Opinion

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# Stem Cells for the Cell and Molecular Therapy of Type 1 Diabetes Mellitus (T1D) between Lights and Shadows

**Riccardo Calafiore*, Giuseppe Basta, Massimiliano Cavallo, Francesco Gaggia and Pia Montanucci**

*Laboratory for Cell Transplants and Biohybrid Organs, Department of Medicine, University of Perugia, Perugia, Italy*

***Corresponding author:** Riccardo Calafiore, Department of Medicine, Laboratory for Cell Transplants and Biohybrid Organs, University of Perugia, Perugia, Italy

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ABSTRACT

The restricted availability of cadaveric human donor pancreases coupled with the invariable need for treating the grafted patients with life-long general pharmacologic immunosuppression sharply limits progress of pancreatic islet cell transplantation into widespread clinical trials for the cure of T1D. While new micro-/macro-devices are being used to avert graft immune rejection, with no host's general immunosuppression, the chronic lack of human insulin-producing donor cells represents a formidable hurdle. Hence, access to possibly unlimited sources of insulin making cells could offer a solution. Human stem cells derived from either embryos, or adult tissues, could yield virtually unlimited cell source. While the former still poses ethical and technical problems, the latter encounters mainly technical obstacles. As for embryonic stem cells, upon differentiation of the original pluripotent stem cells towards endocrine cell lineages, they have been reported to correct hyperglycemia upon graft into immune-incompetent mice, while immune rejection issues are still pending.

However, at this time, only sporadic papers are available, waiting for confirmatory data. The same virtually applies to pilot early safety, sub-therapeutic clinical trials, recently begun in patients with T1D. In terms of adult cellular elements, mesenchymal stem cells derived from either bone marrow, or adipose tissue, or placenta or the umbilical cord Wharton Jelly can be isolated with no particular difficulties. They couple an intrinsic ability to transition into the definitive entoderm, towards beta-like insulin secreting cells, with powerful immunoregulatory properties. Less data is available for adult cells induced into pluripotency, by genetic engineering, there after re-differentiated into insulin producing cells.

## Introduction

T1D consists of selective autoimmune killing of pancreatic islet β-cells that physiologically accomplish the task of secreting insulin on a regulated manner, in order to maintain blood glucose levels within normal range (70-140 mg/dl), under any circumstances. Currently, at the disease clinical onset, the only available therapeutic option is to treat the patients with exogenous insulin. While a life-saving medication, exogenous insulin does not represent a cure for T1D, since even the last generation of analogic insulin molecules available in the market, would never reproduce the stimulus-coupled physiologic endogenous insulin secretory patterns. The consequential afforded imperfect BG control will consent survival, and possibly to delay/attenuate, but never eliminate the risk for developing secondary chronic complications of the disease, linked to abnormal blood glucose values, such as micro- and macro-angiopathy. The latter clearly increases prevalence of cardiovascular disease, renal insufficiency, retinopathy and neuropathic disease with severe increment of disease-related morbidity and mortality. A potential approach to cure the T1D would be to replace the destroyed β-cells with fresh and vital pancreatic endocrine tissue coming from cadaveric donors. However, transplantation of either whole pancreases or isolated islets [1] retrieved from whole organs, over the past three decades, have encountered formidable obstacles, from insufficient organ availability owing to low organ donation rate, to immune rejection of, or recurrent autoimmunity on, the grafted tissue.

Pancreatic organ transplant involves major surgery with still significant operatory complications. With the exception of few reports [2], this approach has been always associated with the graft finite functional life-span. The same applies to graft of isolated islets whose success rate, throughout years of post-transplant follow-up remains low. The islet case is aggravated by the fact that not always a single donor pancreas yields a sufficient islet cell mass to reverse hyperglycemia upon graft in a single T1D recipient. Hence, new β-cell sources are needed to fulfill demand for virtually inexhaustible insulin producing cells.

### Novel Strategies for Stem-Cell-Based Therapy of T1D

**Human Embryonic Stem Cells (hESC):** Progress in unfolding many aspects of endocrine pancreatic developmental pathways has introduced the use of hESC as a potential resource for generating surrogate insulin-producing β-like cells [3]. Aside of ethical issues, associated with use of hESC, in the majority of Western Countries, differentiation protocols applied to embryonic blastocyst inner mass cell to obtain β-like cells, that able to release insulin in response to glucose stimulation, still looks partial, probably due to imperfect/incomplete maturation of β-cell-like elements. Likewise, initial pre-clinical trials in special models of diabetic mice have not yielded convincing evidence of function, in terms of reversal of hyperglycemia. Phase I/II clinical trials of hESC grafts have required either to apply general immunosuppression to treated patients, while use of immune-isolation devices that prevent physical contact between the host's immune system and the grafted tissue, to circumvent the graft immune rejection, is underway. The fact that the initial pre-clinical trials were conducted in immunodeficient rodents, in addition to defective vascularization of the employed macro-devices, actually represent major limits to bring this technology into clinical fruition [4]. Development of more performing microcapsules could help surmounting this specific issue, pending the fact that hESC represent a cell model quite difficult to employ operatively.

**Human Induced Pluripotent Stem Cells (HIPSC):** Within other possible options, hIPSC appeared first in 2006, generated by Yamanaka (Nobel laureate for this discovery in 2012) [5]. Starting from human adult somatic cells, a fibroblast in Yamanaka's system, the protocol aimed at de-differentiating an adult cell, and revert it into pluripotency. This was initially obtained by transfecting the cells with selected genes and related transcription factors including OCT3/4, SOX2, cMYC, and KLF4. Because of potential tumorigenesis associated with some of these genes, alternative strategies have developed in recent years. With special regard to β-cell differentiation, ongoing new protocols are being based on exposure of the original somatic cells to a cocktail of cytokines and small molecules, such as FGF, KAAD-cyclopamine, Nicotinamide, Thyroid hormone, TGFβ pathway inhibitors, retinoic acid etc [6]. Preliminary in vitro and in vivo pre-clinical studies mainly in immune-incompetent rodents have shown initial evidence of only partial function. In fact, although reversion into pluripotency of a somatic adult cell may succeed, re-differentiation into specific and physiologically competent cell elements is not an easy task to achieve. At least not for -cells, whose task is to release specific molecules under fine regulatory mechanisms. For instance, while it is easier that hIPSC generate mesodermal origin cells, like muscle cells, they encounter serious obstacles when applied to generation of sophisticated cells like insulin secreting β-like cells. In fact, assembly of the complex glucose sensing apparatus and its multiple tasks looks extremely difficult to accomplish. While presence of insulin may identifiable in the treated cells, the stimulus-coupled insulin secretion appears still far from reality, and will require additional efforts.

**Adult Mesenchymal Stem Cells (MSC):** Extracted from different sources (bone marrow, adipose tissue, placenta, post-partum umbilical cord Wharton Jelly) hold promises for helping reversal of hyperglycemia in T1D. Two are the main possible approaches to exploit the MSC potential. First, MSC may undergo differentiation procedures into definitive endoderm, by activation of defined genetic pathways [7]. Differentiation into endocrine, and specifically insulin-producing cells could represent the end of this process [8]. Obviously, transition from mesoderm-derived cells like hUCMS into entoderm-cells continues to pose formidable obstacles, which may require time before reasonable success is obtained. Second, an important advantage associated with MSC lies on the fact that these cells hold powerful immunoregulatory properties. These look particularly active with MSC derived from the post-partum umbilical cord Wharton Jelly (hUCMS).

Such an advantage depends on the fact that hUCMS physically stand at the fetal/maternal interface where they protect the fetus from immune attack possibly deriving from the mother herself. Such powerful immunomodulatory properties seem to be associated with HLA genes of class G. We showed in experimental models, that HLA G5, a soluble molecule, could play a role in expanding FOXP3 cells, hence regulatory T lymphocytes (Treg) that induce a state of acquired immune tolerance, leading to interruption of the β-cell directed selective autoimmune destruction [9]. Hence, at early stages of the T1D disease process, the estimated 30% of β-cells, possibly harmed, but still partially viable, could be rescued by microencapsulated hUCMS graft thereby possibly preventing need for exogenous insulin administration. These observations were just recently substantiated by our pre-clinical experimental trial of microencapsulated hUCMS transplantation into NOD mice with recent onset, autoimmune spontaneous T1D [10].

## Conclusion

T1D is a chronic metabolic disorder, burdened with high toll, for the affected patients, in terms of mortality and morbidity. While exogenous insulin administration continues to be mainstay for current management of the disease, this is not a cure. As a consequence, patients may survive but they are not protected from the risk of developing secondary, sometimes devastating complications of the disease. The only way may be the possibility of replacing diseased, insulin secreting beta-cells, with healthy and viable tissue that is able to provide a minute-by-minute, stimulus-coupled insulin secretory patterns, so as to thoroughly control hyperglycemia. While initial efforts, based on whole pancreatic or isolated islet cells from cadaveric donors, have substantially failed in offering a widespread treatment option to the large community of patients with T1D, novel strategies actually look at stem cell-

based therapy. Of the many possible options today envisionable, namely hESC, iPSC and hMSC, none has so far gained sufficient evidence of function. Early pilot clinical trials with these cells have started and are ongoing, but without consistent data. Intense study on insulin producing beta-like cell phenotypes, with special regard to reproduction of the sophisticated glucose sensing apparatus physiologically active in normal beta-cells is more than necessary. Likewise, validation of suitable immunoprotection devices, namely microcapsules and scaffolds made of biocompatible materials is in progress. Only achievement of a stable prototype of these new artificially fabricated cells, proven able to fully and substantially reverse hyperglycemia, within a biohybrid construct, will permit initiation of early pilot clinical trials in patients with T1D with likelihood of success.

## References

1. Rickels MR, Robertson RP (2018) Pancreatic islet transplantation in Humans: Recent progress and future directions. Endocrine Rev 40(2): 631-668.
2. Ricordi C, Goldstein JS, Balamurugan AN, Szot GL, Kin T, et al. (2016) National Institutes of Health-sponsored clinical islet transplantation consortium phae-3 trial: Manufacture of a complex cellular product at eight processing facilities Diabetes. Diabetes 65(11): 3418-3428.
3. Pagliuca FW, Millman JR, Gürtler M, Segel M, Van Dervort A, et al. (2014) Generation of functional human pancreatic β-cells in vitro. Cell 159: 428-439.
4. Rezania A, Bruin JE, Arora P, Rubin A, Batushansky I, et al. (2014) Reversal of diabetes with insulin-producing cells derive in vitro from human pluripotent stem cells. Nat Biotech 32: 1121-1133.
5. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, et al. (2007) Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131: 861-872.
6. Monia Cito, Silvia Pellegrini, Lorenzo Piemonti, Valeria Sordi (2018) The potential and challenges of alternative sources of beta-cells for the cure of type 1 diabetes. Endocr Connect 7(3): R114-R125.
7. Cheng SK, Park EY, Pehar A, Rooney AC, Gallicano GI (2016) Current progress of human trials using stem cell therapy as a treatment for diabetes mellitus. Am J Stem Cells 5(3): 74-86.
8. Rekittke NE, Ang M, Rawat D, Linn T (2015) Regenerative therapy of type 1 diabetes mellitus: From pancreatic islet transplantation to mesenchymal stem cells. Stem Cells International 2: 1-22.
9. Montanucci P, Alunno A, Basta G, Bistoni O, Pescara T, et al. (2016) Restoration of T cell subsets of patients with type 1 diabetes mellitus by microencapsulated human umbilical cord Wharton Jelly-derived mesenchymal stem cells: an in vitro study. Clin Immunology 163: 34-41.
10. Montanucci P, Pescara T, Alunno A, Bistoni O, Basta G, et al. (2018) Remission of hyperglycemia in spontaneously diabetic NOD mice upon transplant of microencapsulated human umbilical cord Wharton Jelly-derived Mesenchymal Stem Cells (hUCMS). Xenotransplantation 15: e12476.

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**Riccardo Calafiore.** Biomed J Sci & Tech Res



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