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Cell Transplantation Therapies to Reverse Type 1 Diabetes: A review

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Abstract

Stem cell technology is demonstrating promising advancements in cure of diseases due its differentiation ability. Type 1 diabetes is mainly caused by autoimmune β cells destruction. In this review, we focus on treatment procedures of Type 1 Diabetes (T1D) with numerous stem cells (SCs) i.e hPSCs, MSCs, hESCs, BMSCs, AFSCs, HSCs and islet cells (that are not stem cells but they are approved worldwide and are being successfully used to permanently reverse T1D). A brief overview of this disease along with the advancements in treatment of T1D with stem cells is discussed. Biomaterial encapsulation to avoid immune rejection and improved immunomodulation and immune tolerance via drugs /bioengineering techniques makes the outcomes of SC therapies more efficient and productive, hence, proving to be another future milestone of completely reversing type 1 diabetes especially in those patients who got clinically diagnosed at an early stage and then received prompt treatment of either restoration of already available β cells functionality or transplantation of purified and functional SCs differentiated insulin producing cells to normalize the glycemic control and homeostasis.

Keywords: Type 1 Diabetes, β-cells, Stem cells, Biomaterial

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1. INTRODUCTION

Type 1 Diabetes mellitus is a hereditary and metabolic illness that results from autoimmune destruction of endocrine, insulin secreting β pancreatic cells inside the Islet of Langerhans[1]. There are three fundamental chromosomal districts that are essentially connected with T1DM: the area of human leukocyte antigen (HLA) on chromosome 6p21, the quality for protein tyrosine-phosphatase non-receptor-type 22 (PTPN22) on chromosome 1p13, and the location of insulin (INS) gene on chromosome 11p15 [2, 3]. The existence of at least one or more autoantibodies such as autoantibodies to glutamic acid decarboxylase(GAD), insulin, islet-associated protein-2 (IA-2) and IA-2β, zinc transporter 8 (ZnT8) and recently recognized tetraspanin 7 is identified as T1D [4, 5]. Islets auto-antibodies can be used as disease expectancy indicators in people who have increased genetic susceptibility years before beginning of T1D [6]. Cell mediated immunity was considered to play a more important role in T1D pathogenesis as opposed to humoral immunity [7]. Thus, the cells of both the innate immune cells and adaptive immune cells, such as dendritic cells, macrophages, natural killer (NK) cells, NKT cells, B cells and T cells incorporating CD4+ T and CD8+ T cells, are regarded as synonymous with immunological occasions for T1D. Recent T1D patients have shown immunopathy in islet-infiltrate patients, where CD8+ cytototoxic T cells, CD4+ T cells, macrophages, and B-cells are available [8]. In addition, T-helper cells (Th, for instance, Th1, Th2, Th17, and regulatory T-cells (Tregs) are involved in T1D pathogenesis [9].

Autoimmune T1Ds (also known as diabetes type 1a) and idiopathic T1Ds (also called diabetes type 1b) can be classified as Autoimmune T1D [10]. No immune responses or autoantibodies have been identified in this latter patient (idiopathic T1D), and the cause for β-cell annihilation is still unclear [11]. There has been a variety of other forms of autoimmune diabetes, such as fulminant type 1 diabetes (FT1D) [12], and adult latent autoimmune diabetes (LADA).

In this review, we have examined victories, concerns and rising stem cell therapy treatments for T1D that are changing how we perceive this ailment, from improving glycemic control to totally making insulin free individuals. It is widely agreed that, by the time therapeutic guidelines based on advancement of histology studies in recent T1D cases, 60-90% of pancreatic β-cells have been killed [13]. At the beginning phase of onset of disease, patients still have 10-40% of insulin making cells that can be retained from being further damaged by CRISPR-Cas9 technology that is utilized to modify the genomes of cells of recipients to make new functional insulin producing β cells. Markers such as glucose levels, C-peptides, autoantibodies such as glutamic acid, protein phosphatase-like IA-2 and cytokines such as IL-1β and IFN-α have been used to test high-risk individuals and assess the danger of developing T1D. These parameters however have reduced potential to diagnose β cell depletion and are more useful for tracking T1D progression. The most promising therapeutic acceptance routine for resistance to date is bone marrow transplantation induced chimerism (MSCs, PSCs, HSCs) in which the haematopoetic grafting of cells from host and donor and focal thyme cancellation of donor reactive and hosts receptive T cells is performed with an immune tolerance against a specific human antigen leukocyte. However, significant health risks and conflicting steadiness of allograft resilience related with this methodology as of now limit its interpretation to T1D [14]. Safer tolerance acceptance approaches include the specific elimination of antigen or energy of auto reactive lymphocytes and the activation of regulatory immune system cells. CD4+ regulatory T (Treg) cells (for example), administration/regulatory immune cells [15], dendritic cells that inhibit and tolerant [16], and on the other hand activated macrophages (M2) [17], paritisation of immune responses by disabling immune cells and symptoms in line with a threat to the antigen or removing digressive self-reacting cell clones. Stem cells from different sources have been appeared to differentiate *in vitro* to insulin producing β cells by furnishing with certain cell culture conditions or implantations with regulatory growth and developmental factors [18].

Concerning all transplantations, stem cells transplantation requires a pre assessment of patient's wellbeing status i.e from how long beginning of T1D has occurred, state of different organs/frameworks of body, HbA1c, C peptide levels and kidney capacities and so forth, If the patient has some other wellbeing inconvenience or not. Furthermore, if yes than connection of that body's particular weakness with the treatment strategy of curing T1D/selection of immunosuppressive methodologies etc. So this way, evaluation of benefit to risk ratio is possible. Likewise, before treatment, patient's consent is taken in the wake of educating him/her about entire method.

Cadaver islet transplantation is detachment of islet cells from solid pancreas, enhancing it's number and purification of cells, prior to implantation. Some of other more effective strategies than Cadaver islet transplantation includes i. SC differentiates into endocrine pancreatic (allogeneic vs. autologous) with the resulting transplantation [19] ii. SC (MSC or potentially HSC) differentiation to islets *in vivo* [20] iii. *In vitro* balance of MSC to insulin producing cells (IPCs) trailed by transplantation/implantation (allogeneic versus autologous) [21], IV. AFSCs (Amniotic fluid stem cells) to utilitarian islet β cells (clinical trials in progress) v. BM derived SCs into islet β cells. (Allogeneic versus autologous), VI. Co-transplantation of MSC/iPSCs with flawless islets to improve islet engraftment and capacity [22], VII. ESC in vitro differentiated into polymer β-cells (to forestall immune rejection) and transplantation through peritoneal infusion [23].

Whole-pancreas transplantation, in any event, when effective, can prompt serious entanglements. As most patients just require restoration of their β cells, islet cell transplantation is an answer affirmed in numerous countries. Techniques to keep away from the requirement for long lasting immunosuppression incorporate the embodiment/encapsulation of islet and β cells. At the point when these cells are encapsulated preceding transplantation, they become segregated from the host's immune framework while as yet having the option to get to supplements and emit insulin [24]. Preclinical and early clinical stage research is continuous, focusing on the implantation of PSC- inferred β cells or pancreatic progenitors, differentiated from either human embryonic stem cells (hESCs) or human induced pluripotent stem cells (hiPSCs) [25].

Most conventions for treatment of patients with T1D utilize autologous HSC transplantation with nonmyeloablative molding with decreased poisonousness and maintaining a strategic distance from the advancement of GVHD. As far as T1D is concerned, autologous origins are usually appraisal able (mostly HSCs/CD34+ inferred from peripheral blood) when the transplantation happens early in patients that did not suffer from ketoacidosis (a low-β-cell mass clinical marker). For sure a few conventions require a satisfactory resting C-peptide level as incorporation rules. Certain patients remain free of residual insulin. However, unfavourable occasions were also likewise revealed.

MSC-based therapy is clinically more limited than autologous HSC transplantation. Experience requires restricted case records and regulated examination changes. Any therapies require mixed SC populations. Allogeneic and autologous transplants were attempted. Conditional protocols or scarcity in that department and method of administration fluctuate [26].

The device is safe and secured in all reports recommended. There is no account of death. The justification for the utilization of related transfers isn't given. One collection used MSCs tailored to in vitro and HSC-not purified IPC and bone marrow cells [27]. Intraportal infusion was used to side-track future pulmonary enclosure [28]. Patients with late disease and using moulding regimes were regularly considered. Progress in C-speptide levels at approximately 2 years of post-transplant-controlled exams with intravenous infusion of patient (autologous) BM-MSC was shown in a 1 year cycle to preserve or increase the level of C-speptide [29]. In combination with HSC transplantation, the information is considered prior to proposing major conventions on mixed SC transplantation, with conditioning and alternative treatment procedures to preserve a strategic distance from lung capture may be useful in early disease patients.

Beta cell death was found before the beginning of Type 1 diabetes. There was emotional increment in slaughtering of β cells in peridiagnosis period. Substitute biological markers were instigated to watch and screen beta cell "health status" during anticipation and mediation contemplates. A solitary fourteen-day treatment with teplizumab postponed the beginning of T1D in non-diabetic family members who were at high hazard for development of clinical T1D. The postponement in the middle opportunity to diabetes was 2 years. 43% of teplizumab treated subjects created T1D as contrasted with 72% of those receiving placebo. Teplizumab can be securely regulated in kids and grown-ups who are in danger for T1D.This is the principal preliminary to show that safe treatment can be utilized to Delay T1D. Certain immunosuppressive medications e.g Golimumab, Etanercept, Canakinumab, Anakinra, Abatacept, Rituximab and Teplizumab and so forth have been concentrated to secure β cells (up to a monstrous degree) from harm in the beginning stage length of T1D.

Alternatively, to treating stem cells, synthetic substances or cytokines are transported to or from the location where antigen exert its capacity to enrol or extend the regulatory immune cells. For instance, Mycophenolate mofetil is an immunosuppressant sedate that is utilized to forestall organ transplant dismissal; Mice are administered along with nutrient D3 or interleukin-10 (IL-10) which has resulted in an expansion in circulating Treg cell volumes, in comparison to naive Treg cells [30].

There is more need of clinical trials to be enhanced to account for the efficacy and concerns of using stem cell therapy to reverse T1D permanently. Clinical needs would require the aspects of optimal plant cell (for unlimited sources of homogenous β cells population on a huge industrial scale and metabolic control after the onset of treatment onwards. The current review is written to point out and highlight the research progress in the generation of IPCs and islet organoids from hPSCs and adult stem cells and the new technologies in stem cell based therapy for T1D.

2. HUMAN PLURIPOTENT STEM CELLS

The cycle of hPSCs into β cells incorporates utilization of various cytokines and signaling compounds to initiate or restrain pathways that assume significant jobs in the capacity, maintenance and differentiation to β cells [31]. Culturing refined hPSCs in a 20 matrigel stage enhance the development of pancreatic progenitor cells. Resulting cells have been transferred to immune-deficient mouse, after cell suspension culture where they develop into glucose responsive insulin producing cells after numerous stages of differentiation [32]. In vivo separation of hPSCs into insulin delivering β cells was seen by Melton et al by first prompting elevated levels of NKX6.1 and PDX1 positive pancreatic progenitor bunches. Then *in vivo* and *in vitro* culturing of cells were accomplished for 28-35 days to consider factors impacting the efficacy of β cells managing

normoglycaemia [33]. At present, CRISPR/Cas9 (indispensable gene editing tool) have been created and widely been utilized in hPSC and other SCs based treatment applications [34].

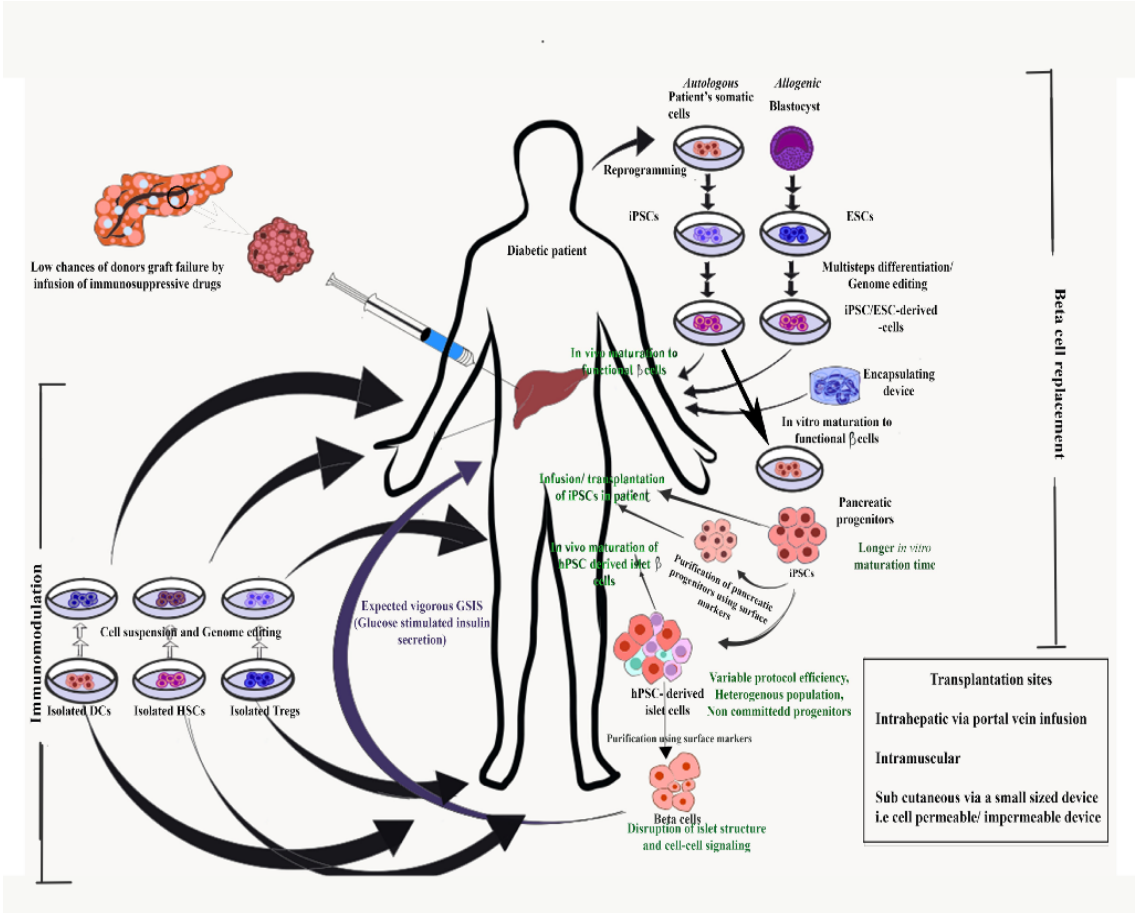

Fig 1. Showing the general procedure of stem cells for diabetes treatment. hiPSCs generated from patient's somatic cells (autologous) and ESCs from blastocyst can be differentiated into pancreatic progenitors and then are encapsulated that mature in vivo into glucose-responsive beta cells following transplantation. Genetic modification and encapsulation is done to avoid teratoma formation or other complications. In vitro maturation can also be done but it produces polyhormonal endocrine cells. Hence, they are purified using cell specific surface markers, that might disrupt the islet architecture recapitulated during differentiation and can cause disturbance in functional properties. In young patients or in those in early phases of T1D, protection of residual β cells from autoimmune attack is done by *in vitro* expansion of patient's autoantigen specific Treg clones, *in vitro* modification of patient's own HSCs, or generation of tolerogenic DCs that is used to increase the recipient's immunity. These modified immunoglobulins are than autologously re-injected into the recipient to provide immunoprotection to β cells.

Therefore, utilization of islet organoids is an exceptionally encouraging remedial procedure for T1D treatment. Organoids are an in vitro cluster of primary cells or iPSCs, which is formed to frame structures that have similar functionality and structural organization to pancreatic in vivo islet cells. Type1 diabetic mice were transplanted with such islet like organoids and effective improvement in graft survival and normoglycaemia was monitored. Subsequently, poor vasculogenesis and development of nerves around engraftment diminish the graft function in organoids transplant [32].

3. DIFFERENTIATION OF HPSCS TO B CELLS

The co-communicating cells inside the developing human embryo of pancreas and duodens homebox 1 (PDX 1) and homeobox protein (NKX6.1) mark multipotent pancreatic buds and trunk progenitors, and later express beta-cells insulin secretion [35]. Differentiation of hPSCs to functional β cells happen in 7 phases/stages.

(Fig 2) In the development of mono-hormone, glucose-responsive beta cells, the co-expression of PDX1 and NKX6.1 (stage 4) has been needed [36]. (Fig 2).

The in vivo production of pancreas progenitors or β-pancreatic cells generated from hPSC basically requires a reasonable transplant site as well as suitable material or system for epitome encapsulation. The pancreas provided the optimal microenvironment to the development and maturation of islets. However, an intervention approach for conveyance and retreivability has constrained the concept of success at a transplant site. A test on transplanted islets in rodents and rats revealed that normaloglycemia was performed in pancreas with lower islets compare to, for example, liver and kidney extra-pancreatic destinations [37].

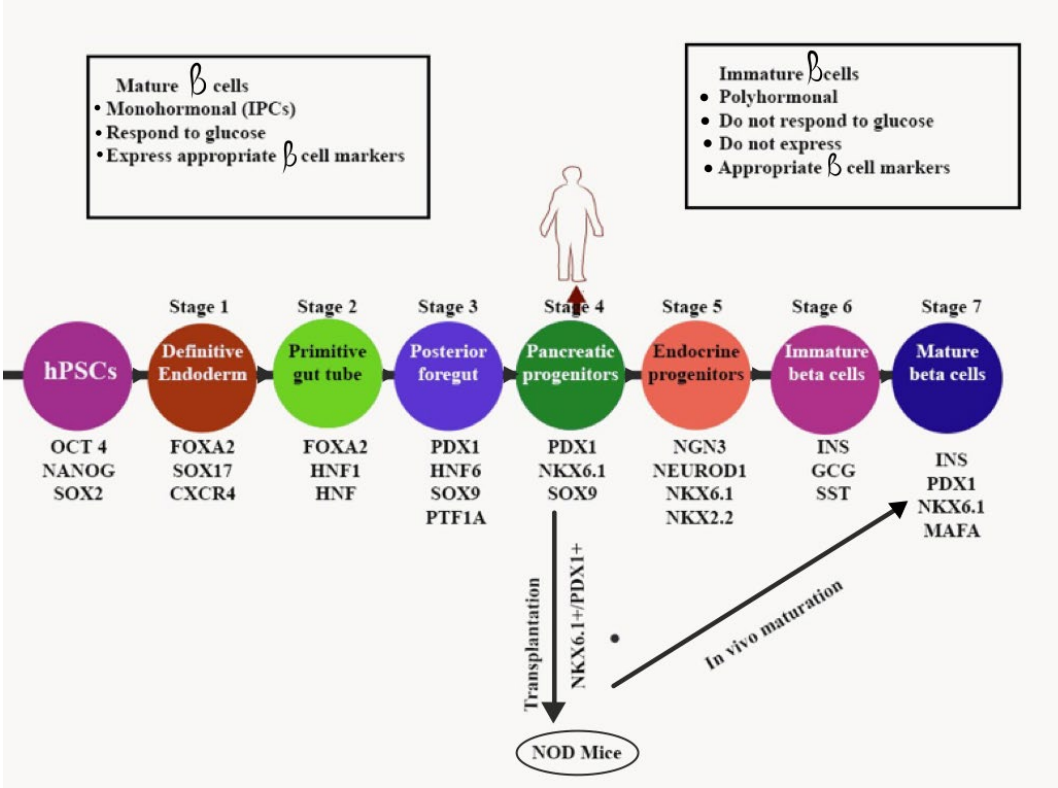

Fig 2. Differentiation of hPSCs to mature β cells Stage specific marker of stage 4 (PDX1, NKX6.1) is in ½ phase of clinical trials for T1D treatments. PDX1, NKX6.1+ mouse transplanted cells differentiate in vivo into mature β-cells (insulin-producing). Direct transplantation of mature β cells from stage-7 can be done in mouse model. Clinical trials in humans are in progress.

4. ENCAPSULATION

By repealing direct host-donor cell touch, durable semipermeable biomaterial obstructions may provide 3D protection to the transplanted cells and avoid allograft rejection. For as long as 30 years, the safety of the islet graft by biomaterial encapsulation has been an active area of exploration, and numerous clinical trials have been performed using immuno-isolated cells [38, 34].

Encapsulation technology may possibly restrict the spread of unregulated cells and defend transplanted cells from the immune cellular antibody of the recipient or complement the interceding assault. In this way, an enveloping/encapsulation system is a vital element affecting the transplanted cells' appearance, because if the transplanted cells are infected with undifferentiated cells, it will influence the progression of teratoma. In addition, if, for example, the cell therapy commodity is sold off-the-shelf hPSC-derived beta cells from an allogeneic source, encapsulation is also a prerequisite at that stage [39]. Compared to unpurified alginate pills, coating with filtered alginate strengthened the endurance of enveloped islets and mildly influenced necrosis

[40]. Microcapsules (using nanoparticles) and macro-encapsulating biomaterial sheets have been approved in rat and rodent models, bigger animals as well as related clinical preliminaries are in progress.

Alginate is most ordinarily utilized for microcapsules, availing its distinctive chemical and physical properties, for example, sub-atomic mass, proportion of D-mannuronic acid and L-guluronic acid deposits, and gelation agents [41]. Allograft protection has been demonstrated by various experiments in T1D rodent rat models for about 90 days by alginate microcapsules (one investigation analysed the material for as long as 350 days in NOD mice) [42]. Fig 3 is showing immune-protection and immunomodulation of β cells with encapsulating biomaterial and 3D scaffold framework/hydrogel; ends up being exceptionally proficient against a wide range of dangerous insusceptible autoimmune reactions.

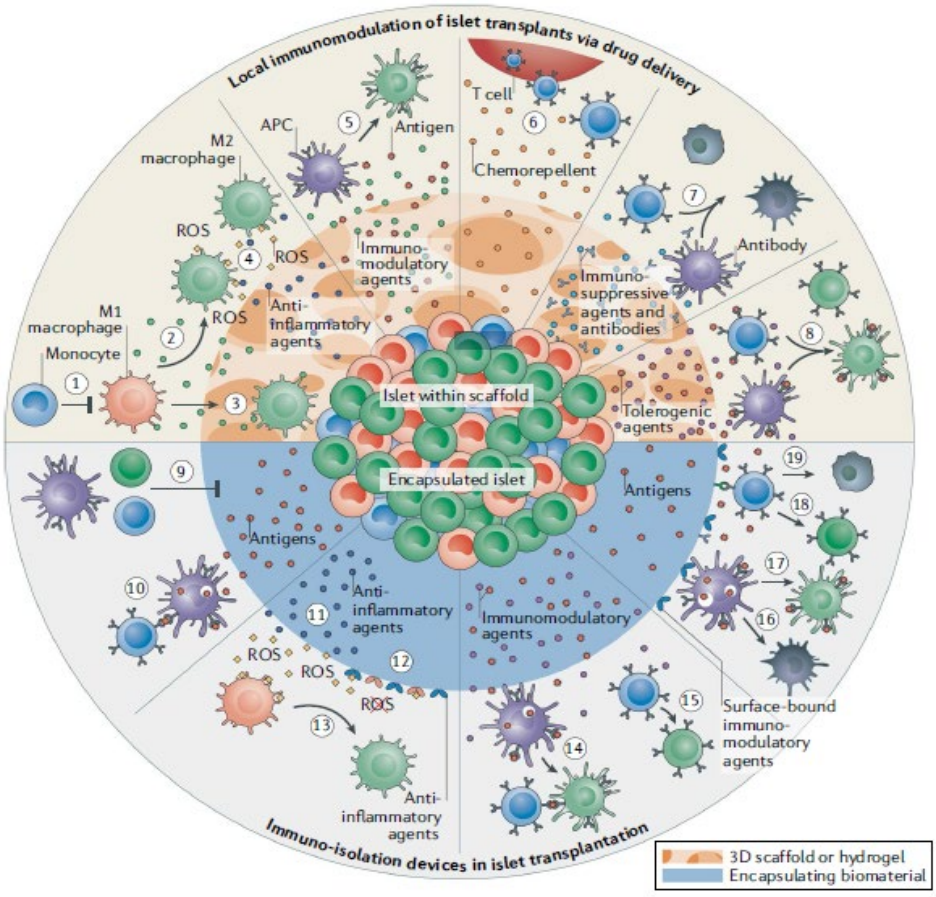

Fig 3. | Immunomodulation of β cells with encapsulating biomaterial and 3D scaffold/hydrogel coating
Scaffolds protecting the islet cells transplant is done in the same way as drug delivery procedure. To control inflammation, scaffolds can release agents that inhibit migration of monocyte or maturation of macrophage (step 1); inhibit macrophage infiltration (step 2); scavenge detrimental products from activated macrophages, such as reactive oxygen species (ROS; step 3); and/or promote an M2-like macrophage phenotype (step 4). To modulate adaptive immunity, drugs can be released or presented to inhibit antigen uptake or promote a tolerogenic dendritic cell (an antigen-presenting cell, APC) phenotype (step 5); to inhibit migration of activated T cells from lymph nodes (step 6); to induce immune cell apoptosis (step 7); and/or to promote a tolerogenic phenotype (step 8). Encapsulation of the foreign transplant blocks direct antigen presentation pathways (step 9) but can activate indirect pathways (step 10). Drugs incorporated within the biomaterial (step 11) or tethered to the material surface (step 12) can dampen inflammatory responses to the material and encapsulated cells by inhibiting macrophage activation, scavenging detrimental agents and/or by promoting an M2-like phenotype (step 13). To dampen adaptive immune responses, immunomodulatory agents can be incorporated into the encapsulating material and released for local modulation of APCs (step 14) and/or T cell activation (step 15). Immunomodulatory agents conjugated to the surface of the biomaterial can instruct immune cells towards apoptotic (steps 16 and 17) and/or tolerogenic (steps 18 and 19) phenotypes. Local antigen delivery by the transplanted cells provides antigen specificity.

5. IMMUNOSUPPRESSION

The convention for first clinically effective transplantation of islet β cells contains an enemy of interleukin-2 i.e receptor antibody (T cell actuation inhibitor), anti-interleukin-2 prior to every imbuement of islet-cells, along with mTOR inhibitors (sirolimus) and low dose of a calcineurin inhibitor tacrolimus (8 "progresses in b). Diverse induction signals were utilized as variations, for instance the application of, T cell-depleting agents (Immunoglobulins, Antilymphocyte, Teplizumab or Alemtuzumab), or inhibitors of lymphocyte (Efalizumab) and (9,12,15,25-28 "propels in b) or other blends of compounds can be utilized e.g Ciclosporin, Everolimus, Belatacept, Mycophenolate, azathioprine, steroids or abatacept can likewise be frequently utilized e.g steroid containing anti-inflammatory substances that repress TNF-α (Infliximab or Etanercept) or IL-1β (Gusperimus hydrochloride/deoxyspergualin or Anakinra). Anti-thrombocyte immunoglobulin as an immunosuppressive medication and methylprednisolone is given as first portion to reduce the reactions of cytokines which are mostly released due to the T cells lysis [43].

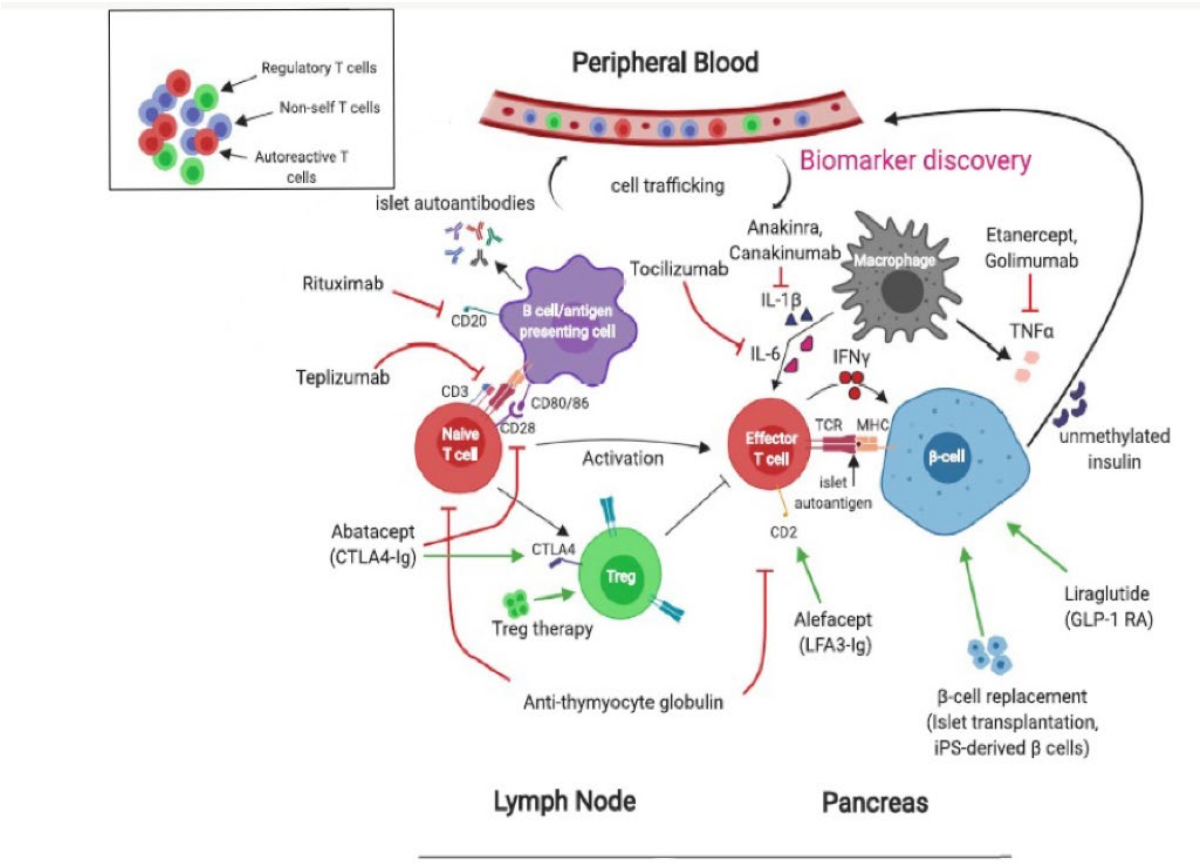

Fig 4. Immune tolerance and Immunosuppression mechanisms in T1D individuals

Regulatory T cells (Tregs) and pathogenic autoreactive T cells recognize autoreactive T cells recognize antigens by themselves but at different affinities and concentrations. In T1D, T cells specific for β cells come in contact with their corresponding epitope portrayed by the HLA of an APC, they will become activated in the lymph node, migrate to the islets and begin the process of T cell destruction. Tregs prevent this process. If body fails to overcome this autoimmune attack on the β cells, T1D occurs. Biomarkers were discovered to carefully examine this process of autoimmune β cell destruction. Immunosuppressive drugs e.g. Etanercept, Golimumab, Anakinra, Teplizumab and Rituximab etc. inhibits autoimmune β cells destruction.

6. TRANSPLANT MONITORING

To screen for transplant entanglements and complications, insignificant immunosuppressive drug is utilized to watch the reoccurrence of autoimmunity. Inconveniences can incorporate neoplasia and deft contaminations. Adequacy of stem cells in restoration of metabolic equalization is monitored. Reliable post translational observing is significant with week by week or month to month visits or according to specific

patient's condition. Significant checking center is towards counteraction of development of teratomas. It is nevertheless essential for subcutaneously or under kidney containers transplanted pancreatic progenitors to have resulted in the differentiation in beta cells functionality, irrespective of their sensitivity to a 'pancreatic' microenvironment [44].

7. ISLET CELLS TRANSPLANTATION

ß cells from Langerhans islets of healthy individuals were effectively used in T1D patients to sustain normaloglycemia by reestablishing the endogenous regulated insulin secretion and various other hormones. In 2000, steady accomplishment of one year insulin freedom in 7 patients was seen because of islet cell transplantation and the advancement was quickened onwards [45]. Implantation of around a few (two to three) islet arrangements is required for insulin freedom with an objective of about 9000 islets for each kg recipient body weight (contingent on the need per person). Numerous centers have reported that a high number of patients with a transplant of 6,000 islets per kg from a unique donor pancreas have been insulin independent [46]. In numerous countries, the propagation of a catheter-small plastic tube through the upper abdomen and through the portal vein of the liver is conducted by a radiologist who uses x-beams and ultrasound. Then the islets are slowly infused into the liver through the catheter. A local anesthetic is given to the patient. In certain cases, a surgeon may conduct a transplant using general sedation by means of a minor puncture/incision. Islets removed from the pancreas of the donor are impregnated into the liver. When combined, insulin is generated and delivered in the islets of beta cells.

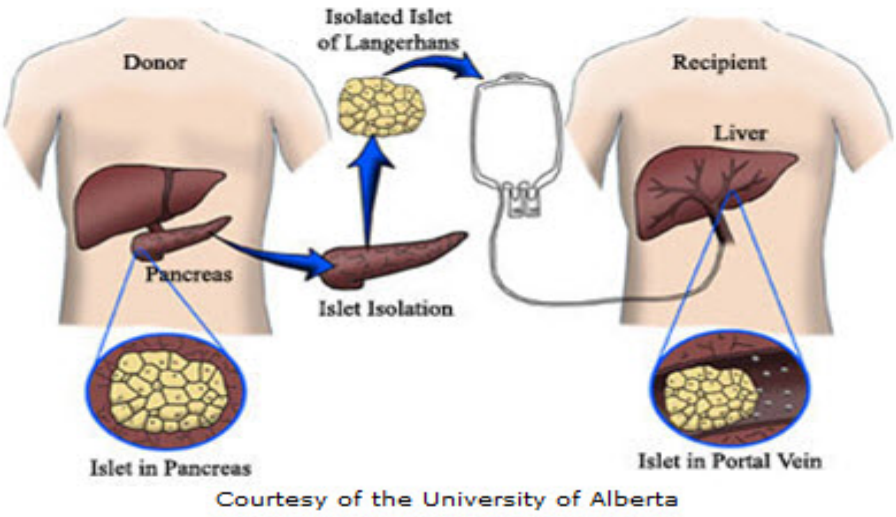

Fig 5. Islet cells are transplanted into the liver portal from the upper abdomen (middle section) by means of a catheter. Image gracefulness of the University of Alberta and the consortium of therapeutic transplants (CIT) sponsored by NIDDK and National Institutes of Allergy and Infectious Diseases (NIAID).

An examination mostly on islet-treated patients compared to several normal infusions/insulin doses [47, 48, 49], was done (table 1). The Edmonton protocol is the isolation of the cadaveric pancreas islets by a combination of enzymes such as liberase. The islets of one to upwards of three donors are received for each recipient. The islets are imbued into the portal vain of patient's and then immune-protection is finished by utilizing immunosuppressants, sirolimus and tacrolimus or monoclonal antibody medications can likewise be utilized (that are utilized in immunosuppression).

Table 1. Examination of islet cells transplantation with everyday exogenous insulin treatment

Reference	Study design	Patient number and kind of	T1D control,	Islet transplantation	Years of	Proportion of	HbA1c	Severe hypoglyca	Adverse occasions

		transplantation	number of patients	Immunosuppression	follow-up	patients who are insulin free, %		emia events	
[48]	Non-randomised, retrospective	Seven ITA, six IAK	17 intraperitoneal pump	Edmonton protocol	3	46%	Lower for islet transplantation vs control: 6·6% vs 8·1%	0·7 hypoglycaemia occasions every week for islet transplantation versus 1·7 for insulin-pump therapy at year 3 versus 2·6 before islet transplantation treatment	Four times higher for islet transplantation versus control
49	Prospective, hybrid cohort	32 ITA	45 seious clinical therapies	Antilymphocyte immunoglobulins plus tacrolimus plus mycophenolate	>5	37%	Lower for islet transplantation vs control: 6·7% vs 7·8%		
47	Non-randomised, retrospective	22 ITA or IAK	Three control batches: 22 preceding transplantation; 70 various everyday infusions or constant subcutaneous insulin imbuement; 13 kidney transplantation Alone	Edmonton protocol	7	9% at 5 years‡	Lower for islet transplantation versus control gatherings: 6·7% vs 8·2%; 6·7% vs 7·6%; 6·7% vs 7·9%	Severe hypoglycaemia occasions per patient every year was lowered after islet transplantation versus control: 0·3 vs 4·5	Higher for islet transplantation versus control: four occasions versus none
50	Multicentre, open nametag, randomised, controlled	25 ITA or IAK	21 constant subcutaneous insulin implantation or various everyday injection	Antilymphocyte Immunoglobulins along with steroid bolus in addition to tacrolimus plus mycophenolate along with etanercept	1	59%	Lower for islet transplantation versus control: 5·8% vs 8·1%	Lower for islet transplantation versus control: 0% vs 2%	Higher for islet transplantation versus control (yet one death Identified with extreme

									hypoglycaemia occasions on transplantation holding up on list)
51	Non-randomised, retrospective	Nine ITA, four IAK	25 concurrent Kidney–pancreas transplantation; five pancreas-after-kidney transplantation	Edmonton protocol	3	Lower for islet Transplantation versus control: around 20% vs 65%	Higher for islet transplantation vs control: 6·3% vs 5·0%	Same for islet transplantation vs control: both 0%	Lower for islet transplantation vs control: 7·7% vs 23·0% relaparotomy; one demise in the benchmark control group
52	Non-randomised, retrospective	33 ITA	33 pancreas transplantation alone	Edmonton convention. or on the other hand antilymphocyte immunoglobulins in addition to mycophenolate along with sirolimus (sirolimus began before transplantation in one subgroup)	1	Lower for islet Transplantation versus control: 59% vs 75%			Lower for islet transplantation vs control: 0% vs 54% relaparotomy
53	Non-randomised, retrospective	38 ITA or SIK	94 concurrent kidney–pancreas transplantation or pancreas-after-kidney transplantation	Edmonton convention then sirolimus changed to mycophenolate, daclizumab changed to basiliximab or antilymphocyte immunoglobulins	>5	Lower for islet transplantation versus control: 9% vs 73%‡	Higher for islet transplantation vs control: 6·5% vs 5·9%	Same for islet transplantation versus control: both dropped by 90% versus before transplantation	Lower for islet transplantation vs control: 10% vs 41% relaparotomy

*ITA (Islet Transplantation Alone) * IAK (Islets after Kidney-Transplant) *SIK (Simultaneous Islet and Kidney transplantation)

8. MESENCHYMAL STEM CELLS

A PubMed identification discovered 271 papers, (till 2017) that indicated more prominent than 30,000 squint explored scientific publications on mesenchymal stem cells MSCs' differentiative ability in reversing T1D totally, immunosuppression and regulations, and emission of cytokines and growth regulatory factors [54].

MSCs were additionally utilized as an immunomodulatory treatment in NOD mice [55]. In order to facilitate the regeneration and survival of β cells, MSCs were transferred to damaged pancreatic area and the micro-environment of islet was changed [56]. Certain intravenous infusion of MSCs were given to diabetic mice. Expanded levels of insulin and decreased hyperglycaemia was observed. Altogether, a solitary treatment of umbilical cord MSCs in people gave enduring/lifetime independency from IIT by recovering β cells and looking after normoglycaemia [57]. In recent studies insulin level, glucid decarboxylase-acid and the insulin antibiotics of 2 patients were lowered in a year by infusing MSCs with a liver puncture and thus, immune-modulated cell resilience/tolerance was achieved [58]. The MSC association reports in NOD mouse recommend that allogeneic rather than autologous MSC will delay starting T1D. Following table shows the clinical trials done with MSCs transplantation in recipients.

Table 2. Demonstrating Summary of clinical trials done with infusion of undifferentiated MSCs to treat T1D

Trial. No.	Phase		Findings	Fresh (FH)/ Frozen (FR)	Status	Reference
NCT01068951	-	Self-treatment with MSCs (estimated 2 cells/kg of body weight) Intravenously	With both the C-peptide high point and C-peptide, patients in the control arm appeared to be decreasing as an area under the curvature during the first year.	FH	Completed in (2014)	59
NCT01374854	½	1 = 106/kg UC-MSCs was injected with interventional therapy with the pancreatic arteries so with the BM-MNCs and 1 week after administration, an equal volume of UC-MSCs was delivered.	In 20 of 21 respondents, c-peptide increased by 105.7%, as compared with a 7.7% decrease in subjects monitored. HbA1C decreased in the care of test subjects by 12.6 per cent compared to 1.2 per cent.	FH	Completed in (2012)	30
NCT01219465	½	The UC-MSCs (2 — 107 cells/kg body mass injectable transfusion)	In the MSC versus saline monitoring, no acute or chronic adverse events have been shown. Both HbA1c and C-peptide were higher during the follow-up time in MSC-treated patients than either pre-treatment projections or saline control patients;	FH	Completed 2012	60
NCT01996228 NCT01350219	½	Within the stem cell mentor, adult UC-MSCs	One therapy offered permanent reversal of autoantibodies, allowing islet β-cells to regenerate and metabolic regulation to be enhanced for people with prolonged T1D.	FH	Recruiting	57
NCT01143168	1	BM-MNC + UC-MSC several implant	Not available	FR	Completed in 2011	61
NCT00646724	½	Islet allograft and MSC autograft co-transplant	Not available	FR	Estimated completion of 2012	N/A

NCT01496339	½	1 to 106/kg MenSCs are injected by or intravenously into the pancreatic artery once a week in four ongoing procedures	Not available	FR	Estimated completion in 2015	-
NCT02644759	½	Gene therapy into the pancreas and capillary arteries of the autologous CD34+/CD133+ cells using internal medicine methods. Established in this study by 3–6 hour auto-incubation of UC-MSCs and by intravenous infusion of auto-WBCs back	Not available	FH	Ongoing	-
NCT01157403	2/3	Injectable allogeneic BMSC transplant (about 2.5 cells per 106 kg body weight)	Not available	FR	Estimated completion was in 2014	N/A

9. AMNIOTIC FLUID STEM CELLS (AFSCS)

A study has shown that in vivo AFSC therapeutic potential to treat type 1 diabetes has prevented loss or damage to β cellular and β cells have been regenerated after pancreas damage by activating Pi3Kinase/Alxt and VEGF-A (VEGF-A) vascular growth factor [62]. Human samples were obtained from the disposed amniocentesis between 15-20 weeks of gestation of normal karyotype and normal foetal ultrasound (second trimester of pregnancy). (Non-adhering AFSCs were isolated, cultured, multiplied, expanded and purified. Characteristic analysis of AFSCs was done by flow cytometry to make sure there is no abnormality (cells are healthy). Media formulation was done under controlled pH, temperature and humidity. For tracking of cells (before infusion, they were labelled with the cell tracker, following the instructions explained. Culture of tracker labelled AFSCs was injected to an immunodeficient NOD/SCID mice with 1 x 10^6 AFSCs. Previously mice was treated with streptozotocin to make it diabetic. After infusion, mice was carefully monitored under isofluorane inhalation anesthesia *In vivo* maturation of AFSCs to β cells was done. After every 2 days, blood glucose level was being monitored for first week and then once per week for the later 4 weeks experiment. The mouse-associated immunosorbent assay has been used to investigate plasma insulin levels. Mice pancreas were harvested after 4 weeks, its tissues were processed and the histological samples were than prepared. Quantification analysis of islet β cells mass was done in comparison with proliferating cells. Polymerase chain reaction arrays were done. The levels of Plasma Insulin in AFSCs treated mice's relative to control groups were significantly higher. Results concluded that protection of physiological functions of β cells and normoglycaemia was achieved in AFSCs transplanted (STZ induced) diabetic mice [62].

10. HEMATOPOIETIC STEM CELLS

Use of immunomodulatory HSCs has provided sufficient metabolic control, independency from IIT, decrement in HbA1c levels and increment in C-peptide levels. Autologous hematopoietic stem cell transplantation (AHSCT) has so far been the most encouraging effects in the field of research. 40% of those who received this therapy were permanently free of insulin. (24 "cell therapy). However, there are adverse effects of this treatment also. Research was carried out using a multi-center cross-sectional analysis in AHSCT (8 years of treatment) treated T1D patients showed that 21% of them encountered microvascular complications. To observe the effect on auto reactive cells, next generation sequencing of β chains of T cell receptor was done before and after infusion of AHSCT. The result showed that patients who had more CD4+ T cells were regenerated after treatment and weren't removed completely. (34 in "cell therapy).

11. HUMAN EMBRYONIC STEM CELLS

At present, human embryonic stem cells are the main foundational stem cells population that can multiply at a pace of > 250 population doublings per year. These cells are proficient to differentiate effectively and quickly to produce cells of all somatic lines by a chain of specific growth/developmental changes and differentiation (Kroon , 2008). Embryonic stem cells (ESCs) inferred β cells were first effectively created *in vitro* by D' Amour et al [63]. During differentiation convention, D' Amour et al, found an EPS monolayer culture that were utilized as explicit portions in a specific arrangement (that performed job of development, growth and motioning) to control the cells via five-stages mechanism that mimics the normal development of β-cells acquired at the end were immature, juvenile and poly-hormonal. All these cells were differentiated into mono-hormonal insulin secreting cells, when transplanted into the immunocompromised mouse, and these cells could become normoglycaemic in the diabetic mice with streptozotocin after 2-3 months [64]. Practically all ESC separation conventions depend on enactment/hindrance of cell signaling and developmental growth factors, controlling cell multiplication, separation and distinguish utilizing suspension societies with regulated mixing to facilitate cell-cell cooperation's and arrangement of islet- like arrangement [65]. Because of these improved conventions, proficiency of glucose responsiveness is expanded and number of polyhormonal cells were diminished. Effectively cells produced utilizing these improved techniques reestablished normoglycaemia in immunocompromised diabetic mice following 2 to 2.5 months of transplantation [66]. The utilization of ESCs has ethical and moral concerns due to its source/origin as embryo/blastocyst whereas other complications of utilizing ESC can include development of teratomas and generation of polyhormonal heterogenous immature cells during differentiation. Additionally, ESC derived β cell graft rejection is the most controversial complications that can be brought about by either alloimmune or persistent autoimmune reactions, resulting patients to rely upon strong immunosuppression [24]. Microencapsulation gadgets may empower the protected conveyance and immune-protection of islets β cells with no prerequisite of immunosuppression.

12. BONE MARROW STEM CELLS

The mouse bone marrow cells have been transplanted into a hereditary irradiated mouse. The procedure of in utero transplantation (IUT) showed β-like cells and insulin in the beneficiary's pancreas without the mix of cells between donor and recipient cells [57].

Two studies in the pancreas of the cell community have confirmed that the above mentioned IUT technique has been used to form human hepatocytes (segretting with monoclonal/polyclonal methods), humans, cardiovascular and gastric cell hemopoietic components [68]. The use of IUT in sheep or irradiation in syngeneous mice facilitates the division of either HSC or MSC into utilitarian β-like cells in this way.

13. CONCERNS

Although the pancreatic progeny derived from HPSC has exceptional assurance for diabetes care, certain questions about their clinical use are possible. One problem is the unregulated formation or de-differentiation of mature endocrinic cells in uncontrolled progenitor cells as the transplant takes place. In the field of teratoms development by transplanted cells, extraordinary progress has been made, one being 'self-destruction switches'. The auto-destruction switch is a gene that has the ability to destroy the unwanted grafted cells in vivo [69]. An inducible gene cassette of Caspase 9, such as the use of a hiPSC lentiviral vector, with EF1a promoter that triggered the degradation of the teratoma generated by modified hiPSCs when exposed to medications that triggers the gene of Caspase 9 in vivo, following transplantation [70]. However, it is possible that the separated therapeutic cells and the vindictive cells will be annihilated after the drug has been exposed.

Accomplishing the suitable islet design *in vitro* utilizing imaginative strategies could upgrade hPSC-derived beta cell usefulness. Furthermore, as beta cell heterogeneity is found on a normal human islet, comparable heterogeneity have some significance. Consequently, incomplete stem cell differentiation or purification places patients in danger of creating teratomas [71]. Islet cells don't go through the differentiation stages, thus they are relatively more secure to use from this aspect.

14. CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Stupendous research progress has been done in the last few years towards development of functional β cells to cure T1D. Advancements in immunomodulation and immune-protective biomaterials is also impressive.

However, there is more need of clinical trials to be enhanced to account for the efficacy and concerns of using stem cell therapy to reverse T1D permanently. Clinical needs would require the aspects of optimal plant cell (for unlimited sources of homogenous β cells population on a huge industrial scale and metabolic control after the onset of treatment onwards. Islet β cells biomaterial encapsulation with anti-inflammatory agents provided very complementary effects on prevention from transplant rejection or autoimmune responses. A novel gene editing technology, CRISPR Cas9 is also being used to up regulate the gene expressions in native β cells of individuals (to prevent them for further damage) or to modify the functional efficiency of transplanted stem cells. ESCs, hPSCs, BMSCs, AFSCs, HSCs, MSCs and various other types of adult cells or bone marrow derived stem cells have been studied demonstrating the capability of differentiating to insulin producing β cells and there is a great hope of functional use of easily available cost effective stem cells transplantation to reverse type1 diabetes. Some of the patients who had gone through islet cells transplantation had also undergone severe hypoglycaemia events that are very dangerous. Certain monitoring on patients undergoing infusion of stem cells is required to avoid serious risks through this treatment. Islet cells are not stem cells although but when stem cells become the approved treatment for T1D than there will be great amount of patients being permanently recovered and insulin free at the initially clinical diagnosis time period. There is a need to have more research on different types of SCs for diabetes treatment and advancement in clinical trials to make it become an official technology into applied medical solution of reversing T1D. Early genome studies done in childhood/ infant is highly effective in preliminary analysis of possibility of diseases (esp autoimmune and genetic) in future. Certain protective measures and drugs are recommended by the experts to either hinder the onset of disease (throughout the life) or modify the genes by numerous genome editing tools.

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