ImmunoTools *special* Award 2014

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Cell-based immunotherapy for type 1 diabetes

Type 1 diabetes (T1D) results from autoimmune attack on the pancreas, directed against specialized insulin-producing β cells in the pancreatic islets of Langerhans. The incidence of T1D among children is increasing in many countries, particularly in children under the age of 15 years, with an overall annual increase estimated to be around 3–5% per year. The prevalence of this disease, its complications and the lack of effective curative and preventive strategies necessitates a significant effort to find the means to restore the tolerance to β cells as the best way to control this disease. In the past 15 years, multiple clinical trials have attempted to find prevention T1D. An ideal immunotherapy should inhibit the antigen-specific autoimmune attack, without systemic side effects, helping regenerative therapies to improve β-cell function and regenerate damaged tissue.

Apoptotic cells -an important source of autoantigens- are cleared by antigen presenting cells (APC) as soon as they appear. A high rate of apoptosis in pre-diabetes or defects in the removal of apoptotic cells contribute to autoimmune diseases, because they turn into late apoptotic bodies and necrosis, favoring inflammation, insulitis and autoimmunity. The synergism of cytokines in the insulitis exacerbates apoptosis, leading to pathogenic consequences. In this context, our interest has been drawn as to whether peripheral tolerance can be restored by 'vaccination' of antigen presenting cells loaded with antigen-specific apoptotic cells.

The main aim of this proposal is to re-establish immunological tolerance to β-cells using a cell-based immunotherapy in the prevention and reversal of autoimmunity of the disease. We have previously demonstrated the efficacy of a new antigen-specific immunotherapy in preventing T1D. Tolerogenic dendritic cells (tolDCs) loaded with apoptotic islet cells re-establishes immunological tolerance in a model of experimental diabetes non obese diabetic (NOD) mouse. The administration of these

tolerogenic cells to NOD mice decreased diabetes incidence and correlated positively with insulitis reduction [*Marin Gallen, S, 2009*]. TolDCs express low level of co-stimulatory molecules and acquire low and stable capability to stimulate autologous T cell proliferation and induce a cytokine profile typical for immature dendritic cells. Moreover, tolDCs acquire suppressive ability after the capture apoptotic cells; which is mediated, at least in part, by PGE_2 production, [*Pujol Autonell I, 2013*]. The tolerogenic behaviour of DCs after apoptotic islet cells efferocytosis points to a mechanism of silencing potential autoreactive T cells in the microenvironment of autoimmunity. Our results suggest that dendritic cells may be programmed to induce specific immune tolerance using apoptotic cells; this is a viable strategy for a variety of autoimmune diseases.

We aimed to use the protocol to generate human tolDCs. We plan to generate myeloid derived dendritic cells (MDDCs) from both healthy-blood donors and T1D patients. We want to determine the tolerogenic ability of tolMDDCs *in vitro* as a preliminary step for future immunotherapy. The characterization of DCs phenotype will be carried out, as well as the cytokine profile. The immunestimulatory capability of tolDCs will be determined in allogeneic mixed leukocyte reaction experiments, as well as, autologous T cell proliferation. Finally, phenotype and function stability will be tested with different proinflammatory stimulus.

The clinical relevance of the here proposed immunotherapy could be very important due its translational potential in pathologies that require the re-establishment of immunological tolerance (autoimmunity, transplantation, use of stem cells in regenerative medicine). Moreover, It should be pointed out that this treatment is antigen specific and does not compromise the correct function of immune system, unlike to the use of immunesuppressors.