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Abstract / project summary
Autoimmune diseases are the result of impaired immune tolerance and animal studies indicate that restoring antigen-specific tolerance permanently can constitute a cure. However, this is very challenging to achieve in humans, because they are highly heterogeneous in their genetic and environmental makeup, and the diseases multifactorial. Meanwhile, the incidence of these diseases is on the rise. This heterogeneity may be overcome by targeting multiple biological pathways of tolerance induction, specifically in disease-driving self-reactive T cells, and possibly within strategic tissue sites. Various combinations of drugs, biologics and/or tolerizing antigens have been tested in therapy, but each component acts independently in this case. What is missing is a single “tolerogenic interface” that enables the antigenic and multiple tolerogenic signals to act together and concomitantly on target T cells, resulting in optimal signal integration, and ultimately, optimal reprograming of these self-reactive T cells. The most clinically beneficial outcome is the reprograming into antigen-specific regulatory T cells (Tregs), which are long-lived and have the ability to perpetuate tolerance by suppressing autoimmune responses to other disease-relevant antigens (infectious tolerance). Dendritic cells (DCs), already tested in the treatment of a variety of human diseases, are among the most versatile antigen-presenting cells that can be manipulated for this purpose. However, the creation of customized and complex interfaces consisting of relevant antigens and optimal combinations of tolerogenic signals has not yet been achieved. With this Exploratory/Developmental grant, we propose to engineer new DC-based tolerogenic interfaces whose components are delivered as mixtures of mRNA by electroporation. Under Specific Aim 1, we will test the expression of several antigens and tolerogenic products in this system, and identify combinations that can most efficiently reprogram diabetogenic T cells into Tregs. The major goals are to find signaling pathways that synergize in inducing highly functional and stable Tregs, and to generate Tregs *in vivo* that are capable of mediating long-lasting protection from disease. Under Specific Aim 2, we will use the same mRNA-based manipulation approach to overexpress specific homing receptors in DCs. The goal is to enhance the migration of tolerogenic DCs to the pancreatic lymph nodes, where diabetogenic T cells are primed, or to the pancreatic islets, where they exert their pathogenic function. DC-based cell therapies have been increasingly tested in clinical trials to treat human disease, mostly cancer, and more recently for autoimmunity. These studies suggest that DCs are devoid of the adverse effects of many drugs and biologics tested to date. The development of tolerogenic DCs that (1) target specific T cells, (2) engage them through multiple biological pathways for efficient reprograming into Tregs and (3) accumulate better and preferentially in relevant tissues will greatly improve both efficacy and safety of cell-based therapies for autoimmune diseases.