Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU25012

Immunotherapies of Type 1 Diabetes: Modulation, Tolerance, Reconstitution and Replacement

Yinji Liu

School of Biological Sciences, The University of Edinburgh, Edinburgh, UK
Garfield.tudou@gmail.com

Abstract. Type 1 diabetes (T1D) is a chronic disease characterized by autoimmune destruction of pancreatic β cells, resulting in a lack of insulin secretion. Current treatments mainly rely on exogenous insulin supply. Although automated insulin infusion systems can effectively control blood sugar, they cannot reverse immunopathology or restore endogenous insulin secretion. This article divides emerging treatments for T1D into three categories: immune regulation, immune tolerance induction, and β cell regeneration and replacement. Immunomodulatory methods such as anti-CD3 antibodies (such as Teplizumab) and mesenchymal stem cell (MSC) infusion have shown some promise in preserving β cell function; tolerance induction therapy is based on autoantigens, such as insulin and GAD65 vaccines, but the efficacy is greatly affected by individual HLA differences. Emerging CAR-Tregs have higher specificity and potential. Regenerative and replacement therapies such as hematopoietic stem cell transplantation and islet-like cell transplantation have significant efficacy, but the need for immunosuppression remains their main challenge. At present, most treatments are still in the clinical trial stage. In the future, we can try to combine therapies with multiple mechanisms in order to achieve a more lasting and fundamental therapeutic effect.

Keywords: Type 1 diabetes, autoimmunity, immune modulation, tolerance.

1. Introduction

Type 1 diabetes (T1D) accounts for 5-10% of all diabetic cases and is more common in children and adolescents than in adults [1]. It is a chronic autoimmune disease where insulin-producing β cells in the pancreatic islets are mistakenly recognised as non-self by the immune system via β cell-expressed autoantigens such as insulin, glutamic acid decarboxylase 65 kDa isoform (GAD65) and islet antigen 2 or insulinoma-associated protein 2 (IA-2), and are subsequently attacked and destroyed [2]. Autoreactive effector CD8+ T cells are responsible for the direct destruction of β cells, whereas CD4+ helper T cells, B cells and the autoantibodies they produce are responsible for enhancing the autoimmune response [2]. The loss of β cells then result in deficiencies in insulin production, thus the loss of the ability to regulate blood glucose level [1, 2]. If left untreated, patients could develop various vascular comorbidities and diabetic ketoacidosis, which would ultimately result in death, therefore patients have to depend on insulin supplement throughout the

DOI: 10.54254/2753-8818/2025.AU25012

rest of their lives, and exogenous insulin supply naturally becomes the main method for T1D management [3].

The administration of exogenous insulin to T1D patients was mainly achieved by regular injections, which could be uncomfortable and disturbing to patients, who also have to monitor their own blood glucose levels regularly. With the advancement in technology, exogenous insulin is now mainly administered by automated insulin delivery systems. Each of these systems is a combination of an insulin pump, a continuous glucose monitor and a dosing algorithm that allows the insulin pump to deliver the appropriate amount of insulin to patients according to the blood glucose level detected by the glucose monitor, so that regular injections are no longer needed [4]. However, even with the combination of blood glucose monitoring and automated insulin delivery technologies, the blood glucose levels of a considerable amount of T1D patients were still less than satisfactory; furthermore, patients have life-long dependence on AID systems and exogenous insulin, therefore the AID system, or the administration of exogenous insulin as a whole, is not an actual cure for the disease [3].

Apart from T1D management with insulin, other treatments that seek to restore insulin production in patients are being developed and tested. These treatments generally aim to preserve or restore the β cells in the pancreas either by partially altering the immune system and how it reacts to β cells, or by introducing β cells directly into patients [5]. This review aims to provide a comprehensive overview of these therapies by categorising them into three groups according to their modes of action: immune modulation, tolerance induction and reconstitution and replacement, and their specific mechanisms, development and efficacy will be highlighted.

2. Immune modulation therapies

2.1. Antibodies

The Antibodies could be used to suppress T1D by blocking signaling pathways in the immune system and thereby restraining the autoimmune attack on β cells. More specifically, antibodies could block signal transduction proteins, immune checkpoints (ICs) and cytokines involved in the activation and proliferation of T cells, the primary killer of β cells, and protect β cells from destruction [2]. There are numerous targets for these therapeutic antibodies due to the complexity of the immune system, but the major target is CD3. It is a T cell co-receptor and an important component of the T cell receptor (TCR) complex, and is therefore expressed in all T cells. In the process of T cell activation, the CD3/TCR complex would interact with the major histocompatibility complex (MHC) or human leukocyte antigen (HLA) along with the antigens they present, and blocking CD3 could interfere with this interaction, resulting in inactivation of T cells, inhibition of T cell-mediated cytotoxicity and apoptosis, and induction of apoptosis or anergy of T cells that have already been activated [5, 6]. Teplizumab is one of the therapeutic anti-CD3 monoclonal antibodies (mAb) for treating T1D, and is currently the only one approved by the FDA. Patients that received teplizumab treatment have exhibited delayed onset of T1D, reduced need for exogenous insulin and increased levels of C-peptide, the marker for insulin production, indicating restoration in insulin production [6]. The levels of glycated haemoglobin A1c (HbA1c), the marker of blood glucose level, also decreased, indicating restored function of controlling blood glucose [6]. The effects lasted for months after ceasing treatment, making teplizumab one of the most effective immune modulatory treatments for T1D [6].

ICs are molecules that help regulate the immune response via co-signaling pathways. In the context of T1D, ICs could assist the activation of T cells and increase the threat to β cells, therefore

DOI: 10.54254/2753-8818/2025.AU25012

blocking them could reduce the autoimmune attack on β cells. CD2 is one of the ICs of interest as it is expressed on the majority of T cells. Anti-CD2 antibodies and fusion proteins derived from these antibodies have shown the ability to block T cell activation and to induce apoptosis in memory effector T cells, with an example being alefacept, but its effect on patients in trials have been less than satisfactory, as the exhibited reduction in exogenous insulin requirement and increase in C-peptide levels were statistically insignificant [6, 7]. Other IC inhibitors targeting CD28 and CTLA-4 are being investigated, and so far, these antibodies have only been able to slow down the decrease in C-peptide levels thus the loss of insulin productivity, suggesting the need for treatment improvement and possibly re-assessment on the mechanisms of blocking ICs [2, 5].

Signaling proteins and ICs on effector T cells hold great therapeutic potential and have been investigated extensively, but the antigen presenting cells (APCs) and B cells are also involved in the autoimmune response of T1D, and are therefore worth studying. CD80 and CD86 are ICs expressed by a variety of immune cells, especially APCs, and they are also the ligands for T cell ICs CD28 and CTLA-4 [7]. Abatacept is an anti-CD80/86 fusion protein derived from CTLA-4 immunoglobulin that could bind to CD80 and CD86 and block their interactions with the receptor CD28 on T cells, which disrupts the activation, proliferation and survival of T cells, again resulting in slower loss of β cell function [5, 6]. CD20 is a surface marker for the antibody-producing B cells, and the anti-CD20 mAb rituximab has the ability to deplete B cells, which would subsequently reduce the production of β cell-targeting autoantibodies and the B cell-mediated antigen presentation and T cell activation [6, 7]. This series of effects could preserve insulin production for months, but the C-peptide level in patients still dropped in long-term follow-up studies, therefore investigating to retain the long-term effects of anti-CD20 mAbs could be a promising direction [6].

Apart from cellular proteins, pro-inflammatory cytokines, including interleukins (ILs) IL-1, IL-6, IL-12/23, IL-21 and tumor necrosis factor-α (TNF-α), have also been studied for targeted blockade [6, 7]. These pro-inflammatory cytokines could promote T cell differentiation and proliferation, and are therefore contributors to the autoimmune attack in T1D. Many anti-cytokine mAbs and derived fusion proteins, such as canakinumab, tocilizumab, ustekinumab, golimumab and etanercept, have been developed and tested [6, 7]. Among these, the anti-TNF-α golimumab and etanercept and the anti-IL12/23 ustekinumab were able to improve C-peptide levels in treated patients, but the anti-IL-1 canakinumab and anti-IL-6 tocilizumab did not give significant therapeutic effects [6, 7]. It could be hypothesized that certain cytokines are not suitable targets for mAb blockade and that there might be a potential causative correlation between the effect of anti-cytokine mAbs and the specific identities and properties of cytokines. This could be investigated by producing different mAbs blocking the same cytokines and testing them to see if the therapeutic outcomes of different mAbs targeting the same designated cytokine is consistent.

To conclude, antibodies could be used to target a variety of signaling molecules in different immune pathways, but the effects of treatments could vary with the specific antibody used, the target selected, the genetic background and immune profile of patients, and the development of disease [2]. But on the other hand, the general treatment could be refined by comparing the effects of different antibodies and of targeting different signaling molecules and screening for the most effective combination, and personalized treatments could be applied on this basis. However, the nature of using antibodies to treat T1D is to suppress the immune system, which could indeed reduce the autoimmune attack on β cells, but it could also affect the normal functioning of the immune system, therefore the balance between therapeutic effect and risk of adverse effect is important.

DOI: 10.54254/2753-8818/2025.AU25012

2.2. Mesenchymal Stem Cells (MSCs)

MSCs are multipotent cells found mainly in the bone marrow. They have multiple characteristics, including their native multi-potency, high self-renewal, secretory and trophic properties, and moreover, immunomodulatory functions, which give MSCs great potential as a therapeutic for T1D [8]. MSCs could secrete various factors, such as IL-10, transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and prostaglandin E2 (PGE2), and these secreted factors could help reduce inflammation and promote the proliferation of Tregs that could also help suppress autoimmunity, reducing the threats to β cells [9]. Apart from modulating the immune system, MSCs themselves could also help treat T1D by homing to damaged pancratic islets, differentiating into progenitor cells, then mediate these progenitor cells to differentiate further into β cells, repairing the damaged tissues and restoring insulin production to a certain extent [2, 9]. In clinical studies, T1D patients received MSC infusion showed significant increase in C-peptide levels and insulin production, along with significant decrease in HbA1c levels, and some patients were able to establish independence from exogenous insulin for months up to a year, suggesting great therapeutic potential [9]. However, the long-term follow-up studies and data for MSC therapy are limited, so it is still unclear if the therapeutic effects of MSC infusion could last longer [6].

To conclude, the multiple functions and the stem cell nature of MSCs enables both immunomodulatory T1D suppression and direct repair of pancreatic tissue and restoration of insulin production, which make MSCs highly valuable as a therapeutic. Subsequent studies could focus on the long-term effect of MSC infusion therapy, utilize the ability of MSCs to repair damaged pancreatic islets and seek to preserve these newly-differentiated β cells..

3. Immune tolerance therapies

3.1. Autoantigen treatments

Another category of therapies was being developed to induce immune tolerance for the autoantigens causing T1D. Instead of directly manipulating the immune system and suppressing the autoimmune responses along with other immune responses, these therapies generally aim to re-educate the immune system to recognize the β cells as self again, so that no autoimmune response would be triggered. The advantage of these therapies is that they do not affect the normal functioning of the immune system, for only the autoantigens would be tolerated. Autoantigen treatments are the main type in this category. Similar to how people with nut or pollen allergies could be administered small doses of allergens in a very controlled manner to reduce the sensitivity of their immune systems and train them to not react to these allergens, autoantigen treatments were designed so that small amounts of T1D autoantigens would be delivered to patients in the forms of medications and vaccines, thus the patients' immune systems would react less to these autoantigens and would gradually be desensitized, and β cells would no longer be attacked.

The major autoantigens in T1D are GAD65, IA-2, zinc transporter 8 (ZnT8) and insulin itself, including proinsulin, among which GAD65 and insulin were studied more for autoantigen treatments [1, 10]. Insulin and proinsulin vaccines and medications administered via subcutaneous, intramuscular and intranasal routes did not have significant effects on the onset of T1D or C-peptide level [6, 7, 10]. Orally administered insulin had no significant effect either at the beginning, but it was soon improved by using carriers such as Lactococcus and Salmonella bacteria to protect insulin from protein digestion after entering the gastrointestinal tract [10]. However, despite the improvement with autoantigen carriers, only some of the treated patients exhibited increased C-

DOI: 10.54254/2753-8818/2025.AU25012

peptide levels, decreased anti-insulin autoantibody levels and delayed T1D progression [6, 7, 10]. On the other hand, GAD65 has been modified into a vaccine via conjugation with the adjuvant aluminum hydroxide (alum) in hydrogel form into GAD-alum and then tested [7]. The vaccine was administered via intradermal and subcutaneous routes and again produced varying levels of C-peptide preservation and HbA1c reduction across different studies and patients [5, 7, 10]. This variation in therapeutic effects of autoantigen treatments was studied further, and It was then discovered that patients with the HLA haplotype DR4-DQ8 generally had higher levels of anti-insulin autoantibodies and were affected more by insulin autoantigen treatments, whereas patients with the DR3-DQ2 haplotype had higher anti-GAD65 autoantibody levels and the GAD-alum vaccine was significantly more effective on them [11]. These discoveries suggest that different HLA haplotypes favor presenting different autoantigens, which would result in varying proportions of different autoantigens presented and varying therapeutic effects of autoantigen treatments.

Apart from HLA haplotypes, other factors influencing the effect of autoantigen treatments, such as routes and locations of administration, were also being investigated. More recent studies on GAD65-based treatment delivered GAD-alum vaccine via intralymphatic routes to get the autoantigens closer to the APCs for greater immunological impacts, and with the supplement of vitamin D, the overall tolerance induction should be more effective [10, 11]. In clinical trials, intralymphatic GAD-alum administration did give satisfactory performance, with the treatment itself well-tolerated, and the preservation of β cell function in treated patients was significantly higher than the control group receiving placebo, which supported the theory of delivering autoantigens directly to the lymphatic system could improve tolerance induction [11]. Similarly, the thymus could be another choice of location for autoantigen delivery, as it is where T cell development and maturation occur, and these include the negative selection of autoimmune T cells, which gives the thymus primary responsibility for establishing tolerance to avoid autoimmune responses, making it a suitable place for re-education of T cells and the immune system [12].

In conclusion, autoantigen treatments are more specific and generally safer as a type of immunotherapy for T1D, for they do not affect the normal functioning of the immune system, but only seek to induce tolerance for the specific autoantigens. However, the effectiveness of autoantigen treatments were inconsistent for various reasons, including the HLA haplotype of patients, the location of treatment administration and the route of delivery. But the correlation between treatment effect, autoantigen of selection and patient HLA haplotype has been identified, so personalized medicine could be applied where the HLA haplotype of patient is detected, and the corresponding effective autoantigen treatment could be applied. Combined therapy is another potential choice for improving therapeutic effect, where different autoantigens could be administered simultaneously for a broad spectrum induction of tolerance. Delivery of therapeutics via the lymphatic system, or more specifically the lymph nodes and the thymus, is also an action that could be applied, as it has been shown to improve the efficacy of tolerance induction and the preservation of β cell function. Further research of the other two major autoantigens, IL-2 and ZnT8 could be carried out as well, for they could cover the remaining areas in the broad spectrum tolerance induction of combined therapy.

3.2. Regulatory T cells (Tregs)

Apart from low-dose autoantigens, tolerance could also be induced by cells. Tregs are the subset of T cells that are responsible for maintaining the balance of the immune system and preventing autoimmunity [2]. In the context of T1D, Tregs could induce and maintain tolerance by suppressing the activity of autoreactive effector T cells that mediate cytotoxicity and apoptosis and destroy β

DOI: 10.54254/2753-8818/2025.AU25012

cells [13]. The first Tregs treatment was the ex vivo expansion of autologous Tregs, where Tregs were isolated from T1D patients and expanded, and then infused back into patients, but these Tregs were only slightly effective in children, and were only able to preserve β cell function for a maximum of two years before all the patients become dependent on exogenous insulin again [2, 13]. It was discovered that the number of Tregs dropped rapidly after infusion, so some attempts to improve the treatment applied low-dose IL-2 that could promote Treg activity, or the anti-CD20 mAb rituximab to remove antigen-presenting B cells [6, 13]. Low-dose IL-2 did maintain the levels of Tregs in the bloodstream, but the effects on the in vivo expansion of Tregs and the preservation of β cells were inconsistent, and there were cases of adverse effects where low-dose IL-2 not only expanded Tregs, but also expanded the inflammatory subset of T cells, nullifying the preserved β cell function [2, 6, 13]. Rituximab on the other hand, did improve the therapeutic effect of Tregs, reducing the need for exogenous insulin and even establishing insulin independence for up to two years [13]. Another improvement on the treatment was the use of chimeric antigen receptor (CAR) technology, where Tregs were genetically engineered to express CARs and become CAR-Tregs that bind to the T1D autoantigens thus the β cells [13, 14]. These CAR-Tregs can localize to the pancreas and become enriched, where they could suppress the autoreactive T cells that target β cells for destruction. However, CAR-Treg is a relatively recent therapy, therefore clinical trials and relevant data are limited. Trials were mainly carried out using CAR-Tregs specific for insulin or peptides from insulin, and the results were generally positive, with cases of improved β cell function and suppressed T1D, but CAR-Tregs specific for soluble insulin were unable to delay the progression of T1D, and the reason is still to be determined [14].

To conclude, Tregs still have a considerable room for improvement. The basic expansion method required parallel treatments for significant therapeutic effects, and CAR-Tregs were still in early stages of development, with three of the four main autoantigens untested. But room for improvement could also suggest promising prospects. Future studies on traditional Tregs treatment could focus on the optimization of combined therapy, and the specificity of CAR-Tregs could be further explored by introducing CARs that bind to GAD65, IA-2 and ZnT8, comparing their effects, and perhaps identifying peptides that confer higher levels of specificity or bringing together different CAR-Tregs to enhance enrichment in pancreas and induced tolerance.

4. Reconstitution and replacement therapies

4.1. Hematopoietic Stem Cells (HSCs)

HSCs are blood-forming stem cells found in bone marrow and peripheral blood [15]. They have been evaluated as having powerful immunoregulatory abilities to the extent of reshaping or resetting the immune system and immune responses into more tolerant states [15, 16]. Transplantation of autologous HSCs has been used in clinical trials as a treatment for numerous autoimmune diseases including T1D and was described to be effective and safe in human subjects [15, 16]. The infusion of HSCs into patients could establish mixed chimerism, where the immune cells of patients coexist with these HSCs, forming an in vivo cellular context that favors the induction of immune tolerance [15]. In T1D clinical trials, patients that received autologous HSC transplantation exhibited increased C-peptide levels and insulin independence with only minor adverse effects in the mid-term of the trial period, the therapeutic effects were also consistent in the follow-up period where their immune systems were generally stabilizing, and there were even cases of patients developing long-term independence from exogenous insulin for up to four years [15, 16]. On this basis, the HSCs were still being improved via genetic engineering to express class II MHCs that are more protective

DOI: 10.54254/2753-8818/2025.AU25012

and tolerogenic, for autoimmune T cells generally do not participate in class II MHC-mediated immune responses, which would further increase the therapeutic effect, and was tested and verified in mice models as their T1D development was halted [15]. But as a type of transplantation for patients with an autoimmune disease, the treatment will require immunosuppression, which would make patients more susceptible to infectious pathogens and other cell abnormalities including cancer, and the immunosuppressive drugs themselves could also cause side effects in patients [16].

To conclude, autologous HSC transplantation is a promising treatment for T1D with varying but overall effective treatment outcomes. However, the effectiveness comes with corresponding risks, not from HSCs themselves, but from the means to stabilize their integration into patients. The reasons behind the establishment of mid-long-term independence from exogenous insulin in certain patients could be worth looking into for the general improvement in the temporal length of insulin independence, and the statuses and mechanisms of mixed chimerism in these patients could be investigated for inspirations to enhance and maintain tolerant in vivo environments..

4.2. Islet transplantation

Islet transplantation is a straightforward and relatively traditional treatment, where the damaged pancreatic islets in patients are replaced by donor islets, restoring the mass of β cells and the production of insulin. The ability of transplanted pancreatic tissue to restore insulin production has been illustrated around 60 years ago in the 1960s, but the effects were limited, until the method of infusing islets via the portal vein was put forward in the early 21st century, which largely improved the therapeutic effect [17]. However, there are multiple limitations of islet transplantation beyond the treatment itself. Patients will require immunosuppressants to prevent rejection before, during and after transplantation, and this requirement would continue throughout their lives, which again would render the patients more vulnerable to infections and malignancies, therefore prophylactic vaccinations and drugs are needed before the transplantation, and anti-infective medications are needed post-transplantation alongside the immunosuppressants [16]. Furthermore, the success of transplantation has a correlation with the number of islets transplanted, and successful grafts generally require large amounts of islets thus multiple donor pancreases, the number of which is relatively limited, and on this basis, the different genetic background of these donor pancreases and islets could worsen the rejection [17].

In attempt to overcome these limitations, the method of differentiating pluripotent stem cells in vitro into β cells was developed, which bypassed the limitation in donor pancreas sourcing as the islets could be derived from a single cell source [17]. Also, cells in the derived islets could be genetically engineered to remove certain antigens, including some of the T1D autoantigens, to avoid destruction, and tolerogenic signaling molecules could be appended to facilitate tolerance induction and preservation of grafts [17]. Another developing method to protect the transplanted islets from autoimmunity and alloimmunity was the encapsulation of islets. The encapsulating devices were generally biocompatible hydrogels, porous scaffolds and semipermeable membranes that could allow small molecule nutrients as well as insulin to diffuse through, while immune cells would be blocked and their interaction with the transplanted islets disabled [17, 18, 19]. The devices have been applied to different animal models including mice, pigs and dogs in trials, and have exhibited reduced inflammation and insulin independence [19].

To conclude, islet transplantation is a straightforward but effective therapy. But again, as a type of transplantation, the necessary immunosuppression comes with risks and side effects. Stem cell modifications and encapsulating devices are being tested to help transplanted islets evade immune attacks, and if successful, these methods could protect the islets from both rejection and

DOI: 10.54254/2753-8818/2025.AU25012

autoimmunity, which would overcome the major limitations of the treatment, and patients could be relieved from T1D itself and the side effects of transplantation. Therefore, future studies could carry on with testing and improvement of these immunoprotective methods.

5. Conclusions

Immune modulation therapies were aimed to alter the immune system directly and stop autoimmune responses. Antibodies that block different points of the immune signaling pathways produced varying effects, with teplizumab blocking T cell coreceptor CD3 standing out, but antibodies targeting ICs and cytokines gave varying results. MSC infusion is a treatment of satisfactory effects and high value, and the only problem so far is the lack of data for long-term effects. So the priority for modulation therapies would be to focus on identifying the antibodies with higher performances and possibly bring them together into different combinations for enhancement of therapeutic effect, to investigate potential adverse events of using these antibodies, and to carry out long-term studies on MSCs.

Tolerance induction therapies were aimed to re-educate and desensitize the immune system to not react towards the autoantigens, thus the autoantigens themselves became part of the treatment. Insulin and GAD65 vaccines have been applied in trials and produced inconsistent effects across patients due to the different HLA haplotypes in the patients. Subsequent researches could test the effects of the other two autoantigens IA-2 and ZnT8 as vaccines and combine different autoantigen vaccines for a broad-spectrum tolerance induction. The emergence of CAR-Tregs was a breakthrough in the field of Tregs treatment, and its specificity for pancreatic tissues holds considerable therapeutic potential.

Reconstitution and replacement therapies generally have larger scales and biological impacts, for populations of cells are involved, but this is also the reason that they require immunosuppression, which is a major downside for the highly effective therapies. The establishment of mixed chimerism by autologous HSCs and the immunoprotective encapsulation devices for stem cell-derived islets could be the directions of future studies.

The development of T1D therapies as a whole is in a fairly early stage, with the vast majority of immunotherapies still in clinical trials and even earlier phases, but the current progresses of different treatment branches have pointed out the directions for following researches, and some of them have already obtained encouraging results, namely teplizumab, MSCs, and HSC transplantation. Apart from these, the theoretical combined autoantigen vaccine, the CAR-Tregs and the application of immunoprotective encapsulation devices for islet transplantation are also promising therapies. This review cannot cover all the details and innovations of these therapies, or the other therapies that are being developed, but it should be able to provide a general overview of what treatments has been studied and tested in the field. And on this basis, certain treatments with different mechanisms with outstanding performances could be carried forward in research and possibly applied together as a combined therapy in the future.

References

[1] Addissouky, T. A., Ali, M. M., El Sayed, I. E. T., & Wang, Y. (2024). Type 1 diabetes mellitus: retrospect and prospect. Bulletin of the National Research Centre, 48(1), 42.

[2] Zarei, M., Sheikholeslami, M. A., Mozaffari, M., & Mortada, Y. (2025). Innovative immunotherapies and emerging treatments in type 1 diabetes management. Diabetes Epidemiology and Management, 17, 100247.

[3] Subramanian, S., Khan, F., & Hirsch, I. B. (2024). New advances in type 1 diabetes. Bmj, 384.

DOI: 10.54254/2753-8818/2025.AU25012

[4] Forlenza, G. P., DeSalvo, D. J., Aleppo, G., Wilmot, E. G., Berget, C., Huyett, L. M., Hadjiyianni, I., Méndez, J. J., Conroy, L. R., Ly, T. T., & Sherr, J. L. (2024). Real-world evidence of omnipod® 5 automated insulin delivery system use in 69, 902 people with type 1 diabetes. Diabetes Technology & amp; Therapeutics, 26(8), 514–525.
[5] Jeun, R. (2025). Immunotherapies for prevention and treatment of type 1 diabetes. Immunotherapy, 17(3), 201–210.
[6] Mondal, S., & Pappachan, J. M. (2025). Current perspectives and the future of disease-modifying therapies in type 1 diabetes. World Journal of Diabetes, 16(1), 99496.
[7] Jacobsen, L. M., & Schatz, D. (2024). Immunotherapy-based strategies for treatment of type 1 diabetes. Hormone Research in Paediatrics, 1-19.
[8] Yang, G., Fan, X., Liu, Y., Jie, P., Mazhar, M., Liu, Y., Dechsupa, N. & Wang, L. (2023). Immunomodulatory mechanisms and therapeutic potential of mesenchymal stem cells. Stem Cell Reviews and Reports, 19(5), 1214-1231.
[9] Al Madhoun, A., Koti, L., Carrió, N., Atari, M., & Al-Mulla, F. (2024). Clinical application of umbilical cord mesenchymal stem cells preserves β-cells in type 1 diabetes. Stem Cells Translational Medicine, 13(2), 101-106.
[10] Ludvigsson, J. (2020). Autoantigen treatment in type 1 diabetes: unsolved questions on how to select autoantigen and administration route. International journal of molecular sciences, 21(5), 1598.
[11] Ludvigsson, J., Sumnik, Z., Pelikanova, T., Nattero Chavez, L., Lundberg, E., Rica, I., Martínez-Brocca, M. A., Ruiz de Adana, M., Wahlberg, J., Katsarou, A., Hanas, R., Hernandez, C., Clemente León, M., Gómez-Gila, A., Lind, M., Lozano, M. F., Sas, T., Samuelsson, U., Pruhova, S., Dietrich, F., Puente Marin, S., Nordlund, A., Hannelius, U. & Casas, R. (2021). Intralymphatic glutamic acid decarboxylase with vitamin D supplementation in recent-onset type 1 diabetes: a double-blind, randomized, placebo-controlled phase IIb trial. Diabetes Care, 44(7), 1604-1612.
[12] Shi, Y., Lu, Y., & You, J. (2022). Antigen transfer and its effect on vaccine-induced immune amplification and tolerance. Theranostics, 12(13), 5888.
[13] Passerini, L., Forlani, A., & Gregori, S. (2025). Advances in Regulatory Cell Therapy for Type 1 Diabetes: Emerging Strategies and Future Directions. European Journal of Immunology, 55(5), e202451722.
[14] Spanier, J. A., Fung, V., Wardell, C. M., Alkhatib, M. H., Chen, Y., Swanson, L. A., Dwyer, A. J., Weno, M. E., Silva, N., Mitchell, J. S., Orban, P. C., Mojibian, M., Verchere, C. B., Fife, B. T., & Levings, M. K. (2023). Tregs with an MHC class II peptide-specific chimeric antigen receptor prevent autoimmune diabetes in mice. The Journal of clinical investigation, 133(18), e168601.
[15] Pastore, I., Assi, E., Ben Nasr, M., Bolla, A. M., Maestroni, A., Usuelli, V., Loretelli, C., Seelam, A. J., Abdelsalam, A., Zuccotti, G. V., D'Addio, F., & Fiorina, P. (2021). Hematopoietic Stem Cells in Type 1 Diabetes. Frontiers in immunology, 12, 694118.
[16] Wan, X. X., Zhang, D. Y., Khan, M. A., Zheng, S. Y., Hu, X. M., Zhang, Q., Yang, R. H., & Xiong, K. (2022). Stem Cell Transplantation in the Treatment of Type 1 Diabetes Mellitus: From Insulin Replacement to Beta-Cell Replacement. Frontiers in endocrinology, 13, 859638.
[17] Hogrebe, N. J., Ishahak, M., & Millman, J. R. (2023). Developments in stem cell-derived islet replacement therapy for treating type 1 diabetes. Cell stem cell, 30(5), 530–548.
[18] Cuscino, N., Castelbuono, S., Centi, C., Tinnirello, R., Cimino, M., Zito, G., Orlando, A., Pinzani, M., Conaldi, P. G., Mattina, A., & Miceli, V. (2025). A Bioartificial Device for the Encapsulation of Pancreatic β-Cells Using a Semipermeable Biocompatible Porous Membrane. Journal of Clinical Medicine, 14(5), 1631.
[19] Toftdal, M. S., Grunnet, L. G., & Chen, M. (2024). Emerging Strategies for Beta Cell Encapsulation for Type 1 Diabetes Therapy. Advanced Healthcare Materials, 13(19), 2400185.