Type 1 diabetes (T1D) mellitus can best be characterized as a disorder of gluco-regulation due to the insufficient production of a single critical hormone: insulin. Since the middle of the last century the most efficient pharmacologic solution has been to administer the hormone to the patient daily. Increasingly sophisticated dosing schedules together with the availability of recombinant variants of the hormone have succeeded in granting normal lifespan to type 1 diabetics. Nevertheless, no matter the degree of sophistication, current even aggressive regimens have not proven capable of faithfully recapitulating the normal performance of the endogenous insulin producing beta cells in response to glucose. This limit leads to the inevitable principal causes of morbidity and mortality associated with T1D, namely the complications of kidney and heart together with ocular and neural diseases.

While insulin replacement continues to be the primary treatment, the need to establish physiologic gluco-regulation in order to avoid complications has led to multiple avenues of alternative interventions, most of which are at the experimental stage. What all of these interventions have in common, however, is the hurdle imposed by the immune system at the level of ongoing autoimmunity and, in some cases, at the level of transplant rejection by the host. Autoimmunity in T1D is characterized by an inflammatory response against the insulin-producing beta cells of the pancreas, a chronic inflammation around and in the pancreatic islets of Langerhans termed “peri-insulitis” and “insulitis”, respectively. As studied in the two classic rodent models of the disease (diabetes-prone Bio-Breeding, DP-BB, rat and non obese diabetic, NOD, prone mouse), early on in the acute phase of the immune attack the islets exhibit an abundant cell infiltration by mononuclear cells, macrophages and dendritic cells (DC). With time, T-cells become the major constituent of the insulitis and are responsible for the greatest beta cell damage and destruction. The clinical onset manifests once the number of surviving beta cells cannot secrete sufficient insulin to satisfy the body’s needs.

A strong genetic predisposition is a conditio sine qua non of T1D and a large body of studies support that key genetic susceptibility loci affect the genesis, function and survival of immune cell subsets. To understand the critical role played by the genetic predisposition in T1D, it is necessary to consider the processes that shape...
Evidence of beta cell regeneration promoted by bone marrow or stem cell allo-transplantation in new-onset disease NOD mice has been observed by several groups. On this basis we were not surprised to see that in the NOD mouse as well, abrogation of autoimmune activity is sufficient to promote regeneration or rescue of the insulin-producing beta cells in the host endocrine pancreas even after the onset of the disease. These studies suggest that, although the physiological state of islet cells tends towards a fully differentiated phenotype, the lack of autoimmune aggression, together with the “danger” signals generated by massive beta cell destruction may trigger processes inside progenitors (whether islet-resident or ductal epithelium-resident) that result in some degree of islet cell regeneration in T1D pathogenesis is then a dynamic process. Once self tolerance is lost and beta cells begin to be destroyed, the system reaches a new equilibrium in which the newly-differentiated beta cells are in turn eliminated by the ongoing autoimmune process.

Interestingly, we have recently shown that the in vitro treatment of DC with CD40, CD80, and CD86 antisense oligodeoxynucleotides (AS-ODN), reduce co-stimulatory molecule levels at their surface, producing functionally-immature DC capable of preventing or reversing new onset diabetes in the NOD mouse. This was accomplished while maintaining T-cell responsiveness to alloantigens in animals that received repeated injections of modified DC. Co-stimulatory depleted DC also augmented the number of T regulatory cells (Treg) that were CD4+ CD25+ Foxp3+ through short-range IL-7 signaling. We also are currently conducting an NIH-funded, FDA-approved phase I clinical trial that is designed to test the safety of AS-ODN-treated autologous DC into T1D patients with established disease (fig. 1). Leukocytes of the patient are obtained by apheresis and DC are generated in vitro from them and engineered in GMP facilities with the addition of AS-ODN. In turn, these DC, which express low levels of CD40, 80, and CD86, are injected into the patient by intradermal administration at an anatomical site proximal to the pancreas. DC will migrate to the nearest, i.e., pancreatic, lymph nodes, where they are able to interrupt the vicious circle that maintains islet-specific inflammation, i.e., insulitis. In the pancreas, DC acquire beta cell specific antigens from apoptotic cells, leading to the eventual display of these antigens to naive T-cells in the pancreas-draining lymph nodes. The lack of co-stimulatory molecules will result in an anergizing signal to the T-cells, induce regulatory immune cells (like Foxp3+ Treg), and interrupt the T-cell mediated anti-beta cell epitope-spreading phenomenon. Within the endocrine pancreas, once the insult of autoimmunity is abrogated, the physiologic process of regeneration might continue efficiently, eventually replenishing the population of insulin-producing cells to a number sufficient to maintain euglycemia, thus curing the diabetic recipient.

Thus far, we have not observed adverse events of any
sort, nor did the patients experience even subjective discomforts; the hematological and immunologic profiles after DC administration in all of the first six treated diabetic patients are similar if not identical to those measured at baseline pre-screening; there is no evidence of latent viral activation; there is no evidence of induction of any additional autoimmune reaction; there is no worsening of glycaemia or increased insulin requirements; physical examinations and all biochemistry is within the normal range.

**Conflict of interest**

The author declares he has no conflict of interest.

**REFERENCES**

Trucco M. Gene-environment interaction in type 1 diabetes mellitus


