into polyclonal human Tregs. A recent study showed that polyclonal Tregs transduced with TCR chains from two human islet-specific CD4+ clones exhibited improved antigen-specific suppression and enhanced potency compared to polyclonal Tregs. However, these islet-specific Tregs were less responsive to their cognate antigen than T-cells with virus-specific TCRs, indicating that further optimization and better TCR clones are still necessary.

Another study found that insulin-specific CAR-Tregs were functional, suppressive, and capable of surviving in vivo, although they were unable to prevent spontaneous diabetes in NOD mice. This result was expected, as insulin is a soluble antigen that fluctuates in concentration throughout the body. Additionally, this approach may not be efficient for T1D patients, as their low endogenous insulin levels, coupled with daily insulin injections, could interfere with the normal insulin concentration gradient that would otherwise guide the insulin-specific CAR-Tregs into the pancreas.

Thus, identifying and studying new β cell-specific molecules for proper CAR-Treg targeting is crucial. Promising molecules, such as DPP6, FXYD2γa, and NTPDase3, have been identified, but further research is required to confirm their specificity and to isolate appropriate monoclonal antibodies for recognizing human β cells in vivo before developing a CAR construct for T1D treatment. [26]

VI. CONCLUSION

The global diabetes epidemic has become a critical health issue, and the absence of effective and comprehensive treatments contributes significantly to the rising prevalence of the condition. Recent advancements in biomedical research have led to the development of various diabetes management and therapeutic strategies (as shown in Fig. 6), including immunotherapy, artificial pancreas, and cell-based therapies, which show great potential in treating diabetes through unique and powerful mechanisms. Immunotherapy works by modulating the immune system to prevent the destruction of β-cells, thus preserving insulin production. Although early clinical trials have yielded promising results, there remain unresolved questions regarding the best timing, dosage, and duration of immunotherapy, as well as concerns about long-term side effects. The artificial pancreas, which can automatically adjust insulin delivery based on real-time glucose readings, holds promise. However, improvements in glucose sensor accuracy and the optimization of control algorithms are necessary to enhance the effectiveness of the artificial pancreas for diabetes treatment.

A variety of therapeutic strategies are being explored for Type 1 Diabetes Mellitus (T1DM), ranging from immunomodulation and transplantation to combinations of these approaches, and even the potential to induce regulatory immune cells and differentiated islet cells in vivo. Biologics, such as antibodies and cytokines, have been used in clinical settings to induce immune tolerance, showing better results than traditional small molecule drugs like steroids. Cellular therapy is a more recent method aimed at providing targeted immune suppression and promoting stem cell-mediated regeneration. Among these, Tregs (regulatory T cells) have gained attention as a potential treatment for T1DM due to their ability to suppress autoimmune responses without causing widespread immunosuppression.

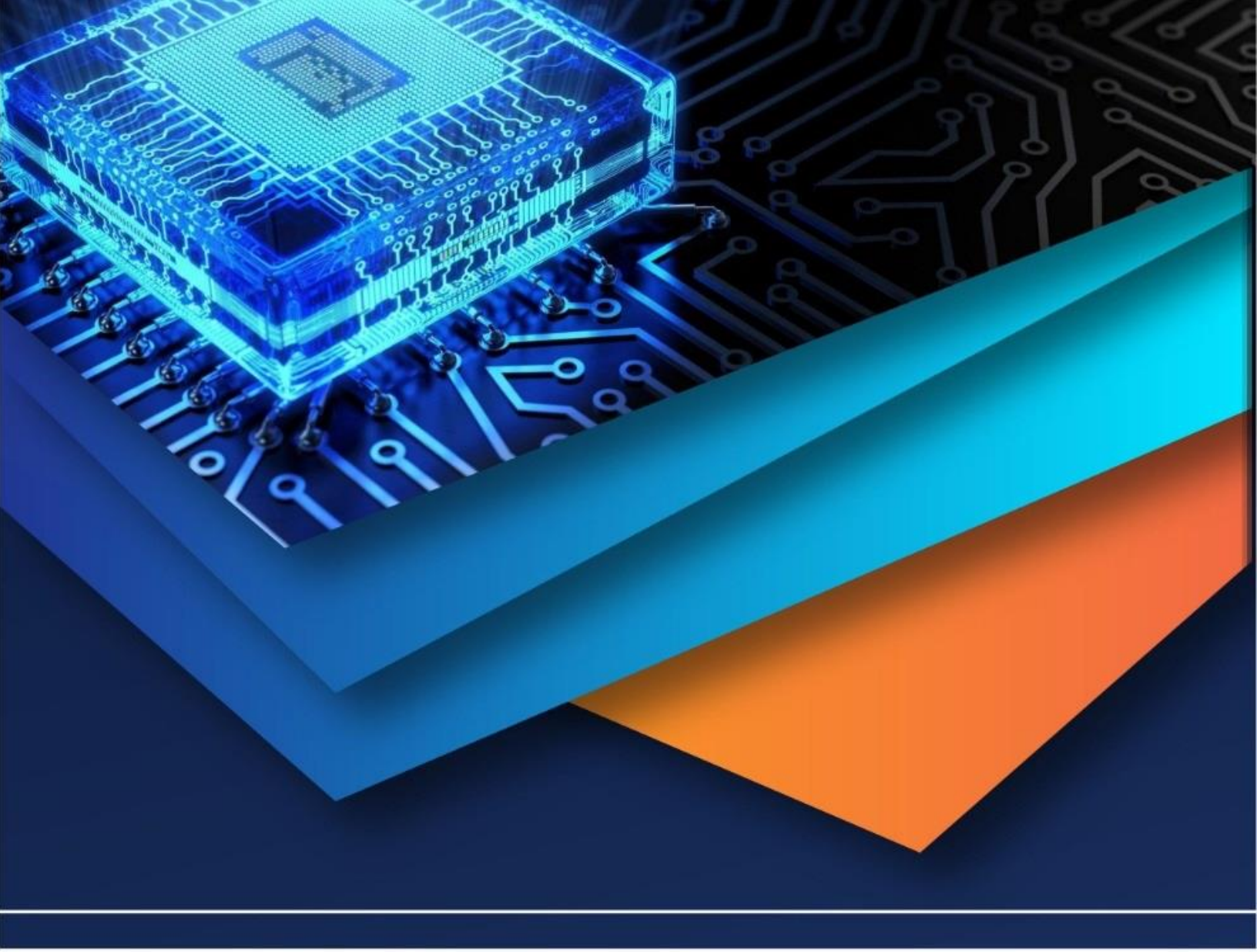
However, a major challenge remains in effectively and consistently inducing or expanding Tregs.

The main challenges in T1DM treatment lie in improving the patient's quality of life and ensuring that the treatments are sustainable over time. While islet transplants and immunosuppressants can be used, the side effects of non-selective small molecule drugs must be considered. If islet encapsulation is chosen as a treatment option, issues such as insulin/nutrient exchange, protection from immune damage, hypoxia, and fibrosis of the capsules need to be addressed. A significant issue with islet encapsulation is that the microencapsulation methods often result in large capsule sizes, which can impair insulin diffusion. This can reduce insulin secretion, increase islet necrosis, and raise the risk of hypoxia. Therefore, preparing suitable implantation sites for the islet capsules, considering the large volume of encapsulated islets or β-cells, is critical. Other important factors include enhancing capsule and device stability, minimizing the volume and size of the engraftment, and reducing immune responses. Despite advances in new technologies, several obstacles remain. These include the fragility of transplant devices and the potential need for "refills" of islets. Additionally, approaches such as immunotherapy using Tregs are becoming more prominent as potential treatments for T1DM. While each treatment option faces challenges, the most important consideration, beyond the effectiveness of any treatment, is the overall well-being and quality of life of the patient.[25,26,27,28,29]

REFERENCES

[1] Patterson, C.; Guariguata, L.; Dahlquist, G.; Soltesz, G.; Ogle, G.; Silink, M. Diabetes in the young—Aglobal view and worldwide estimates of numbers of children with type 1 diabetes. Diabetes Res. Clin. Pract.2014, 103, 161–175. [CrossRef] [PubMed]
[2] Maahs, D.M.; West, N.A.; Lawrence, J.M.; Mayer-Davis, E.J. Epidemiology of type 1 diabetes. Endocrinol. Metab.Clin. N. Am. 2010, 39, 481–497. [CrossRef] [PubMed]
[3] Barrett, J.C.; Clayton, D.G.; Concannon, P.; Akolkar, B.; Cooper, J.D.; Erlich, H.A.; Julier, C.; Morahan, G.;Nerup, J.; Nierras, C.; et al. Genome-wide association study and meta-analysis find that over 40 loci affectrisk of type 1 diabetes. Nat. Genet. 2009, 41, 703–707. [CrossRef] [PubMed]
[4] Pociot, F.; Akolkar, B.; Concannon, P.; Erlich, H.A.; Julier, C.; Morahan, G.; Nierras, C.R.; Todd, J.A.; Rich, S.S.;Nerup, J. Genetics of type 1 diabetes: What's next? Diabetes 2010, 59, 1561–1571. [CrossRef] [PubMed]
[5] Nerup, J.; Platz, P.; Andersen, O.O.; Christy, M.; Lyngsoe, J.; Poulsen, J.E.; Ryder, L.P.; Nielsen, L.S.;Thomsen, M.; Svejgaard, A. HL-A antigens and diabetes mellitus. Lancet 1974, 2, 864–866. [CrossRef]
[6] Clark, M.; Kroger, C.J.; Tisch, R.M. Type 1 Diabetes: A Chronic Anti-Self-Inflammatory Response.Front. Immunol. 2017, 8, 1898. [CrossRef] [PubMed]
[7] Shapiro, A.M.; Ricordi, C.; Hering, B.J.; Auchincloss, H.; Lindblad, R.; Robertson, R.P.; Secchi, A.;Brendel, M.D.; Berney, T.; Brennan, D.C.; et al. International trial of the Edmonton protocol for islet transplantation. N. Engl. J. Med. 2006, 355, 1318–1330. [CrossRef]
[8] Perseghin, G.; Fiorina, P.; De Cobelli, F.; Scifo, P.; Esposito, A.; Canu, T.; Danna, M.; Gremizzi, C.; Secchi, A.;Luzi, L.; et al. Cross-sectional assessment of the effect of kidney and kidney-pancreas transplantation onresting left ventricular energy metabolism in type 1 diabetic-uremic patients: A phosphorous-31 magneticresonance spectroscopy study. J. Am. Coll. Cardiol. 2005, 46, 1085–1092. [CrossRef]
[9] Simmons, K.M.; Michels, A.W. Type 1 diabetes: A predictable disease. World J. Diabetes 2015, 6, 380–390.[CrossRef]
[10] Regnell, S.E.; Lernmark, A. Early prediction of autoimmune (type 1) diabetes. Diabetologia 2017, 60, 1370–1381.[CrossRef]
[11] Di Lorenzo, T.P.; Peakman, M.; Roep, B.O. Translational mini-review series on type 1 diabetes: Systematic analysis of T cell epitopes in autoimmune diabetes. Clin. Exp. Immunol. 2007, 148, 1–16. [CrossRef] [PubMed]
[12] Wherrett, D.K.; Chiang, J.L.; Delamater, A.M.; DiMeglio, L.A.; Gitelman, S.E.; Gottlieb, P.A.; Herold, K.C.;Lovell, D.J.; Orchard, T.J.; Ryan, C.M.; et al. Defining pathways for development of disease-modifyingtherapies in children with type 1 diabetes: A consensus report. Diabetes Care 2015, 38, 1975–1985. [CrossRef]Laidlaw BJ, Craft JE, Kaech SM. The multifaceted role of CD4(+) T cells inCD8(+) T cell memory. Nat Rev Immunol (2016) 16:102–11. doi:10.1038/nri.2015.10
[13] Krummel MF, Bartumeus F, Gerard A. T cell migration, search strategies andmechanisms. Nat Rev Immunol (2016) 16:193–201. doi:10.1038/nri.2015.16
[14] Ettinger R, Kuchen S, Lipsky PE. The role of IL-21 in regulating B-cellfunction in health and disease. Immunol Rev (2008) 223:60–86. doi:10.1111/j.1600-065X.2008.00631.x
[15] McGuire HM, Walters S, Vogelzang A, Lee CM, Webster KE, Sprent J, et al.Interleukin-21 is critically required in autoimmune and allogeneic responsesto islet tissue in murine models. Diabetes (2011) 60:867–75. doi:10.2337/db10-1157
[16] Spolski R, Kashyap M, Robinson C, Yu Z, Leonard WJ. IL-21 signaling iscritical for the development of type I diabetes in the NOD mouse. Proc NatlAcad Sci U S A (2008) 105:14028–33. doi:10.1073/pnas.0804358105
[17] Levine AG, Mendoza A, Hemmers S, Moltedo B, Niec RE, Schizas M, et al.Stability and function of regulatory T cells expressing the transcription factorT-bet. Nature (2017) 546:421–5. doi:10.1038/nature2236
[18] Eizenberg-Magar I, Rimer J, Zaretsky I, Lara-Astiaso D, Reich-Zeliger S,Friedman N. Diverse continuum of CD4(+) T-cell states is determined byhierarchical additive integration of cytokine signals. Proc Natl Acad Sci U S A(2017) 114:E6447–56. doi:10.1073/pnas.161559011
[19] Bluestone JA, Mackay CR, O'Shea JJ, Stockinger B. The functional plasticity ofT cell subsets. Nat Rev Immunol (2009) 9:811–6. doi:10.1038/nri265
[20] Zhou L, Chong MMW, Littman DR. Plasticity of CD4(+) T cell lineage dif-ferentiation. Immunity (2009) 30:646–55. doi:10.1016/j.immuni.2009.05.00
[21] Das J, Ho M, Zikherman J, Govern C, Yang M, Weiss A, et al. Digital signalingand hysteresis characterize Ras activation in lymphoid cells. Cell (2009)136:337–51. doi:10.1016/j.cell.2008.11.051
[22] O'Garra A, Gabrysova L, Spits H. Quantitative events determine the differ-entiation and function of helper T cells. Nat Immunol (2011) 12:288–94.doi:10.1038/ni.2003
[23] Mayya V, Dustin ML. What scales the T cell response? Trends Immunol(2016) 37:513–22. doi:10.1016/j.it.2016.06.005
[24] Miossec P, Korn T, Kuchroo VK. Mechanisms of disease: interleukin-17and type 17 helper T cells. N Engl J Med (2009) 361:888–98. doi:10.1056/NEJMra0707449

[25] Ferraro A, Socci C, Stabilini A, Valle A, Monti P, Piemonti L, et al. Expansion of Th17 cells and functional defects in T regulatory cells are key features of the pancreatic lymph nodes in patients with type 1 diabetes. Diabetes (2011) 60:2903–13. doi:10.2337/db11-0090
[26] Emamaullee JA, Davis J, Merani S, Toso C, Elliott JF, Thiesen A, et al. Inhibition of Th17 cells regulates autoimmune diabetes in NOD mice. Diabetes (2009) 58:1302–11. doi:10.2337/db08-1113
[27] Miyara M, Ito Y, Sakaguchi S. TREG-cell therapies for autoimmune rheu-matic diseases. Nat Rev Rheumatol (2014) 10:543–51. doi:10.1038/nrrheum.2014.105
[28] Lernmark A, Larsson HE. Immune therapy in type 1 diabetes mellitus. Nat Rev Endocrinol (2013) 9:92–103. doi:10.1038/nrendo.2012.237
[29] Herold KC, Vignali DAA, Cooke A, Bluestone JA. Type 1 diabetes: translating mechanistic observations into effective clinical outcomes. Nat Rev Immunol(2013) 13:243–56. doi:10.1038/nri3422
[30] Roep BO, Tree TIM. Immune modulation in humans: implications for type 1 diabetes mellitus. Nat Rev Endocrinol (2014) 10:229–42. doi:10.1038/nrendo.2014.2
[31] Mohammadi MR, Nojoomi A, Mozafari M, Dubnika A, Inayathullah M, Rajadas J. Nanomaterials engineering for drug delivery: a hybridization approach. J Mater Chem B (2017) 5:3995–4018. doi:10.1039/C6TB03247H
[32] Concannon P, Rich SS, Nepom GT. Genetics of type 1A diabetes. N Engl J Med (2009) 360:1646–54. doi:10.1056/NEJMra0808284
[33] Ramsdell F, Ziegler SF. FOXP3 and scurfy: how it all began. Nat Rev Immunol(2014) 14:343–9. doi:10.1038/nri3650
[34] Lu L, Barbi J, Pan F. The regulation of immune tolerance by FOXP3. Nat Rev Immunol (2017) 17(11):703–17. doi:10.1038/nri.2017.75
[35] Kuhn C, Weiner HL. Therapeutic anti-CD3 monoclonal antibodies: from bench to bedside. Immunotherapy (2016) 8:889–906. doi:10.2217/imt-2016-0049
[36] Chatenoud L, Thervet E, Primo J, Bach JF. Anti-CD3 antibody induces long-term remission of overt autoimmunity in nonobese diabetic mice. Proc Natl Acad Sci U S A (1994) 91:123–7. doi:10.1073/pnas.91.1.123



10.22214/IJRASET

45.98

IMPACT FACTOR: 7.129

IMPACT FACTOR: 7.429

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY