ABSTRACT
Diabetes is now considered a growing global epidemic with sizable negative effects on patients’ quality of life and life expectancy, and escalating economic impact (41% growth in the past five year), now representing health care expenditure impact of 256 Billion/year in the US alone. Objectives of cellular therapies and regenerative medicine strategies for treatment of diabetes are to reverse the disease condition and prevent the development of the severe chronic complications that can affect most organ systems in a large proportion of patients over time. Cell based therapies include the combination of immunomodulatory approaches aimed at restoring self tolerance (i.e., in the case of autoimmune diabetes) and at inducing permanent acceptance of transplanted tissues (in the case of allogeneic donors), or immune protection (i.e., engineered microenvironment and/or encapsulation) so that the immune system can no longer destroy the new insulin producing cells introduced either by regenerating, reprogramming or replacement. Several approaches are currently under evaluation for restoration of beta cell mass. The prototype strategy for Replacement is pancreatic islet transplantation, which is now an approved procedure in several countries. Reprogramming from non insulin-producing cells or Regeneration strategies could represent an appealing alternative to overcome shortage of deceased donor organs for transplantation. The selection of the most appropriate source for insulin producing cells is still not defined and the selected alternatives between replacement, reprogramming and regeneration strategies will be further developed in pre-clinical model systems and pilot clinical trials, while carefully assessing safety, efficacy and cost-effectiveness, as well as the challenges imposed by scaling up the selected technologies to meet the demand of the millions of affected patients who could benefit from these strategies.

Diabetes is now considered a global epidemic with over 350 million patients affected worldwide and projected to surpass the 500 million mark within the next two decades. The economic impact of diabetes is also escalating with a 41% growth in the past five year, now representing health care expenditure impact of 256 Billion/year in the US alone.

Type 1 Diabetes is one of the most severe forms of the disease condition, where an autoimmune attack is responsible for the total or near-total destruction of the patient own insulin producing cells (beta cells) contained in the pancreatic islets (Islets of Langerhans) occurs. Objectives of cellular therapies and regenerative medicine strategies for treatment of diabetes are to reverse the disease condition and prevent the development of the severe chronic complications that can affect most organ systems in a large proportion of patients over time. In T1DM, the additional challenge of the underlying autoimmune condition imposes consideration of strategies that would restore self-tolerance or abrogate the effects of autoimmunity, so that the immune system can no longer destroy the new insulin producing cells introduced either by regenerating, reprogramming or replacement (e.g., transplantation of pancreatic islets or stem cell derived insulin producing cells). Abrogation of autoimmunity or its effects could be achieved by either tolerance induction strategies or immune protection (e.g., engineered microenvironment or selective permeability physical barriers like those introduced by micro-, conformal- or nano-encapsulation). Any therapeutic strategy, to be considered must avoid side effects such as those associated with life-long immunosuppression, which now limits the indications of adult islet transplantation to the most severe cases of T1DM.
Several approaches are currently under evaluation for restoration of beta cell mass. The prototype strategy for Replacement is pancreatic islet transplantation\(^1\), which is now an approved procedure in several countries, including Canada, England, Switzerland and Australia. A multicenter Phase III trial of transplantation of adult pancreatic islet has recently been completed in the US and is moving towards a Biological License Application (BLA). However, adult pancreatic islet transplantation will never provide a suitable source of insulin producing tissue, because of the limitation imposed by the scarcity of organ deceased donors in contrast with the epidemic prevalence of diabetes worldwide. Therefore, it becomes of critical importance to define effective strategies to develop a suitable, unlimited source of insulin producing cells. Stem cell differentiation\(^2,3\), Reprogramming from non-insulin-producing cells\(^4\) or Regeneration\(^5\) strategies, could offer such alternative.

Stem cells or beta cell regenerative strategies could very well replace islets transplantation in the near future. However, the jury is still out regarding the safest and most efficient approach. Strategies with human embryonic stem cells are approaching clinical trials for treatment of diabetes, such as those planned by the California-based ViaCyte, using an intermediate differentiation protocol in vitro, with final differentiation and beta cell maturation in vivo. A limitation of embryonic stem cell derived strategies, is that being allogeneic in nature they are susceptible to immune rejection in addition to autoimmune recurrence and they therefore require immunosuppression or immunosolation approaches. Because of the increased risk of cancer and teratoma formation using immunosuppression, most current approaches using embryonic derived insulin producing cells are focusing on retrievable macro devices with selective permeability for immunoprotection.

Current differentiation methods for autologous adult stem cells are attractive because once resolved the problem of autoimmunity with effective strategies for restoration of self-tolerance, these cell sources would not require any anti-rejection strategy. However, we still do not have a gold standard method for Adult Stem Cell to beta cell differentiation similar to what the ViaCyte protocol represents for hES cells. The basic idea behind reprogramming (also termed transdifferentiation) or epigenetic conversion\(^6\) is that even a terminally differentiated tissue might be converted into another under the appropriate conditions.

Earlier this decade, Ferber and colleagues pioneered this approach by delivering the Pdx1 gene (a vital regulator of pancreatic development and beta cell homeostasis)\(^7\) into recipient mice by means of adenoviral vehicles. Ectopic expression in the liver led to the activation of beta cell genes and dramatic reductions in blood glucose levels, which outlived the period during which the adeno virus was expected to remain in the system. Induction of Pdx1 expression appeared promising also in reprogramming human hepatic mesenchymal stromal cells in vitro\(^8\). Other groups reported similar results either with Pdx1 alone or together with other reprogramming genes, including Doug Melton group at Harvard, which recently reported that the transfer of three factors (Pdx1, Ngn3 and MafA) led to the reprogramming of pancreatic acinar tissue towards beta cells\(^9\). More recently, the Heimberg group at Vrije Universiteit in Brussels and collaborators described pancreatic acinar cell reprogramming and regeneration of functional beta cells following in vivo exposure to cytokines (namely, epidermal growth factor, EGF, and ciliary neurotrophic factor, CNTF), rather than by genetic modification\(^10\). Furthermore, the recent discovery that the Smad network of intracellular TGF-β regulators is involved in the regulation of β-cell proliferation may open new exciting opportunities for the restoration of β-cell function in patients with diabetes\(^11\).

In conclusion, while, the selection of the most appropriate source for insulin producing cells is still not defined and the selected alternatives between replacement, reprogramming and regeneration strategies will be further developed in pre-clinical model systems and pilot clinical trials, while carefully assessing safety, efficacy and cost-effectiveness, as well as the challenges imposed by scaling up the selected technologies to meet the demand of the millions of affected patients who could benefit from these strategies.

**Conflict of Interest:**
The Authors declare that they have no conflict of interests.

**References**