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# CURRENTLY TRENDING AND FUTURISTIC BIOLOGICAL MODALITIES IN THE MANAGEMENT OF DIFFERENT TYPES OF DIABETES: A COMPREHENSIVE REVIEW

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## Abstract

**Objectives:** *Diabetes mellitus* (DM) is a global health issue with a rising incidence of cardiovascular, renal, ketoacidosis, and cutaneous consequences. This rising pandemic affects over 415 million people globally, with a large percentage diagnosed with type 1 diabetes. Diabetes is projected to triple by 2040, straining global healthcare systems. Malaysia anticipates 21.6% diabetes prevalence by 2020, including a notable portion of T1D cases. Inflammation and oxidative stress underlie T2D development and its consequences. Obesity increases pro-inflammatory cytokines like IL-6, which can lead to insulin resistance and T2D. In T1D and T2D, inflammation and oxidative stress can destroy pancreatic beta cells. Cardiovascular complications in T2D are linked to inflammation and oxidative stress. Insulin therapy, a significant diabetes breakthrough, poses challenges in maintaining tight glycemic control without hypoglycemia and weight gain, revealing an unmet need in diabetes care.

**Methods:** This review centres on the premise that, despite the pivotal role of insulin therapy in diabetes care, it possesses limitations. The pursuit of stringent glycemic control, a cornerstone in averting diabetes-related complications, can, at times, be overshadowed by the specter of hypoglycemia—a potentially life-threatening condition. In light of these hurdles, the quest for alternative approaches or adjuncts to insulin therapy becomes imperative. Overcoming the constraints of insulin treatment mandates the development of innovative strategies.

**Conclusions:** This review explores alternative biological methods aimed at delivering safer and more effective means of achieving optimal glycemic control while circumventing the drawbacks of conventional insulin administration.

**Keywords:** Diabetes mellitus, Glycaemic Control, insulin, hypoglycaemia,

## *1) Introduction*

Diabetes mellitus (DM) is a chronic pathological condition characterized by dysregulation of blood glucose levels, which subsequently gives rise to a myriad of complications involving the cardiovascular system, renal function, ketoacidosis, and dermal manifestations [1]. Diabetes mellitus is a rapidly emerging pathological condition [1]. According to the estimations provided by the International Diabetes Federation in 2015, the global prevalence of diabetes was reported to exceed 415 million individuals. Among this population, approximately 5% were diagnosed with type 1 diabetes (T1D) [2]. The prevalence of diabetes is exhibiting an upward trend and is projected to undergo a twofold escalation by the year 2040 [2]. The management of individuals with diabetes incurs substantial financial burdens. In a study conducted in 2015, compelling evidence emerged indicating that the economic implications of this phenomenon posed a significant burden on the health maintenance schemes of both developing and developed nations. The annual monetary value of this quantity is estimated to be approximately USD673 billion, as reported in reference [3]. According to current projections, it is anticipated that the prevalence of diabetes among the adult population in Malaysia will experience a notable increase, reaching approximately 21.6% by the year 2020. According to empirical data, it has been observed that individuals diagnosed with T1D constitute a proportion of 0.6% within the larger population afflicted with diabetes in Malaysia [3].

T2D is well recognized as an inflammatory disease, and inflammation and oxidative stress have been linked to T2D etiology and related consequences [4]. Pro-inflammatory cytokines, such as IL-6, are frequently raised in obese adults, and this elevation is linked to the development of insulin resistance and is predictive of fully-established T2D [5,6]. Furthermore, inflammation and oxidative stress may damage and eradicate pancreatic beta cells, which are seen in both T1D and T2D [7]. Furthermore, diabetes consequences, such as cardiovascular disease, are significantly linked to increased expression of inflammatory mediators and oxidative stress. This shows that inflammation and oxidative stress are important factors in the development of T2D and associated consequences.

A significant progress has been made in understanding the origin, effects, and persistence of diabetes mellitus. Among these breakthroughs, the discovery of insulin and its analogues stands out as a watershed moment, changing diabetes therapy [5,6]. Despite these impressive advances, a key problem remains: obtaining adequate glycemic control while avoiding negative side effects such as hypoglycemia and weight gain [8-11]. This delicate balance between maintaining goal blood glucose levels while avoiding the hazards of low blood glucose and weight gain highlights a substantial unmet need in diabetes therapy.

Our study's premise is based on the awareness that, while insulin therapy has been a cornerstone in diabetes care, it is not without limits. The goal of tight glycemic control, a crucial precept in the prevention of diabetes-related problems, sometimes comes at the expense of hypoglycemia—an acute illness with potentially fatal implications. In view of these obstacles, the search for alternate approaches or adjuncts to insulin becomes critical. The need to overcome the limits of insulin treatment necessitates the development of innovative techniques. In this review, we looked into alternative biological techniques that sought to provide safer and more effective means of achieving optimum glycemic control while avoiding the drawbacks of standard insulin administration. Researchers and clinicians are attempting to harness the body's own mechanisms to achieve glucose regulation that is less prone to fluctuations and adverse effects by investigating diverse biological avenues such as stem cell therapy, immunomodulatory interventions, gut microbiota modulation, and other novel approaches.

## *2) Currently available medications for diabetes mellitus*

### *2.1.) Sulfonylurea*

Diabetes drugs in the sulfonylurea family enhance endogenous insulin secretion from pancreatic -cells. Common examples are Tolbutamide (first generation) and Glibenclamide, Glyburide, Glipizide, Gliclazide, and Glimepiride (second generation). Their principal targets are -cell adenosine triphosphate-sensitive potassium channels (KATP), and they are only active in residual pancreatic -cells [12]. Sulfonylurea has no well-established protective effects on -cell activity but can accelerate -cell function [13]. Following that, there is an initial drop in BGL and an increase in HbA1c levels. BGL levels decline by 20%, whereas HbA1c levels reduce by 1-2%. Weight gain is a bothersome symptom [14].

### *2.2.) Biguanides*

Biguanides, anti-diabetic medications, have sparked considerable attention in the last two decades due to their possible anticancer characteristics. One critical question has been how they function at the molecular level. According to most research, biguanides inhibit a cellular component known as mitochondrial complex I, resulting in decreased energy generation and compensatory reactions, which leads to their therapeutic effects. However, the quantities required to inhibit complex I are too high for use in practice, increasing the potential of additional mechanisms.

The reaction of 2-cyanoguanidine with dimethylammoniumchloride produces metformin, also known as 3-(diaminomethylidene)-1,1-dimethylaniline. The molecule has two methyl substituents at position 1 [15]. Type 2 diabetics use immediate-release or extended-release metformin pills. The rapid-release formulation is usually taken 2–3 times a day, whereas the delayed release formulation is taken once. Organic cation transporters 1 and 3 (OCT1 and OCT3) help enterocytes transfer metformin [16,17]. The OCT3 helps transport metformin into enterocytes via the apical membrane. In contrast, OCT1 transports metformin into interstitial fluid via the basolateral membrane [18]. The OCT1 and OCT3 proteins are found on the basolateral membrane of hepatocytes. These transporters are essential for metformin absorption in the liver [19]. The increased expression of OCT leads to metformin buildup in mice's livers, culminating in a 40 μM concentration. This concentration is much greater than the serum concentration of 5 μM metformin [20]. According to research by Ma et al., treating mouse primary hepatocytes with 5 μM metformin for 48 hours resulted in an intracellular concentration of 25-40 μM. This shows that metformin can accumulate in cells 5-8-fold.

### *2.3.) Thiazolidinediones*

Thiazolidinediones (TZDs) are PPR-activated receptor (PPR-γ)) activators that enhance insulin affectability in liver adipocytes and cardiac muscle [21]. These are utilized as a treatment strategy for insulin-resistant type 2 diabetes patients [22]. Weight gain is the most prevalent TZD side effect [23]. In T2DM patients, TZD may diminish the width of the carotid arteries. Rosiglitazone was recently forbidden by the FDA due to a high frequency of cardiovascular events; however, the prohibition was later restored. Pioglitazone and Rosiglitazone are examples of this class, as they are contraindicated in people with class III and IV heart failure. It is, nevertheless, tolerated in patients with severe renal impairment [24].

### *2.4.) Dipeptidyl peptidase-4 inhibitors*

Current therapy drugs include dipeptidyl peptidase-4 (DPP4) inhibitors or gliptins, which work by inhibiting the enzyme DPP4. Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin, and Linagliptin are common examples in this group. Incretin hormones such as glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), which are related to physically maintaining glucose homeostasis, are inactivated due to enzyme inhibition [25]. GLP-1 and GIP enhance pancreatic β-cell insulin production [26]. GLP-1 also lowers glucagon production from pancreatic β-cells. Their findings lead to improved glycemic management in T2DM patients. These medications have fewer negative effects and a decreased risk of hypoglycemia [27].

### *2.5.) GLP-1 analogues*

GLP-1 analogs are incretin-based therapies that increase insulin secretion in a glucose-dependent manner while decreasing glucagon secretion and hepatic glucose synthesis [28]. Nonetheless, as DPP4 inhibitors, these medicines are intolerable. HbA1c levels were found to be lower and weight loss was promoted [29]. Endothelial dysfunctions, such as delayed stomach emptying, improved lipid profiles, and lower blood pressure, were corrected [30]. There is also some advanced evidence that incretin-based therapies have a good influence on inflammation (by reducing levels of responsive protein), sleep, the sensory system, and cardiovascular and hepatic health [31]. Exenatide and Liraglutide are two common examples in this group.

### *2.6.) SGLT2 inhibitors*

Sodium-glucose co-transporter-2 (SGLT2) inhibitors, commonly referred to as gliflozins, exert their therapeutic effects by diminishing the absorption of sodium. This leads to a subsequent reduction in glucose levels via the renal route, achieved by impeding the uptake of glucose in the proximal tubules of the renal nephron [32]. Dapagliflozin, Empagliflozin, and Canagliflozin are representative compounds belonging to a specific pharmacological class. These pharmaceutical agents are employed in the treatment of individuals diagnosed with diabetes due to their ability to exert independent effects on insulin [33]. Due to the presence of glucosuria, these pharmacological interventions have the potential to enhance the functional capacity of β-cells, ameliorate insulin sensitivity, and augment glucotoxicity. The intervention under consideration has been observed to yield a reduction in HbA1c levels within the range of 0.5-1%, alongside concomitant reductions in weight and blood pressure [34]. Urinary tract infections, as well as genital mycotic contaminations, particularly among the female population [35].

## *3) Trending Biological Modalities for the Management of Diabetes Mellitus*

### *3.1.) Stem cell therapy*

Stem cells exhibit considerable promise as a novel therapeutic approach for diabetes and its associated comorbidities, owing to their remarkable immunomodulatory properties, ability to differentiate into multiple lineages, and capacity for regeneration [36,37]. Various stem cell populations, such as umbilical cord blood stem cells (UCB), peripheral blood mononuclear cells (PB-MNCs), and bone marrow mononuclear cells (BM-MNCs), encompassing bone marrow mesenchymal stromal cells (BM-MSCs) and bone marrow hemopoietic stem cells (BM-HSCs), have been subjected to rigorous investigation to assess their potential in regenerating fully functional insulin-producing cells. Extensive research efforts have been dedicated to the exploration of pancreatic and liver stem cells [9].

In their study, Bhansali et al. demonstrated remarkable therapeutic efficacy by employing bone marrow-derived stem cells for the treatment of patients diagnosed with T2D [36].Also, Voltarelli et al. demonstrated the safety and efficacy of utilizing hematopoietic stem cells (HSCs) as a therapeutic intervention to enhance -cell functionality in individuals recently diagnosed with T1D [37]. In contrast, Giannopoulou et al. conducted a study that established the safety of utilizing cord blood in infants diagnosed with T1D However, their findings indicated that this intervention did not effectively preserve beta-cell function [38]. Nevertheless, there are still numerous unresolved inquiries pertaining to the specific types of stem cells utilized to ensure optimal effectiveness in the management of diabetes, the transplantation technique employed, and the prospects for sustained recuperation over an extended period [39].

#### *3.1.1) Mesenchymal stem cells*

Mesenchymal stem cells (MSCs), alternatively referred to as mesenchymal stromal cells, are a population of multipotent non-hematopoietic stem cells. Stem cells can be procured from various sources, including bone marrow, liver, kidney, adipose tissue, urine, umbilical cord blood, umbilical tissue, Wharton's jelly, placenta, and even endometrium, specifically menstrual blood-derived

endometrial stem cells (MenSC). MSCs can be discerned through the utilization of diverse surface markers, such as CD73, CD90, and CD105. These cells possess the remarkable ability to undergo differentiation into diverse cell lineages, rendering them highly suitable for the purpose of tissue regeneration in cases of tissue injury [40-42].

As depicted in Figure 1, numerous mechanisms have been elucidated regarding the involvement of MSCs in the regulation of T1D. MSCs have garnered significant interest in the treatment of T1D due to their ability to regulate fibrosis and tissue regeneration, as well as to modulate immunological function. In addition, they secrete a variety of secretory compounds, such as cytokines and exosomes, which are essential for T1D therapy [43]. Rats administered MSCs experienced a significant reduction in hyperglycemia, as measured by a decrease in blood glucose and an increase in insulin and C-peptide levels. Additionally, they were able to restore normal levels of lipid fractions. In diabetic rodents, MSCs decreased blood levels of both liver and kidney function markers, indicating their hepato-renal protective benefits in T1D [44].

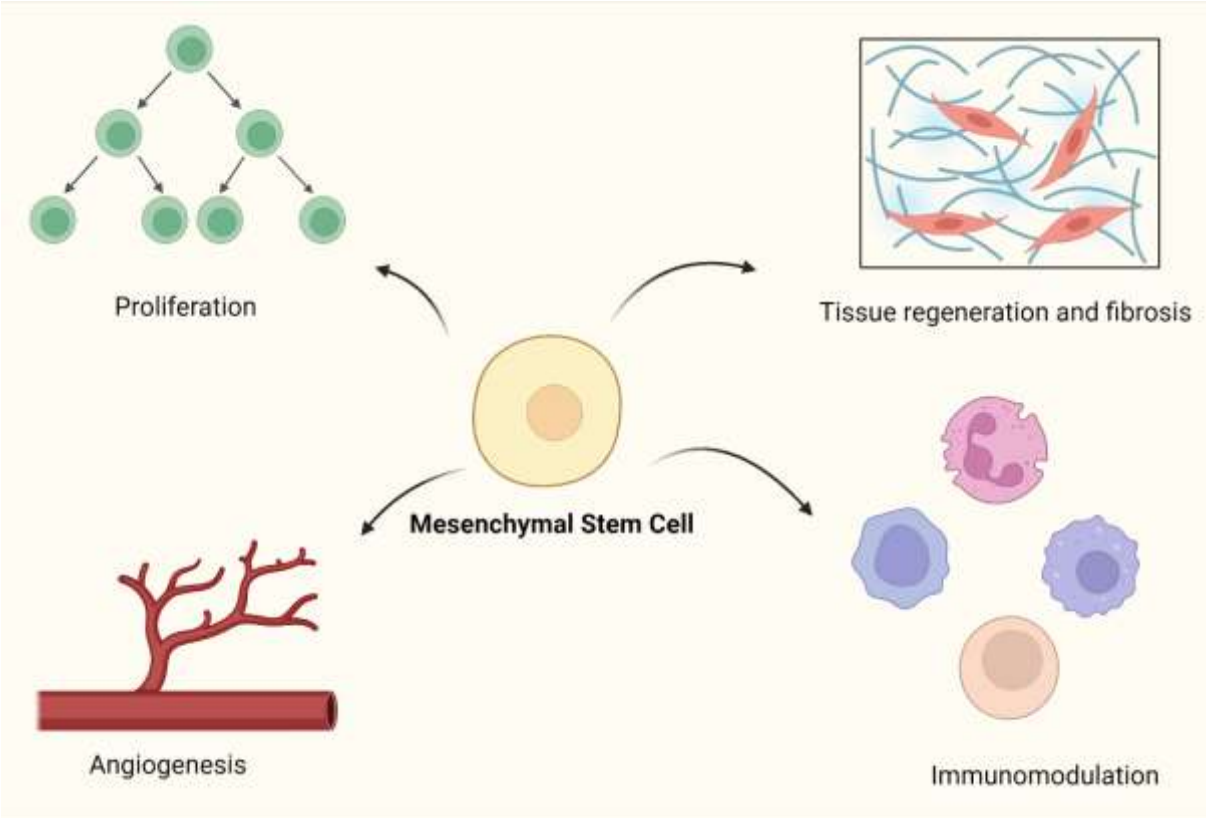


***Figure 1.*** Different mechanisms of action of Mesenchymal Stem Cells.

MSCs, including bone marrow stromal cells, have been observed to facilitate the process of angiogenesis by releasing specific cytokines, such as basic fibroblast growth factor and vascular endothelial growth factor (VEGF) [45]. Furthermore, these entities assume a pivotal function in the process of immunomodulation through their ability to migrate towards sites of inflammation and induce alterations in the phenotype of various immune cells, including dendritic cells, T cells, B cells, and natural killer cells. The observed phenomenon involves the downregulation of proinflammatory cytokines and the evasion of apoptosis induced by CD8+ T cells. Additionally, it has been observed that this process inhibits the maturation of dendritic cells, while concurrently suppressing the proliferation of T-lymphocytes. These effects are mediated through the actions of transforming growth factor-beta 1 (TGF-β1), hepatocyte growth factor, and nitric oxide. The production of regulatory T cells influences the immunomodulatory effects of MSCs, in which TGF-β1 plays a crucial role. MSCs have been observed to enhance the functionality, viability, and transplantation success of neonatal porcine islets. This is achieved through the upregulation of genes associated with

the development of endocrine cells, insulin production, and platelet-derived growth factor alpha (PDGFR-α) expression. The suppression of Notch 1 signaling by PDGFR-α has been observed to have a consequential effect on the downregulation of transcription factors that are crucial for the formation of endocrine cells and insulin. This, in turn, leads to the maturation and development of islet cells [45]. In their study, Zhou et al. made a significant discovery regarding the regulatory mechanisms underlying the immunomodulatory properties of MSCs in the context of T1D [46]. Specifically, they elucidated the role of wild-type p53-induced phosphatase 1, a serine/threonine phosphatase, in this process. Researchers found that this phosphatase exerts its regulatory influence by modulating the expression of interferon-alpha and bone marrow stromal cell antigen 2.

Despite the evidence from various studies demonstrating the immunoregulatory potential of MSCs, it is important to acknowledge that these cells still face the challenge of immune-mediated clearance. This implies that even if a successful therapeutic approach utilizing MSCs for T1D is developed, it will be imperative to incorporate immunomodulatory strategies to ensure their survival and efficacy [47]. When employing β-cells derived from an allogeneic stem cell reservoir, the introduction of donor antigens is likely to elicit an alloreactive immune response, unless the stem cells are procured from the patient's autologous cell population. In order to overcome this challenge, scientific researchers have undertaken extensive investigations into the implementation of encapsulation strategies that utilize semipermeable immune barriers. The primary objective of these strategies is to establish immune shielding, thereby effectively preventing the occurrence of graft rejection [46,47]. Several studies have provided evidence indicating that the utilization of suicide genes in conjunction with stem cell transplantation effectively enhances immune reconstitution, consequently mitigating the risk of graft-versus-host disease in patients [47].

The phenomenon of MSCs undergoing programmed cell death has been empirically validated in both the circulatory system of the host organism and in the engrafted tissues subsequent to their administration within the patient's physiological framework. This intricate process of cellular demise assumes a pivotal function in the therapeutic efficacy of MSCs in the context of type 1 diabetes. In the course of apoptosis, a highly regulated form of programmed cell death, apoptotic extracellular vesicles (apoEVs), previously referred to as apoptotic bodies, have garnered attention as influential modulators of various biological processes, surpassing their previous classification as mere cellular debris. ApoEVs, or apolipoprotein-enriched extracellular vesicles, have been demonstrated to exert regulatory effects on the immunological function of T cells and macrophages. Additionally, they have been found to possess the ability to stimulate tissue repair processes, such as skin regeneration and vascular protection [48].

### *3.2.) Islet cell transplantation*

The transplantation of islet cells, also known as Islet Cell Transplant (ICT), is a highly promising and effective approach that can serve as a viable alternative for a specific subset of patients. Through ongoing advancements in this field, there is a potential for ICT to evolve from being a mere treatment option to a potentially curative intervention in the future.

Shapiro et al. [49] made a groundbreaking contribution to the field of ICT by recognizing the immense possibilities of utilizing cell-based therapies to treat T1D. Their study demonstrated remarkable outcomes, as they successfully achieved complete insulin independence in seven consecutive patients within one year after implementing ICT. Notably, this achievement was accomplished without the need for glucocorticoid-based immunosuppression, further highlighting the potential of this novel approach.

ICT has demonstrated significant efficacy as a treatment modality for individuals diagnosed with T1D who experience severe and recurrent episodes of hypoglycemia or exhibit severe glycemic lability [50]. The attainment of sustained insulin independence over an extended period subsequent to the initial encounter has exhibited variability. However, advancements in transplantation methodologies, immunosuppressive regimens, and the utilization of stem cell-derived islets are

progressively propelling islet cell transplantation toward a more widely acknowledged therapeutic approach [51,52]

### *3.2.1) Current trials reporting the efficacy of ICT in T1D patients*

The existing body of evidence overwhelmingly substantiates the enduring safety of ICT over extended periods of time. The long-term survival of patients who have undergone ICT for the treatment of T1D has been found to be comparable to that of other cohorts of T1D patients, even in the presence of chronic immunosuppression [53]. According to recent reports, there is evidence indicating a 10-year graft survival rate of 78%. Additionally, these reports suggest that there have been consistent enhancements in glycemic control and reductions in insulin doses over the same time period [54]. The principal indication for the use of ICT continues to be the management of severe and recurrent episodes of hypoglycemia. In this context, the findings exhibit a near-complete resolution of severe hypoglycemic episodes (SHEs) subsequent to ICT [54-56]. Hypoglycemic unawareness, a debilitating outcome resulting from repeated episodes of hypoglycemia, exhibits a significant reduction for a duration of up to 3 years of ICT. This reduction occurs concurrently with SHEs, which experience a substantial decrease ranging from 70% to 100% [54,56]. The resolution of SHEs does not compromise glycemic control. In a recent multicenter phase 3 clinical trial, the efficacy of islet after-kidney transplantation was evaluated. The results indicated that 62.5% of the participants achieved the desired outcomes of both abrogation of severe hypoglycemic events and maintaining a level of HbA1c at 6.5% or less, or at least a 1% reduction, at the one-year mark following the transplant [56].

A preliminary report from a single center in 2020 involving 272 ICT patients from the University of Alberta indicates an insulin independence rate of 77.2% after ICT, which is marginally lower than after a pancreas transplant but substantially lower in morbidity [50]. Simultaneously, advances in islet isolation protocols, immunosuppression regimens, and overall clinical experience have enhanced insulin independence rates, with current 5-year insulin independence rates ranging from 50 to 80 percent [57]. Ongoing clinical trials aspire to further enhance ICT outcomes for all T1D patients ***(Table 1***).

***Table 1.*** Key clinical trials for the use of ICT in all patients with T1D. ICT, islet cell transplantation; T1D, type 1 diabetes.

| Clinical trial name | Identifier number | Location | Further details |
|---|---|---|---|
| Sequential Transplantation of UCBSCs and Islet Cells in Children and Adolescents with Monogenic Immunodeficiency T1DM | NCT03835312 | Children's Hospital of Fudan University, Shanghai, China | Assessing efficacy of injecting umbilical cord blood followed by ICT in newly T1D diagnosed adolescents |
| A Safety, Tolerability, and Efficacy Study of VC-01 Combination Product in Subjects with Type I Diabetes Mellitus | NCT02239354 | Multicenter, support from California Institute for Regenerative Medicine (CIRM) and Viacyte | Evaluating the safety and efficacy of human embryonic stem cells to mature and eliminate insulin requirements within an immune protected subcutaneous device |
| A Safety, Tolerability, and Efficacy Study of VC-02 Combination Product in Subjects with Type 1 Diabetes Mellitus and Hypoglycemia Unawareness | NCT03163511 | Multicenter, support from California Institute for Regenerative Medicine (CIRM) and Viacyte | Evaluating the safety and efficacy of human embryonic stem cells to mature and eliminate insulin requirements within a nonimmune protected subcutaneous device |
| A Safety, Tolerability, and Efficacy Study of VX-880 in Participants with Type 1 Diabetes | NCT04786262 | United Stated, Vertex Pharmaceuticals Incorporated | Evaluating the safety, tolerability and efficacy of ICT from allogeneia human stem cell derived islets (VX-880) |
| A Safety, Tolerability, and Efficacy Study of Sernova's Cell Pouch for Clinical Islet Transplantation | NCT03513939 | University of Chicago, Chicago, Illinois, United States | Assessing safety and efficacy of the Cell Pouch, a subcutaneous device for ICT |

| | | | |
|---|---|---|---|
| Health Economic Analysis of Islet Cell Transplantation for the Stabilization of the Severe Forms of Type 1 Diabetes (STABILOT) | NCT02854696 | University Hospital, Grenoble, Besancon, France | Cost-utility analysis comparing ICT vs. sensor-augmented insulin pump therapy |

### *3.3 Allogeneic Stem Cell-derived Islets and Encapsulation Devices*

In light of the constraints posed by tissue supply, there has been a rapid advancement in the exploration of islets derived from human embryonic stem cells (hESC). The stepwise process for maturing islet cells from human embryonic stem cells (hESCs) was initially documented by Kroon et al. in 2008. Since then, further research has been conducted to optimize this process [58-61] (*Figure 2*). Concurrently, the emergence of apprehensions pertaining to off-target proliferation prompted an investigation into potential implantation locales for intracranial tissue grafts that facilitate convenient retrieval, such as the subcutaneous region. Preclinical investigations have exhibited compelling evidence of the proficient maturation and optimal functionality of hESC-derived islets when implanted in the subcutaneous region. These studies have successfully demonstrated the feasibility and potential of this approach [62]. In an alternative approach, the utilization of cellular encapsulation holds promise as a supplementary protective measure against off-target proliferation. This technique has the potential to facilitate transplantation without the need for immunosuppression. In the context of this matter, it has been observed through preclinical investigations that the utilization of stem-cell-derived islets and cellular encapsulation techniques exhibit compatibility [63]. This compatibility is maintained even when these approaches are combined with a subcutaneous implantation method [62,64-66].

In a recent study, Via Cyte Inc. conducted tests on two subcutaneous devices, namely the PEC Direct (VC02) and PEC-Encap (VC01), which have been developed to facilitate subcutaneous delivery of human embryonic stem cell (hESC)-derived ICT, The VC01 subcutaneous macro-encapsulation device facilitates the transportation of oxygen and nutrients to the enclosed human embryonic stem cell-derived islets, while also offering immunoprotection. In contrast, the VC02 endeavors to elucidate the process of maturation and viability of hESC-derived islets when implanted in the subcutaneous region, employing a perforated macro-encapsulation apparatus. Ongoing clinical trials (NCT02239354 and NCT03163511) are currently being conducted to investigate the efficacy of these two approaches. The results of these trials are expected to be available in 2021. The initial findings from our ongoing research, which have not yet been published, show promising results. These findings indicate that after the implantation of VC01, a significant proportion of patients with T1D exhibit detectable levels of C-peptide in their peripheral blood samples. Importantly, this observation is strongly associated with the presence of fully developed islet cells that express insulin within the implanted devices.

The persistent challenge of achieving sustained insulin independence lies in the foreign body response elicited by encapsulation devices. Fortunately, ongoing research is being conducted to explore innovative biomaterials with low fouling properties. The study successfully showcased the achievement of immunosuppression-free long-term insulin independence and a minimal foreign body response through the utilization of subcutaneous and intraperitoneal encapsulated ICT employing low-fouling biomaterials [64,65]. Ongoing efforts are being made by various research groups to further enhance the efficiency of innovative encapsulation devices that facilitate reduced foreign body responses and fibrosis [66,67].

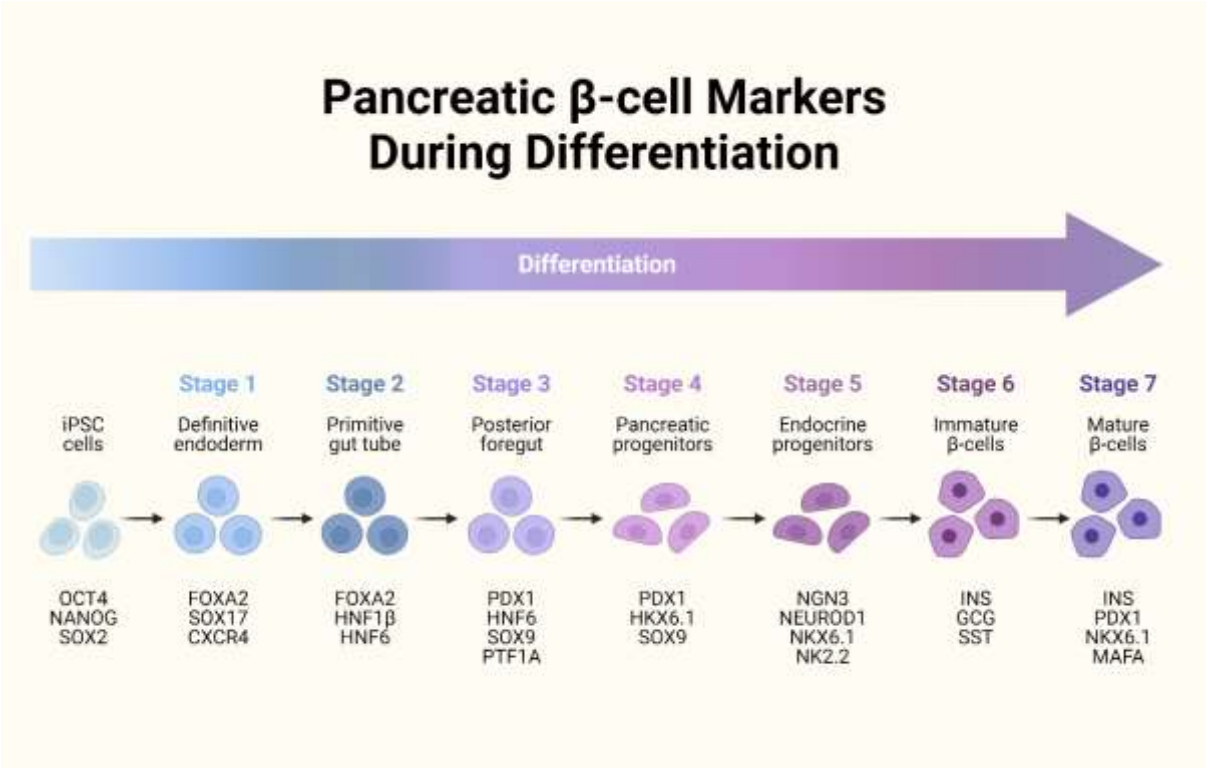


*Figure 2.* The differentiation process of pancreatic beta cell development encompasses various distinct stages. These stages are characterized by intricate molecular and cellular events that orchestrate the transformation of progenitor cells into fully functional beta cells. Understanding these stages is crucial for unraveling the complex mechanisms underlying beta cell development and may hold significant implications for regenerative medicine and diabetes research. As per the protocol established by Rezania et al., the process of differentiating human pluripotent stem cells (hPSCs) into pancreatic beta cells involves a sequential progression through seven distinct stages. These stages are identified and validated by the examination of specific markers that are characteristic of each stage [8]. The utilization of Stage 4 pancreatic progenitors, characterized by the co-expression of PDX1 and NKX6.1 (PDX1+/NKX6.1+), is presently being employed in clinical trials aimed at the treatment of diabetes. The transplantation of PDX1+/NKX6.1+ cells into a murine model has been observed to result in in vivo differentiation, leading to the development of fully mature insulin-secreting cells. Moreover, it is worth noting that the in vitro generation of the mature beta cell stage holds the potential for direct transplantation into a mouse model.

### *3.4. Gene Therapy for T1D*

T1D can be attributed to the downregulation of multiple genes. Given the inherent limitations of activating or modulating genes through instrumental or surgical interventions, the field of gene therapy has experienced significant growth in order to address the pressing needs associated with the treatment of T1D. The investigation conducted by Mallol et al. delved into the phenomenon of insulin-like growth factor 1 (IGF1) overexpression within the β-cells of transgenic non-obese diabetic (NOD) mice [68]. IGF1 possesses the capacity to modulate immune functions and augment the essential factors required for the maturation and functionality of β-cells. Furthermore, IGF1 exhibits mitogenic properties specifically targeting β-cells [69].

The introduction of the IGF1 coding gene sequence into the pancreas of NOD mice led to the achievement of normoglycemia in 80% of the NOD mice by the 28th week, as reported in reference [68]. The findings of this study have provided evidence supporting the notion that downregulation of the IGF1 gene expression can potentially impede the progression of T1D [68]. ***Figure 3*** depicts the process of gene transfer. In the year 2015, it was reported that there was an observed upregulation of

Reg3g, a gene encoding for Regenerating islet-derived protein 3 gamma, within the pancreatic islets [70,71].

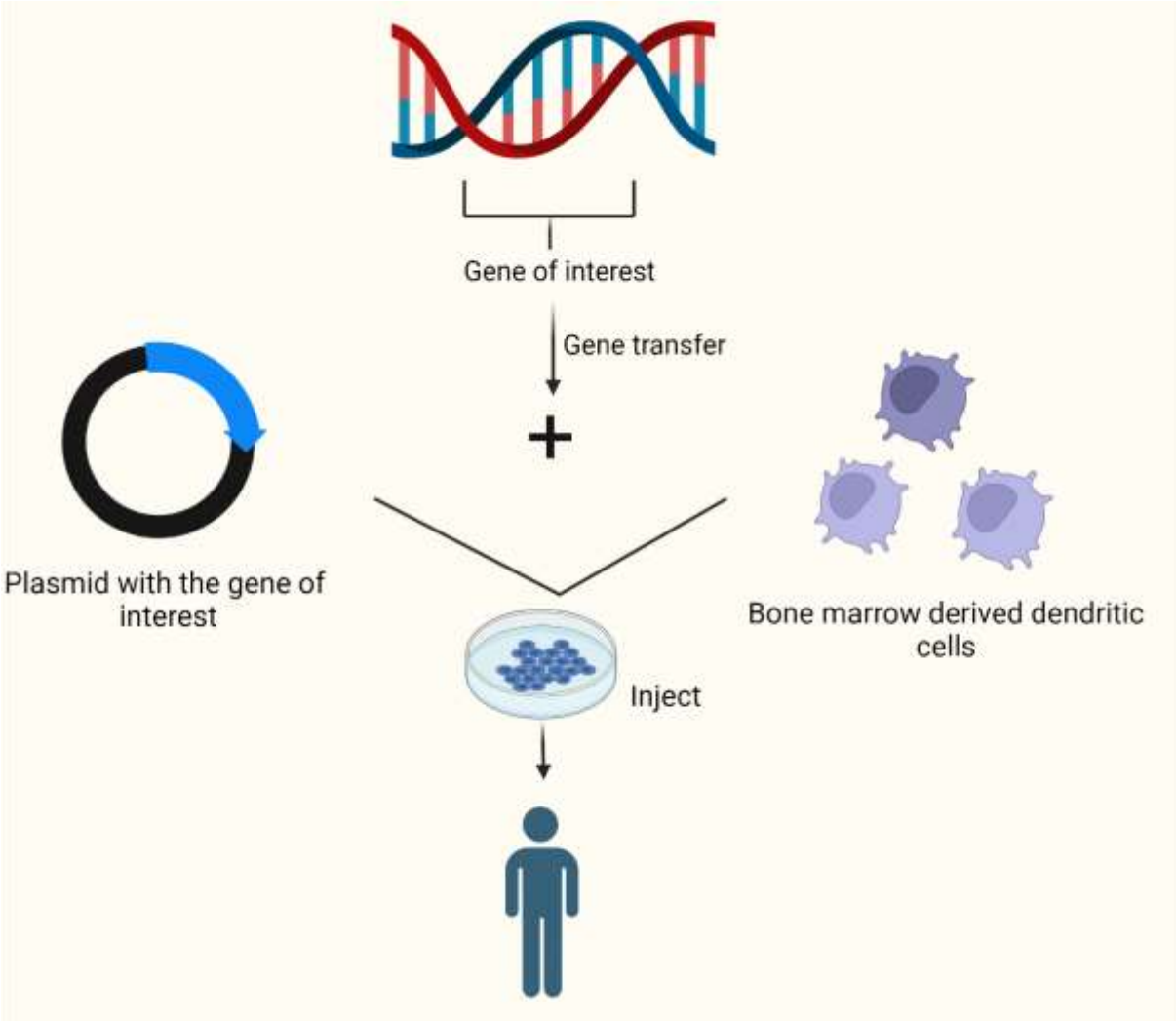


*Figure 3.* Schematic diagram illustrating the process of gene transfer. The gene of interest is successfully identified and subsequently subjected to genetic engineering techniques, wherein it is incorporated into a plasmid vector. Additionally, bone marrow-derived dendritic cells are utilized as the host cells for the gene transfer process. Following the successful engineering of the gene into the plasmid and dendritic cells, the resulting genetic construct is introduced into the biological system under investigation.

In their study, Xia et al. demonstrated the novel potential of regenerating islet-derived 3 gamma gene therapy in the context of β cell regeneration and the preservation of β cells against autoimmune damage [70]. In addition to the aforementioned findings, a comprehensive investigation has documented the intricate control of blood glucose levels in individuals with T1D through the stimulation of glucose-6-phosphatase (G6Pase) gene expression within the hepatic tissue [72]. The experimental findings have revealed that the presence of glucose exerts a stimulating effect on the expression of this particular gene, as evidenced by the observed increase in its activity [72].
Conversely, the hormone insulin has been shown to exert an inhibitory effect on the expression of the gene, leading to a decrease in its activity [72]. The findings of this study indicate that a significant increase in glucose utilization was observed, accompanied by the attainment of normoglycemia within a period of 4 hours following a meal. Furthermore, it is noteworthy to mention that the experimental subjects under investigation did not exhibit any instances of hypoglycemia [72]. Islet transplantation emerged as a groundbreaking therapeutic approach for T1D [73]. Nevertheless, the

transplantation of tissues or organs presents a myriad of challenges, including the necessity for long-term administration of immunosuppressive agents, the risk of graft rejection, and the constrained availability of human islets relative to the demand for them.

In a study conducted by Rao et al. in 2004, the researchers investigated the effects of hepatocyte growth factor (HGF) overexpression in rodents' islets by employing adenovirus-mediated transfer of HGF genes [73]. Upon transcription and subsequent translation, the expression of these specific genes has been observed to induce the replication of beta cells, leading to an enhancement in their overall survival and functional capabilities [73]. Furthermore, it is noteworthy to mention that this particular modality of gene therapy has demonstrated a reduction in the number of islets necessary for successful islet transplantation in murine models of severe combined immunodeficiency [73]. A significant advancement in the field of gene therapy for T1D materialized with the identification of the Klotho gene. The gene in question is known to possess anti-aging properties and has been observed to be actively expressed in various organs, including the kidneys, brain choroid plexus, and more recently, the pancreatic islets of mice [74]. The primary objective of the investigation was to examine the potential impact of Klotho deficiency on the progression of T1D [74]. In the presence of Klotho deficiency, a notable occurrence of beta cell apoptosis was observed [74]. In the experimental setting, the utilization of a viral vector as a delivery mechanism for the Klotho gene, in conjunction with a beta cell-specific promoter (recombinant adeno-associated virus carrying the modified Klotho gene, denoted as rAAV-mKL), resulted in the manifestation of Klotho overexpression and the subsequent successful preservation of beta cell functionality [74].

### *3.4.1) Proteins Involved in T1D*

Several proteins have been identified to possess significant roles in the process of islet cell formation, glucose metabolism, anti-inflammatory effects, and other related factors that exert direct or indirect influence on the treatment or prevention of T1D

Neurogenin-3 (Ngn3) is a transcription factor that is observed to be expressed in a position preceding Neuro D (also known as BETA2) within the endocrine differentiation cascade [75]. In the absence of Neurogenin-3, a critical transcription factor, a notable consequence is the complete absence of endocrine cells within the pancreas, as evidenced by previous studies [75]. In a research endeavor undertaken in November 2009, the administration of Ngn3 and betacellulin (BTC) was accomplished through the utilization of helper-dependent adenoviral vectors (HD Ads) in streptozotocin-diabetic mice. As a result of this intervention, the emergence of periportal neo-islets was duly noted [76]. The neo-islets that have been induced exhibit a remarkably close resemblance to pancreatic islets in terms of their gene expression profile and structural characteristics [76]. The restoration of glucose-stimulated insulin secretion and reversal of hyperglycemia and ketonemia were observed in these animals through the presence of periportal neo-islets. Additionally, hepatic glucose secretion was normalized [76]. In a separate investigation carried out in October 2017, a cohort of NOD mice was subjected to a therapeutic intervention involving the administration of anti-TCRβ (anti-T-cell receptor beta chain) monoclonal antibody, Ngn3, and BTC [77]. The administration of this combined therapeutic regimen resulted in the consistent and prolonged development of periportal neo-islets within the NOD mouse model [77].

Alpha-1 anti-trypsin (AAT) is a proteinaceous molecule that acts as a potent inhibitor of proteases. It has been extensively studied and has been found to possess notable anti-inflammatory properties [78]. T1D arises as a consequence of the autoimmune destruction of pancreatic beta cells. It has been hypothesized that AAT may potentially exert a modulatory effect on the progression of T1D [78]. The administration of AAT via a recombinant adeno-associated virus vector (rAAV) to NOD mice has demonstrated a significant decrease in levels of insulin autoantibodies, as well as a reduction in the intensity of insulitis and the occurrence of overt T1D [79]. The therapeutic potential of AAT in the prevention or deceleration of T1D progression has been proposed [78].

Leptin, a hormone known for its significant involvement in maintaining energy balance within the body, has garnered limited attention in relation to its potential connection to the development of T1D

in recent years [79]. The inhibitory effect of leptin on insulin secretion appears to be observed exclusively at physiological concentrations, and only under conditions where the islets are maximally stimulated by high levels of glucose [80]. The presence of hyperleptinemia has been empirically shown to elicit the pathophysiological initiation of both T1D and T2D [79]. Euglycemia, defined as the maintenance of normal blood glucose levels, was successfully attained and consistently maintained throughout the entire 7-week duration of the experiment conducted on severely insulinopenic Akita mice. These mice are known to possess a dominant mutation in the Ins 2 gene, resulting in a deficiency of insulin production. The achievement of euglycemia was made possible through the administration of leptin, a hormone involved in the regulation of energy balance, via a recombinant adeno-associated virus vector known as rAAV-Lep [79]. Furthermore, the efficacy of recombinant adeno-associated virus expressing the leptin gene (rAAV-Lep) was assessed in the context of streptozotocin-induced T1D in rats. Remarkably, euglycemia, the maintenance of normal blood glucose levels, was successfully achieved throughout the entire duration of the experiment, which spanned a period of one year [79].

### *3.5 Immunomodulatory Therapies in Type1 Diabetes*

Since CD4+ and CD8+ cells have a significant role in the destruction of pancreatic β-cells leading to T1D development, Researches have explored therapeutic strategies that target T-cells, such as the use of monoclonal antibodies that target CD3 molecule on the surface of T-cells. The exact mechanism for which anti-CD3 antibodies work isn't fully understood but is thought to deplete the autoreactive T-cells and promote regulatory T-cells [81]. Studies done on non-obese diabetic mice have shown that treatment with anti-CD3 antibodies results in; long-standing remission of the disease, restoring normal blood glucose levels, and preserving pancreatic β-cells [82]. Muromonab-CD3 was the first anti-CD3 monoclonal antibody to be approved in the US in 1986. However, due to its side effect new modified humanized anti-Cd3 antibodies were developed including Teplizumab and Otelixizumab [83,84].

Low-dose Anti-Thymocyte Globulin (ATG) was also trailed in the prevention and reversal of T1D by targeting and suppressing autoreactive T-cells. However, compared to ant-CD3 therapies, such as Teplizumab, it is less specific [85]. A recent study investigated the effect of low-dose ATG in patients with new onset of T1D. A combination was tried of ATG with Granulocyte Colony-Stimulating Factor (GCSF), a growth factor that stimulates the production of white blood cells. They concluded that the ATG-alone group didn't fully restore the normal blood sugar level, however, it did slow the rate of decline in pancreatic B-cell dysfunction and significantly reduced the level of HbA1C to placebo group. When they combined ATG with GCSF, they observed a lower rate of insulin secretion compared to the ATG-alone group indicating that GCSF lowered the positive effect of ATG [86].

Although T1D is considered a T cell-mediated autoimmune disease, B cells also have a pathogenic role in T1D related to their function as APCs and modulators of the pancreatic microenvironment. Recent studies showed that therapies directed against B-lymphocytes may show some benefits in treating T1D. In those studies, Rituximab -a monoclonal antibody targeted against CD20 on the surface of B-lymphocyte, suppressing their activity- was given to patients who were recently diagnosed with T1D and after a follow up they showed that while Rituximab delays the decline in C-peptides in those patients, it's effect declines over time suggesting that rituximab did preserve the function of betta-cells, rather than changing the underlying process of the disease [87].

Since inflammation plays an important role in T1DM, studies have shown that calcitriol, the active form of Vitamin D has a significant role in regulating both innate and adaptive immunity. Calcitriol binds to receptors expressed on the surface of immune cells including neutrophils and Antigen Presenting Cells (APCs) like Dendritic cells and Macrophages [88]. Calcitriol can regulate Toll Like Receptors (TLRs)- a protein responsible in initiating an immune response against pathogens- by doing so it reduces the activation of molecule called (NF-KB)-p65, which is involved in inflammation leading to decrease in the production of inflammatory mediators like IL-1b and TNF-a [89]. Those studies investigated the effectiveness of Vitamin D in patients with Latent autoimmune diabetes in

adults “LADA” (defined by the American Diabetes Association as a subtype of T1D with a slower Betta-cell destruction which allowed for a broader extent of pharmacological intervention) [90,91]. They demonstrated that 1-a(OH)D3 combined with insulin therapy protected the pancreatic Betta-cell function in LADA patients [92].

### *3.5.1) Autoantigen specific therapy*

These therapies specifically target the antigens located on pancreatic B-cells. By doing so, their aim is either promoting regulatory T-cells or suppressing the activity of autoreactive T-cells [93,94]. One of the approaches is the use of peptide vaccines like Insulin Mimotope, these resulted in the conversion of naïve T-cells into FOXP3+ Tregs [95].

Furthermore, APC-based therapies involve using tolerogenic DC and Macrophages loaded with autoantigens which induce insulin-specific regulatory T-cells and maintain C-peptide levels thus preserving pancreatic B-cell function in patients with T1D [96,97].

Cytokines like IL-2 also prevent autoimmunity in T1D. IL-2 plays a role in activating T-cells and promoting the growth of FOXP3+ Treg. Scientist found that FOXP3+ Treg responds better to low IL-2 than other T-cells [98]. They also tested a recombinant IL-2 called Aldesleukin on patients with T1D, using small amount of the Aldesleukin made an increase in Tregs without adverse side effects [99].

### *3.6 Gut Microbiota*

The gut microbiota has emerged as a promising avenue for therapeutic intervention in the treatment of DM [100,101]. The manipulation of the intestinal microbiome has emerged as a promising strategy for mitigating the onset of DM and addressing the escalating prevalence of chronic diseases worldwide [102]. An investigation was conducted utilizing metagenomic clusters to discern, within a cohort of individuals exhibiting prediabetic conditions, those who displayed metabolic characteristics resembling T2D or normoglycemic metabolism based on their fecal microbiome composition. Consequently, this study suggests the potential utility of employing such metagenomic analysis as a means to categorize the likelihood of diabetes development in individuals with prediabetes.

### *a) Lifestyle changes*

changes in lifestyle have attracted significant attention in the scientific community. Researchers have been diligently investigating the various factors that contribute to these alterations and their subsequent impact on human health and well-being

Lifestyle optimization, encompassing the adoption of a healthy diet and regular engagement in physical activity, stands out as a potent therapeutic approach to addressing obesity and its associated conditions, notably T2D.

### *b) Healthy diet*

The dietary regimen plays a pivotal role in shaping the composition of the gut microbiota. Research conducted on animals has provided evidence that alterations in the composition of gut microbiota can be attributed to dietary modifications in a significant proportion of 57%, whereas host genetic mutation accounts for a comparatively smaller proportion of 12% [103]. In the aforementioned investigation, it was noted that within the cohorts subjected to high-fat diets, the presence of Bifidobacterium spp., known for their significant contributions to the preservation of the gut barrier, was conspicuously lacking across all specimens [103]. In a comprehensive investigation conducted on human subjects, a comparative analysis was carried out to assess the microbiota composition of European children in contrast to African children hailing from Burkina Faso, who adhere to a plant-based high-fiber dietary regimen. The results of this study revealed noteworthy disparities between the two cohorts under investigation. The microbial composition of African children's microbiota exhibited a notable prevalence of Bacteroidetes, specifically Prevotella and Xylanibacter genera,

which displayed a distinctive ability to enzymatically break down cellulose and xylan. Conversely, this capability was absent in the microbiota of European children. Additionally, the quantities of Firmicutes and Enterobacteriaceae, including Shigella and Escherichia, were observed to be diminished in African children. The observed alterations in the composition of the microbiota were found to be correlated with higher levels of short-chain fatty acids (SCFA) in pediatric individuals adhering to a plant-based dietary regimen [104].

The significance of safeguarding the unique bacterial strains found within the microbiome of individuals adhering to traditional lifestyles and plant-based dietary patterns has been emphasized by the study's authors. This is crucial for the preservation of human microbiota biodiversity, particularly among ancient communities, given the potential adverse consequences of globalization. In reference to the correlation between the risk T2D and alterations in the overall plant-based diet index and health plant-based diet index over a span of four years, a recent publication based on data from the Nurses' Health Study (NHS) has demonstrated that a 10% increase in scores for these indices is linked to a 7-9% reduction in the likelihood of developing T2DM[105].

The modulation of gut microbiota is not solely influenced by the fiber content of food. Research investigations examining the protein composition of dietary regimens have revealed a positive correlation between protein consumption and the overall diversity of microorganisms present. However, it is important to note that distinct disparities exist when considering the sources of protein, specifically differentiating between animal-derived and plant-derived sources. The consumption of plant-derived proteins has been observed to be positively correlated with elevated levels of Bifidobacterium and Lactobacillus, while concurrently leading to a reduction in Bacteroides fragilis and Clostridium perfringens populations [106]. Conversely, the ingestion of animal-derived proteins has been found to promote an increase in Bacteroides, Alistipes, and Bilophila populations. Furthermore, there exists a correlation between the protein/carbohydrate ratio and alterations in the composition of the gastrointestinal microbiota. Diets characterized by a high protein and low carbohydrate composition have been observed to exhibit reduced abundance of Roseburia and Eubacterium rectale, as well as diminished levels of SCFA, which could potentially have adverse effects on the overall health of the colon [107].

The guidelines for the prevention and clinical management of DM recommend the adoption of a Mediterranean dietary pattern. The potential impact on human health and disease may be partially attributed to the modulation of the gut microbiome. In individuals with obesity, the Mediterranean diet exhibited a notable reduction in the abundance of Prevotella genus, while simultaneously enhancing the presence of Roseburia and Oscillospira genera. These alterations were concomitant with notable improvements in insulin sensitivity [108]. A recently published study has elucidated the impact of the Mediterranean diet on the gut microbiome composition among elderly individuals, thereby leading to notable enhancements in their overall health status. This improvement was assessed through various indices, including measures of frailty, cognitive function, and inflammation. The present study encompassed a cohort of over six hundred individuals hailing from five distinct European nations, namely the United Kingdom, France, Netherlands, Italy, and Poland. These participants were subjected to a comprehensive dietary intervention for a duration of one year. Remarkably, the findings of this investigation revealed a noteworthy alteration in the composition of the bacterial populace responsible for the production of short or branched chain fatty acids. Notably, this positive modification exhibited a direct correlation with the duration of the intervention and the degree of adherence to the Mediterranean diet regimen, thereby highlighting the significance of prolonged exposure and strict compliance to this specific dietary plan [109].

The implementation of a gluten-free dietary regimen has been observed to induce alterations in the composition of intestinal microbiota in individuals without any underlying health conditions. Specifically, this dietary intervention leads to an increase in the prevalence of unclassified species belonging to the Clostridiales and Lachnospiraceae families, while simultaneously causing a decrease in the abundance of Bifidobacterium (four species), Lachnospiraceae (two species), Blautia, Dorea (including longicatena and another species), Eubacterium hallii, and Anaerostipes hadrus [110]. In

individuals exhibiting active gastro-intestinal symptoms of celiac disease, the adoption of a gluten-free diet has been observed to stimulate the proliferation of Proteobacteria while suppressing the growth of Bacteroidetes and Firmicutes. Conversely, in asymptomatic patients, this dietary intervention has been found to alter the abundance of Bifidobacteria per gram of fecal matter [110-111].

***c) Physical activity***

Exercise exerts an indirect influence on the composition and diversity of gut microbiota through its ability to modulate various aspects of gut physiology and morphology. According to recent scientific findings, engaging in low-intensity physical activity has been observed to have a positive impact on reducing the time it takes for food to pass through the intestines. Conversely, it has been noted that engaging in prolonged exercise can potentially lead to an increase in the permeability of the gastrointestinal tract [112]. The observation that a non-ingestible factor has the potential to exert an influence on the composition and function of the gut microbiota is indeed intriguing. A comprehensive investigation conducted on murine subjects yielded compelling evidence suggesting that the engagement in voluntary wheel-running exercise resulted in a subsequent elevation in the cecal concentration of n-butyrate [113].

A recent investigation conducted on murine subjects has unveiled compelling evidence suggesting that engagement in physical exercise may serve as a potent preventive measure against weight gain in animals subjected to a high-fat diet. The engagement in physical activity has been observed to induce alterations in the ratio of Bacteroides to Firmicutes, two prominent bacterial phyla in the gut microbiota. Notably, these modifications exhibit a direct correlation with the overall distance covered during running activities [114].

***d) The Impact of Nutraceuticals on Gut Microbiota***

Lactobacillus casei, a probiotic strain that has garnered significant attention in scientific research, has been extensively investigated for its potential effects on the gut microbiota composition. Notably, it has been observed that the administration of Lactobacillus casei can lead to an increase in the relative abundance of Bacteroidetes, while concurrently reducing the abundance of Firmicutes. This phenomenon is accompanied by the proliferation of Bacteroides and Allobaculum, two bacterial taxa that have been implicated in various aspects of gut health [115]. Another species that has been the subject of investigation is Lactobacillus rhamnosus, which has demonstrated the potential to enhance fasting blood glucose levels, glucose tolerance, and lipid profile, while concurrently reducing levels of free fatty acids and oxidative stress markers such as superoxide dismutase (SOD) and catalase. Additionally, L. rhamnosus has shown promise in mitigating the levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). The observed metabolic effects seem to arise as a result of the downregulation of glucose-6-phosphatase expression in the hepatic tissue of rats exhibiting diabetes induced by streptozotocin [116-117].

***Conclusion***

Our comprehensive exploration of various biological methodologies in the realm of diabetes management has unearthed highly encouraging pathways that hold immense potential for transforming the landscape of treatment. Islet Cell Transplantation (ICT) exhibits promising prospects in its capacity to evolve from a therapeutic modality to a curative intervention for a specific subset of patients. The investigation into the utilization of islets derived from hESCs presents a promising avenue for overcoming limitations in tissue availability, thereby establishing a sustainable resource. Novel implantation sites, such as the subcutaneous region, have been shown to significantly improve the feasibility of implantation procedures. The application of gene therapy, specifically through the overexpression of IGF1, exhibits considerable potential in the modulation of immune functions and the enhancement of β-cell activity. Immunomodulatory therapies, such as the utilization of humanized anti-CD3 antibodies like Teplizumab and Otelixizumab, have demonstrated promising

prospects in the cessation of β-cell destruction in individuals diagnosed with Type 1 Diabetes. The gut microbiota has recently garnered significant attention as a promising therapeutic frontier in the field of medicine. The advent of metagenomic analysis has provided researchers with a powerful tool to investigate and understand the complex microbial communities residing in the gastrointestinal tract. This analytical approach has the potential to revolutionize personalized interventions by allowing for targeted and tailored treatments based on an individual's unique gut microbiota composition.

**Data availability statement**

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***References***

1. Abdull Razis AF, Ismail EN, Hambali Z, Abdullah MN, Ali AM, Mohd Lila MA. Expression of recombinant human epidermal growth factor in Escherichia coli and characterization of its biological activity. *Appl Biochem Biotechnol*. 2008;144(3):249-261. doi:10.1007/s12010-007-8019-9
2. Abraham EJ, Kodama S, Lin JC, Ubeda M, Faustman DL, Habener JF. Human pancreatic islet-derived progenitor cell engraftment in immunocompetent mice. *Am J Pathol*. 2004;164(3):817-830. doi:10.1016/S0002-9440(10)63170-7
3. Akerblom HK, Vaarala O, Hyöty H, Ilonen J, Knip M. Environmental factors in the etiology of type 1 diabetes. *Am J Med Genet*. 2002;115(1):18-29. doi:10.1002/ajmg.10340
4. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract. 2014;105(2):141-150. doi:10.1016/j.diabres.2014.04.006
5. Kubaszek A, Pihlajamäki J, Komarovski V, et al. Promoter polymorphisms of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. Diabetes. 2003;52(7):1872-1876. doi:10.2337/diabetes.52.7.1872
6. Tokuyama Y, Sturis J, DePaoli AM, et al. Evolution of beta-cell dysfunction in the male Zucker diabetic fatty rat. *Diabetes*. 1995;44(12):1447-1457. doi:10.2337/diab.44.12.1447
7. Ma K, Nunemaker CS, Wu R, Chakrabarti SK, Taylor-Fishwick DA, Nadler JL. 12-Lipoxygenase Products Reduce Insulin Secretion and {beta}-Cell Viability in Human Islets. *J Clin Endocrinol Metab*. 2010;95(2):887-893. doi:10.1210/jc.2009-1102
8. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-986. doi:10.1056/NEJM199309303291401
9. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes: A Meta-analysis. JAMA. 2016;316(3):313-324. doi:10.1001/jama.2016.9400
10. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabolism. 2016;65(2):20-29. doi:10.1016/j.metabol. 2015.10.014

11. Weight gain associated with intensive therapy in the diabetes control and complications trial. The DCCT Research Group. *Diabetes Care*. 1988;11(7):567-573. doi:10.2337/diacare.11.7.567
12. Proks P, Reimann F, Green N, Gribble F, Ashcroft F. Sulfonylurea stimulation of insulin secretion. Diabetes. 2002;51 Suppl 3:S368-S376. doi:10.2337/diabetes.51.2007.s368
13. Sola D, Rossi L, Schianca GP, et al. Sulfonylureas and their use in clinical practice. *Arch Med Sci*. 2015;11(4):840-848. doi:10.5114/aoms.2015.53304
14. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Ann Intern Med*. 2012;157(9):601-610. doi:10.7326/0003-4819-157-9-201211060-00003
15. Graham GG, Punt J, Arora M, et al. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet*. 2011;50(2):81-98. doi:10.2165/11534750-000000000-00000
16. Choi MK, Song IS. Organic cation transporters and their pharmacokinetic and pharmacodynamic consequences. *Drug Metab Pharmacokinet*. 2008;23(4):243-253. doi:10.2133/dmpk.23.243
17. Hilgendorf C, Ahlin G, Seithel A, Artursson P, Ungell AL, Karlsson J. Expression of thirty-six drug transporter genes in human intestine, liver, kidney, and organotypic cell lines. *Drug Metab Dispos*. 2007;35(8):1333-1340. doi:10.1124/dmd.107.014902
18. Müller J, Lips KS, Metzner L, Neubert RH, Koepsell H, Brandsch M. Drug specificity and intestinal membrane localization of human organic cation transporters (OCT). *Biochem Pharmacol*. 2005;70(12):1851-1860. doi:10.1016/j.bcp.2005.09.011
19. Gong L, Goswami S, Giacomini KM, Altman RB, Klein TE. Metformin pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenet Genomics*. 2012;22(11):820-827. doi:10.1097/FPC.0b013e3283559b22
20. Chandel NS, Avizonis D, Reczek CR, et al. Are Metformin Doses Used in Murine Cancer Models Clinically Relevant?. *Cell Metab*. 2016;23(4):569-570. doi:10.1016/j.cmet.2016.03.010
21. Eldor R, DeFronzo RA, Abdul-Ghani M. In vivo actions of peroxisome proliferator-activated receptors: glycemic control, insulin sensitivity, and insulin secretion. *Diabetes Care*. 2013;36 Suppl 2(Suppl 2):S162-S174. doi:10.2337/dcS13-2003
22. Defronzo RA, Tripathy D, Schwenke DC, et al. Prevention of diabetes with pioglitazone in ACT NOW: physiologic correlates. *Diabetes*. 2013;62(11):3920-3926. doi:10.2337/db13-0265
23. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA. Thiazolidinediones improve beta-cell function in type 2 diabetic patients. *Am J Physiol Endocrinol Metab*. 2007;292(3):E871-E883. doi:10.1152/ajpendo.00551.2006
24. Jearath V, Vashisht R, Rustagi V, Raina S, Sharma R. Pioglitazone-induced congestive heart failure and pulmonary edema in a patient with preserved ejection fraction. *J Pharmacol Pharmacother*. 2016;7(1):41-43. doi:10.4103/0976-500X.179363
25. Singh AK. Dipeptidyl peptidase-4 inhibitors: Novel mechanism of actions. *Indian J Endocrinol Metab*. 2014;18(6):753-759. doi:10.4103/2230-8210.141319
26. Pathak R, Bridgeman MB. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors In the Management of Diabetes. *P T*. 2010;35(9):509-513.
27. Brunton S. GLP-1 receptor agonists vs. DPP-4 inhibitors for type 2 diabetes: is one approach more successful or preferable than the other?. *Int J Clin Pract*. 2014;68(5):557-567. doi:10.1111/ijcp.12361
28. Bunck MC, Cornér A, Eliasson B, et al. Effects of exenatide on measures of β-cell function after 3 years in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2011;34(9):2041-2047. doi:10.2337/dc11-0291
29. Stonehouse AH, Darsow T, Maggs DG. Incretin-based therapies. *J Diabetes*. 2012;4(1):55-67. doi:10.1111/j.1753-0407.2011.00143.x

30. Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin*. 2008;24(1):275-286. doi:10.1185/030079908x253870
31. Reed J, Bain S, Kanamarlapudi V. Recent advances in understanding the role of glucagon-like peptide 1. *F1000Res*. 2020;9:F1000 Faculty Rev-239. Published 2020 Apr 6. doi:10.12688/f1000research.20602.1
32. Kalra S. Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors: A Review of Their Basic and Clinical Pharmacology [published correction appears in Diabetes Ther. 2015 Mar;6(1):95]. *Diabetes Ther*. 2014;5(2):355-366. doi:10.1007/s13300-014-0089-4
33. Abdul-Ghani MA, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. *Endocr Rev*. 2011;32(4):515-531. doi:10.1210/er.2010-0029
34. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014;129(5):587-597. doi:10.1161/CIRCULATIONAHA.113.005081
35. Peng BY, Dubey NK, Mishra VK, et al. Addressing Stem Cell Therapeutic Approaches in Pathobiology of Diabetes and Its Complications. J Diabetes Res. 2018;2018:7806435. Published 2018 Jun 25. doi:10.1155/2018/7806435
36. Bhansali A, Upreti V, Khandelwal N, et al. Efficacy of autologous bone marrow-derived stem cell transplantation in patients with type 2 diabetes mellitus. Stem Cells Dev. 2009;18(10):1407-1416. doi:10.1089/scd.2009.0164
37. Voltarelli JC, Couri CE, Stracieri AB, et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. JAMA. 2007;297(14):1568-1576. doi:10.1001/jama.297.14.1568
38. Giannopoulou EZ, Puff R, Beyerlein A, et al. Effect of a single autologous cord blood infusion on beta-cell and immune function in children with new onset type 1 diabetes: a non-randomized, controlled trial. Pediatr Diabetes. 2014;15(2):100-109. doi:10.1111/pedi.12072
39. Bani Hamad FR, Rahat N, Shankar K, Tsouklidis N. Efficacy of Stem Cell Application in Diabetes Mellitus: Promising Future Therapy for Diabetes and Its Complications. Cureus. 2021;13(2):e13563. Published 2021 Feb 26. doi:10.7759/cureus.13563
40. Birtwistle L, Chen XM, Pollock C. Mesenchymal Stem Cell-Derived Extracellular Vesicles to the Rescue of Renal Injury. Int J Mol Sci. 2021;22(12):6596. Published 2021 Jun 20. doi:10.3390/ijms22126596
41. Sun YL, Shang LR, Liu RH, et al. Therapeutic effects of menstrual blood-derived endometrial stem cells on mouse models of streptozotocin-induced type 1 diabetes. World J Stem Cells. 2022;14(1):104-116. doi:10.4252/wjsc.v14.i1.104
42. Kawada-Horitani E, Kita S, Okita T, et al. Human adipose-derived mesenchymal stem cells prevent type 1 diabetes induced by immune checkpoint blockade. Diabetologia. 2022;65(7):1185-1197. doi:10.1007/s00125-022-05708-3
43. El-Sawah SG, Rashwan HM, Althobaiti F, et al. AD-MSCs and BM-MSCs Ameliorating Effects on The Metabolic and Hepato-renal Abnormalities in Type 1 Diabetic Rats. Saudi J Biol Sci. 2022;29(2):1053-1060. doi:10.1016/j.sjbs.2021.09.067
44. Kinnaird T, Stabile E, Burnett MS, et al. Marrow-derived stromal cells express genes encoding a broad spectrum of arteriogenic cytokines and promote in vitro and in vivo arteriogenesis through paracrine mechanisms [published correction appears in Circ Res. 2005 Aug 5;97(3):e51]. Circ Res. 2004;94(5):678-685. doi:10.1161/01.RES.0000118601. 37875.AC
45. Song N, Scholtemeijer M, Shah K. Mesenchymal Stem Cell Immunomodulation: Mechanisms and Therapeutic Potential. Trends Pharmacol Sci. 2020;41(9):653-664. doi:10.1016/j.tips.2020.06.009

46. Zhou N, Liu W, Zhang W, et al. Wip1 regulates the immunomodulatory effects of murine mesenchymal stem cells in type 1 diabetes mellitus via targeting IFN-α/BST2. Cell Death Discov. 2021;7(1):326. Published 2021 Oct 29. doi:10.1038/s41420-021-00728-1
47. von Scholten BJ, Kreiner FF, Gough SCL, von Herrath M. Current and future therapies for type 1 diabetes. Diabetologia. 2021;64(5):1037-1048. doi:10.1007/s00125-021-05398-3
48. Lupo-Stanghellini MT, Provasi E, Bondanza A, Ciceri F, Bordignon C, Bonini C. Clinical impact of suicide gene therapy in allogeneic hematopoietic stem cell transplantation. Hum Gene Ther. 2010;21(3):241-250. doi:10.1089/hum.2010.014
49. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med. 2000;343(4):230-238. doi:10.1056/NEJM200007273430401
50. Marfil-Garza BA, Hefler J, Verhoeff K, et al. Pancreas and Islet Transplantation: Comparative Outcome Analysis of a Single-centre Cohort Over 20-years [published correction appears in Ann Surg. 2023 Aug 1;278(2):e429]. Ann Surg. 2023;277(4):672-680. doi:10.1097/SLA.0000000000005783
51. Pepper AR, Bruni A, Shapiro AMJ. Clinical islet transplantation: is the future finally now?. Curr Opin Organ Transplant. 2018;23(4):428-439. doi:10.1097/MOT.0000000000000546
52. Shapiro AM, Pokrywczynska M, Ricordi C. Clinical pancreatic islet transplantation. Nat Rev Endocrinol. 2017;13(5):268-277. doi:10.1038/nrendo.2016.178
53. Lemos JRN, Baidal DA, Ricordi C, Fuenmayor V, Alvarez A, Alejandro R. Survival After Islet Transplantation in Subjects With Type 1 Diabetes: Twenty-Year Follow-Up. *Diabetes Care*. 2021;44(4):e67-e68. doi:10.2337/dc20-2458
54. Vantyghem MC, Chetboun M, Gmyr V, et al. Ten-Year Outcome of Islet Alone or Islet After Kidney Transplantation in Type 1 Diabetes: A Prospective Parallel-Arm Cohort Study [published correction appears in Diabetes Care. 2020 May;43(5):1164]. *Diabetes Care*. 2019;42(11):2042-2049. doi:10.2337/dc19-0401
55. Marfil-Garza BA, Shapiro AMJ, Kin T. Clinical islet transplantation: Current progress and new frontiers. *J Hepatobiliary Pancreat Sci*. 2021;28(3):243-254. doi:10.1002/jhbp.891
56. Markmann JF, Rickels MR, Eggerman TL, et al. Phase 3 trial of human islet-after-kidney transplantation in type 1 diabetes. *Am J Transplant*. 2021;21(4):1477-1492. doi:10.1111/ajt.16174
57. Wisel SA, Gardner JM, Roll GR, et al. Pancreas-After-Islet Transplantation in Nonuremic Type 1 Diabetes: A Strategy for Restoring Durable Insulin Independence. *Am J Transplant*. 2017;17(9):2444-2450. doi:10.1111/ajt.14344
58. Verhoeff K, Henschke SJ, Marfil-Garza BA, Dadheech N, Shapiro AMJ. Inducible Pluripotent Stem Cells as a Potential Cure for Diabetes. *Cells*. 2021;10(2):278. Published 2021 Jan 30. doi:10.3390/cells10020278
59. Kroon E, Martinson LA, Kadoya K, et al. Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nat Biotechnol 2008; 26:443–452.
60. Rezania A, Bruin JE, Arora P, et al. Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. *Nat Biotechnol*. 2014;32(11):1121-1133. doi:10.1038/nbt.3033
61. Hogrebe NJ, Augsornworawat P, Maxwell KG, Velazco-Cruz L, Millman JR. Targeting the cytoskeleton to direct pancreatic differentiation of human pluripotent stem cells. *Nat Biotechnol*. 2020;38(4):460-470. doi:10.1038/s41587-020-0430-6
62. Pepper AR, Bruni A, Pawlick R, et al. Posttransplant Characterization of Long-term Functional hESC-Derived Pancreatic Endoderm Grafts. *Diabetes*. 2019;68(5):953-962. doi:10.2337/db18-0788

63. Marfil-Garza BA, Polishevska K, Pepper AR, Korbutt GS. Current State and Evidence of Cellular Encapsulation Strategies in Type 1 Diabetes. *Compr Physiol*. 2020;10(3):839-878. Published 2020 Jul 8. doi:10.1002/cphy.c190033
64. Bose S, Volpatti LR, Thiono D, et al. A retrievable implant for the long-term encapsulation and survival of therapeutic xenogeneic cells. *Nat Biomed Eng*. 2020;4(8):814-826. doi:10.1038/s41551-020-0538-5
65. Vegas AJ, Veiseh O, Gürtler M, et al. Long-term glycemic control using polymer-encapsulated human stem cell-derived beta cells in immune-competent mice [published correction appears in Nat Med. 2016 Apr;22(4):446]. *Nat Med*. 2016;22(3):306-311. doi:10.1038/nm.4030
66. Yu M, Agarwal D, Korutla L, et al. Islet transplantation in the subcutaneous space achieves long-term euglycaemia in preclinical models of type 1 diabetes. *Nat Metab*. 2020;2(10):1013-1020. doi:10.1038/s42255-020-0269-7
67. Liu Q, Chiu A, Wang L, et al. Developing mechanically robust, triazole-zwitterionic hydrogels to mitigate foreign body response (FBR) for islet encapsulation. *Biomaterials*. 2020;230:119640. doi:10.1016/j.biomaterials.2019.119640
68. Mallol C, Casana E, Jimenez V, et al. AAV-mediated pancreatic overexpression of *Igf1* counteracts progression to autoimmune diabetes in mice. *Mol Metab*. 2017;6(7):664-680. Published 2017 May 17. doi:10.1016/j.molmet.2017.05.007
69. Hill DJ, Hogg J. Expression of insulin-like growth factors (IGFs) and their binding proteins (IGF BPs) during pancreatic development in rat, and modulation of IGF actions on rat islet DNA synthesis by IGF BPs. *Adv Exp Med Biol*. 1992;321:113-122. doi:10.1007/978-1-4615-3448-8_12
70. Xia F, Cao H, Du J, Liu X, Liu Y, Xiang M. Reg3g overexpression promotes β cell regeneration and induces immune tolerance in nonobese-diabetic mouse model. *J Leukoc Biol*. 2016;99(6):1131-1140. doi:10.1189/jlb.3A0815-371RRR
71. Parikh A, Stephan AF, Tzanakakis ES. Regenerating proteins and their expression, regulation and signaling. *Biomol Concepts*. 2012;3(1):57-70. doi:10.1515/bmc.2011.055
72. Chen R, Meseck ML, Woo SL. Auto-regulated hepatic insulin gene expression in type 1 diabetic rats. *Mol Ther*. 2001;3(4):584-590. doi:10.1006/mthe.2001.0299
73. Rao P, Cozar-Castellano I, Roccisana J, Vasavada RC, Garcia-Ocaña A. Hepatocyte growth factor gene therapy for islet transplantation. *Expert Opin Biol Ther*. 2004;4(4):507-518. doi:10.1517/14712598.4.4.507
74. Lin Y, Sun Z. Antiaging Gene Klotho Attenuates Pancreatic β-Cell Apoptosis in Type 1 Diabetes. *Diabetes*. 2015;64(12):4298-4311. doi:10.2337/db15-0066
75. Samson SL, Chan L. Gene therapy for diabetes: reinventing the islet. *Trends Endocrinol Metab*. 2006;17(3):92-100. doi:10.1016/j.tem.2006.02.002
76. Yechoor V, Liu V, Paul A, et al. Gene therapy with neurogenin 3 and betacellulin reverses major metabolic problems in insulin-deficient diabetic mice. *Endocrinology*. 2009;150(11):4863-4873. doi:10.1210/en.2009-0527
77. Xie A, Li R, Jiang T, et al. Anti-TCRβ mAb in Combination With Neurogenin3 Gene Therapy Reverses Established Overt Type 1 Diabetes in Female NOD Mice. *Endocrinology*. 2017;158(10):3140-3151. doi:10.1210/en.2016-1947
78. Song S, Goudy K, Campbell-Thompson M, et al. Recombinant adeno-associated virus-mediated alpha-1 antitrypsin gene therapy prevents type I diabetes in NOD mice. *Gene Ther*. 2004;11(2):181-186. doi:10.1038/sj.gt.3302156
79. Yoon JW, Jun HS. Recent advances in insulin gene therapy for type 1 diabetes. *Trends Mol Med*. 2002;8(2):62-68. doi:10.1016/s1471-4914(02)02279-7
80. Paz-Filho G, Mastronardi C, Wong ML, Licinio J. Leptin therapy, insulin sensitivity, and glucose homeostasis. *Indian J Endocrinol Metab*. 2012;16(Suppl 3):S549-S555. doi:10.4103/2230-8210.105571

81. Penaranda C, Tang Q, Bluestone JA. Anti-CD3 Therapy Promotes Tolerance by Selectively Depleting Pathogenic Cells While Preserving Regulatory T Cells. J Immunol (2011) 187(4):2015–22. doi: 10.4049/jimmunol.1100713
82. Chatenoud L, Thervet E, Primo J, Bach J-F. Anti-CD3 Antibody Induces Long-Term Remission of Overt Autoimmunity in Nonobese Diabetic Mice. Proc Natl Acad Sci (1994) 91(1):123–7. doi: 10.1073/pnas.91.1.123
83. Kung P, Goldstein G, Reinherz EL, Schlossman SF. Monoclonal Antibodies Defining Distinctive Human T Cell Surface Antigens. Science (1979) 206(4416):347–9. doi: 10.1126/science.314668
84. Kuhn C, Weiner HL. Therapeutic Anti-CD3 Monoclonal Antibodies: From Bench to Bedside. Immunotherapy (2016) 8(8):889–906. doi: 10.2217/imt-2016-0049
85. Haller, M.J., Schatz, D.A., Skyler, J.S., Krischer, J.P., Bundy, B.N., Miller, J.L., Atkinson, M.A., Becker, D.J., Baidal, D., DiMeglio, L.A., et al.; Type 1 Diabetes Trial Net ATG-GCSF Study Group (2018). Low-Dose Anti-Thymocyte Globulin (ATG) Preserves b-Cell Function and Improves HbA1c in New-Onset Type 1 Diabetes. Diabetes Care 41, 1917–1925.
86. Haller, M.J., Long, S.A., Blanchfield, J.L., Schatz, D.A., Skyler, J.S., Krischer, J.P., Bundy, B.N., Geyer, S.M., Warnock, M.V., Miller, J.L., et al.; Type 1 Diabetes Trial Net ATG-GCSF Study Group (2019). Low-Dose Anti-Thymocyte Globulin Preserves C-Peptide, Reduces HbA1c, and Increases Regulatory to Conventional T-Cell Ratios in New-Onset Type 1 Diabetes: Two-Year Clinical Trial Data. Diabetes 68, 1267–1276.
87. Pescovitz MD, Greenbaum CJ, Krause Steinrauf H, et al.; Type 1 Diabetes Trial Net Anti-CD20 Study Group. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med 2009; 361:2143–2152
88. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and Immune Function. Nutrients (2013) 5(7):2502–21. doi: 10.3390/nu5072502
89. Du T, Zhou ZG, You S, Huang G, Lin J, Yang L, et al. Modulation of Monocyte Hyperresponsiveness toTLR Ligandsby1,25-DihydroxyVitamin D3 From LADA and T2DM. Diabetes Res Clin practice. (2009) 83(2):208–14. doi: 10.1016/j.diabres.2008.09.046
90. Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, et al. UKPDS 25: Autoantibodies to Islet-Cell Cytoplasm and Glutamic Acid Decarboxylase for Prediction of Insulin Requirement in Type 2 Diabetes. UK Prospective Diabetes Study Group. Lancet (London England) (1997) 350 (9087):1288–93. doi: 10.1016/S0140-6736(97)03062-6
91. Tuomi T, Groop LC, Zimmet PZ, Rowley MJ, Knowles W, Mackay IR. Antibodies to Glutamic Acid Decarboxylase Reveal Latent Autoimmune Diabetes Mellitus in Adults With a non-Insulin-Dependent Onset of Disease. Diabetes (1993) 42(2):359–62. doi: 10.2337/diab.42.2.359
92. Li X, Liao L, Yan X, Huang G, Lin J, Lei M, et al. Protective Effects of 1Alpha-Hydroxyvitamin D3 on Residual Beta-Cell Function in Patients With Adult-Onset Latent Autoimmune Diabetes (LADA). Diabetes/Metabolism Res Rev (2009) 25(5):411–6. doi: 10.1002/dmrr.977
93. Serra P, Santamaria P. Antigen-Specific Therapeutic Approaches for Autoimmunity. Nat Biotechnol (2019) 37(3):238–51. doi: 10.1038/s41587-019-0015-4
94. Smith EL, Peakman M. Peptide Immunotherapy for Type 1 Diabetes—Clinical Advances. Front Immunol (2018) 9:392. doi: 10.3389/fimmu.2018.00392
95. Genomic Annotation for Vaccine Target Identification and Immuno informatics-Guided Multi-Epitope-Based Vaccine Design against Songling virus (SGLV) through screening its whole https://www.frontiersin.org/articles/10.3389/fimmu.2023.1284366/full
96. Eggenhuizen PJ, Ng BH, Ooi JD. Treg Enhancing Therapies to Treat Autoimmune Diseases. Int J Mol Sci (2020) 21(19):7015. doi: 10.3390/ijms21197015
97. Nikolic T, Zwaginga JJ, Uitbeijerse BS, Woittiez NJ, de Koning EJ, Aanstoot H-J, et al. Safety and Feasibility of Intradermal Injection With Tolerogenic Dendritic Cells Pulsed With

Proinsulin Peptide—for Type 1 Diabetes. Lancet Diabetes Endocrinol (2020) 8(6):470–2. doi: 10.1016/S2213-8587(20)30104-2
98. Grinberg-Bleyer Y, Baeyens A, You S, Elhage R, Fourcade G, Gregoire S, et al. IL-2 Reverses Established Type 1 Diabetes in NOD Mice by a Local Effect on Pancreatic Regulatory T Cells. J Exp Med (2010) 207(9):1871–8. doi: 10.1084/jem.20100209
99. Marcovecchio ML, Wicker LS, Dunger DB, Dutton SJ, Kopijasz S, Scudder C, et al. Interleukin-2 Therapy of Autoimmunity in Diabetes (ITAD): A Phase 2, Multicentre, Double-Blind, Randomized, Placebo-Controlled Trial. Wellcome Open Res (2020) 5. doi: 10.12688/wellcomeopenres.15697.1
100. Karlsson FH, Tremaroli V, Nookaew I, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature. 2013;498(7452):99-103. doi:10.1038/nature12198
101. Delzenne NM, Cani PD, Everard A, Neyrinck AM, Bindels LB. Gut microorganisms as promising targets for the management of type 2 diabetes. Diabetologia. 2015;58(10):2206-2217. doi:10.1007/s00125-015-3712-7
102. Brunkwall L, Orho-Melander M. The gut microbiome as a target for prevention and treatment of hyperglycaemia in type 2 diabetes: from current human evidence to future possibilities. Diabetologia. 2017;60(6):943-951. doi:10.1007/s00125-017-4278-3
103. https://jgeb.springeropen.com/articles/10.1186/s43141-023-00568-9 Mutational screening of GDAP1 in dysphonia associated with Charcot-Marie-Tooth disease: clinical insights and phenotypic effects.
104. De Filippo C, Cavalieri D, Di Paola M, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci U S A. 2010;107(33):14691-14696. doi:10.1073/pnas.1005963107
105. Chen Z, Drouin-Chartier JP, Li Y, et al. Changes in Plant-Based Diet Indices and Subsequent Risk of Type 2 Diabetes in Women and Men: Three U.S. Prospective Cohorts. Diabetes Care. 2021;44(3):663-671. doi:10.2337/dc20-1636
106. Singh RK, Chang HW, Yan D, et al. Influence of diet on the gut microbiome and implications for human health. J Transl Med. 2017;15(1):73. Published 2017 Apr 8. doi:10.1186/s12967-017-1175-y
107. Russell WR, Gratz SW, Duncan SH, et al. High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. Am J Clin Nutr. 2011;93(5):1062-1072. doi:10.3945/ajcn.110.002188
108. Haro C, Montes-Borrego M, Rangel-Zúñiga OA, et al. Two Healthy Diets Modulate Gut Microbial Community Improving Insulin Sensitivity in a Human Obese Population. J Clin Endocrinol Metab. 2016;101(1):233-242. doi:10.1210/jc.2015-3351
109. Ghosh TS, Rampelli S, Jeffery IB, et al. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. Gut. 2020;69(7):1218-1228. doi:10.1136/gutjnl-2019-319654
110. Caio G, Lungaro L, Segata N, et al. Effect of Gluten-Free Diet on Gut Microbiota Composition in Patients with Celiac Disease and Non-Celiac Gluten/Wheat Sensitivity. Nutrients. 2020;12(6):1832. Published 2020 Jun 19. doi:10.3390/nu12061832
111. Dinh P, Tran C, Dinh T, et al. Hsa_circRNA_0000284 acts as a ceRNA to participate in coronary heart disease progression by sponging miRNA-338-3p via regulating the expression of ETS1. *J Biomol Struct Dyn* 2023; 1–14.
112. Boytar AN, Skinner TL, Wallen RE, Jenkins DG, Dekker Nitert M. The Effect of Exercise Prescription on the Human Gut Microbiota and Comparison between Clinical and Apparently Healthy Populations: A Systematic Review. Nutrients. 2023;15(6):1534. Published 2023 Mar 22. doi:10.3390/nu15061534

113. Matsumoto M, Inoue R, Tsukahara T, et al. Voluntary running exercise alters microbiota composition and increases n-butyrate concentration in the rat cecum. Biosci Biotechnol Biochem. 2008;72(2):572-576. doi:10.1271/bbb.70474
114. Evans CC, LePard KJ, Kwak JW, et al. Exercise prevents weight gain and alters the gut microbiota in a mouse model of high fat diet-induced obesity. PLoS One. 2014;9(3):e92193. Published 2014 Mar 26. doi:10.1371/journal.pone.0092193
115. Wang G, Li X, Zhao J, Zhang H, Chen W. Lactobacillus casei CCFM419 attenuates type 2 diabetes via a gut microbiota dependent mechanism [published correction appears in Food Funct. 2017 Oct 18;8(10):3814]. Food Funct. 2017;8(9):3155-3164. doi:10.1039/c7fo00593h
116. Singh S, Sharma RK, Malhotra S, Pothuraju R, Shandilya UK. Lactobacillus rhamnosus NCDC17 ameliorates type-2 diabetes by improving gut function, oxidative stress and inflammation in high-fat-diet fed and streptozotocintreated rats. Benef Microbes. 2017;8(2):243-255. doi:10.3920/BM2016.0090
117. Manzoor U, Ali A, Ali SL, et al. Mutational screening of GDAP1 in dysphonia associated with Charcot-Marie-Tooth disease: clinical insights and phenotypic effects. *J Genet Eng Biotechnol* 2023; 21: 1–11.