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Perspective

Opposites in the Clinical Translation of Stem Cells in the Treatment of Diabetes: A Middle Eastern Perspective

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Perspective

The biotechnology and pharmaceutical enterprises apparently lead the world in advancement while working under rigid directions set by healthcare regulatory bodies. The current enthusiasm over the capacity of stem-cell therapy to enhance results and ultimately cure diseases is comprehensible. Adjustable pathways are being progressively developed to accelerate the approval and advancement of therapies for critical conditions or unmet medical needs. Yet, regulatory organizations around the world are under immense pressure from powerful lobbies looking to loosen meticulous and traditional guidelines of safety and efficacy. New regulatory emendations in Japan now permit regenerative medicine products to be commercialized on the premises of solely prefatory evidence of safety and decreased thresholds for adequate therapeutic efficacy. In the United States, the designation of "Regenerative Advanced Therapy" was created by the 21st Century Cures Act of 2016 (Public Law 114-255) to advance the progress of these products and boost their regulatory assessment. This movement is steered by profit-oriented excitement for stem cell-based products which provide the latest mechanisms to tackle various diseases ranging from Alzheimer's to diabetes. Although promising, stem-cell–based therapy remain experimental and unproven with absence of compelling evidence from well-controlled clinical trials, except those derived from peripheral blood or bone marrow for hematopoietic reconstitution, which are widely accepted standards of care. Nevertheless some commercial stem-cell centers and clinics throughout the Middle East and many other countries now assert that stem cells are capable of restoring health, because they can sense their microenvironment and differentiate in a pattern that repairs any defect without gathering enough evidence on safety and efficacy, ultimately offering a wide range of cell therapies for a giddying range of medical needs.

Many of these clinics and centers claim that their offered regenerative therapies are quite safe because they use cells from an autologous source subjected to minimal manipulation—thereby bypassing regulatory supervision—and market such interventions outside the setting of clinical trials, directly through the Internet and social media platforms like Youtube, Facebook, and Twitter [1]. Unreliable reports without hard evidence to demonstrate the effectiveness of cellular products, and a huge industry advocating stem-cell therapy has emerged, which the FDA, ministries of health, and health regulatory agencies are powerless to control. This insufficiency of scientific evidence is alarming. The literature is crowded with examples of therapeutic procedures conducted based on specialist perspective and patient approval that eventually proved ineffective or harmful when studied in well-controlled trials comparing them with the standard of care.

In a recent paper published in Journal Nature Cell Biology, Löf-Öhlin et al. [2] describe how using human stem cells can produce insulin-producing cells that in the future can be transplanted into diabetes patients. Diabetes Mellitus (DM), is the leading cause to a number of complications and in many cases be potentially fatal. Although targeted therapies that promote the production of sufficient insulin have proved successful in the management of diabetes in patients, the replacement of lost beta cells holds theoretical appeal that pancreatic functional beta tissue could be restored. One approach to the treatment of DM in clinical trials requires the transplantation of a product called PEC-Direct™ which delivers stem cell-derived pancreatic progenitor cells in a device designed to allow direct vascularization of the cells, and is being developed for patients with Type 1 diabetes (T1D) that are at high risk for acute complications, including coma and death. The PEC-01 progenitor cells are designed to mature into human pancreatic islet cells, including glucose-responsive insulin-secreting beta cells, following implant [3]. To date, a considerable amount of patients have been treated with stem cells derived from different human sources (produced in accordance with Good Manufacturing Practice standards) in clinical trials authorized by the FDA; the initial outcomes of these trials suggest a favorable safety profile, but the reality is that translation to successful treatments in humans may not be readily achievable [4].

In a milestone study, Ameriet al. identified GP2 as a specific marker of human Pancreatic Endoderm Cells (PECs) and demonstrated that isolated GP2+ PECs generate cultures enriched in glucose-responsive insulin-producing cells. By eliminating undifferentiated hESCs, this work suggests a safer route toward manufacture of endocrine cells for future diabetes cell therapy [5]. In another landmark study, Fiorina et al. revealed that immunologically based clinical trials performed so far have failed to cure Type 1 Diabetes (T1D), in part because these approaches were nonspecific. As the disease is driven by auto-reactive CD4 T cells, which destroy β cells, transplantation of Hematopoietic Stem and Progenitor Cells (HSPCs) has been recently offered as a therapy for T1D. The transcriptomic profiling of HSPCs in this study showed that these cells are deficient in Programmed

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Death Ligand 1 (PD-L1), an important immune parameter, in the T1D Non-Obese Diabetic (NOD) mouse model. Remarkably, the immune-regulatory molecule PD-L1 plays a key role in regulating/inhibiting activated T cells and hence maintains immune tolerance. Genetically engineered or pharmacologically modulated HSPCs over-expressing PD-L1 inhibited the autoimmune response *in vitro*, reversed diabetes in newly hyperglycemic NOD mice *in vivo*, and homed to the pancreas of hyperglycemic NOD mice. The PD-L1 expression defect was confirmed in human HSPCs in T1D patients as well, and pharmacologically modulated human HSPCs also inhibited the autoimmune response *in vitro*. Targeting a specific immune checkpoint defect in HSPCs may contribute to establishing a cure for T1D [6].

Moreover, in clinical trials for the treatment of T1D in patients by means of transplantation of stem cell-derived PEC-01 pancreatic progenitor cells. It is anticipated that T1D patients receiving the PEC-Direct implant will also no longer require insulin administration or glucose monitoring, effectively amounting to a functional cure. Like an organ transplant, the PEC-Direct product will be used in conjunction with immune suppression to prevent immune rejection of the implanted cells. While the requirement to take immune suppressive medications with PEC-Direct introduces some risk, it is expected that for the high-risk T1D patients, the benefit of a functional cure will far outweigh the potential risks. In an exercise of extreme caution, the investigators decided to give Edmonton Protocol medications, utilized for patients receiving islet transplants, will also be protective for PEC-Direct. The Edmonton Protocol has demonstrated a very good safety profile to date [7,8].

In stark contrast to the wisdom demonstrated by Ameriet al. and the prudence exercised by Fiorina et al. and the above mentioned clinical trials is the incautious treatment of T1D in Middle Eastern patients who undergo stem cell therapy by injecting poorly determined fractions of autologous bone marrow–derived stem cells in the pancreatic artery, harvested from the bone marrow or umbilical cord, isolated by magnetic cell sorting techniques (intended for research purposes only), and cultured. Such fraction has been outed as a source of regenerative stem cells and is used widely for treating spinal cord injuries, osteoarthritis, muscular dystrophy and Crohn's disease. Some of the above mentioned procedures were not presented scientifically and appropriately published in peer reviewed journals. They have been marketed in press conferences, newspapers, magazine interviews, and social media platforms, thus provide patients with false hope and misleading information. Local reports and articles join a small but growing medical literature emphasizing the dangers of such malicious application of cellular therapy [9].

While stem cells represent current curative strategies to repair and rejuvenate tissues impaired by injury or disease, much persists to be learned about how stem cells can be manufactured, expanded and delivered safely to merge into living tissue framework and restore function. The International Society for Stem Cell Research (ISSCR) has recently announced guidelines for clinical translation of stem cells [10]. The guidelines highlight the noticeable difference between the novel treatments that are developed on coherent preclinical evidence, proven in diligent clinical trials, and agreed for marketing after regulatory review and the unproven treatments that are provided by practitioners who are inexperienced regarding the biological and medical complications of stem cells or by hoaxers selling the present analogous of coconut oil. The presentation of autologous cellular "treatments" outside the exploratory clinical trial setting —and for gain basis —is an offensive infringement of professional and perhaps legal standards; it carries the danger of aggravating human health and breaches the well-established medical tradition of "first, do no harm".

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