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Project Summary

The development of Type 1 diabetes (T1D) is due to faulty induction and maintenance of self-tolerance. Genetic factors that confer increased risk for T1D development encode HLA and immunomodulatory molecules and these factors likely collaborate to promote immune cell-mediated attack of pancreatic islets. Abnormalities are observed in immunoregulatory cell populations of T1D patients and in the T1D susceptible Non Obese Diabetic (NOD) mice. However, functional studies of immune regulatory cell populations in T1D patients have been restricted to analysis of PBMCs after T1D onset. Therefore, it is unclear which abnormalities are genetically programmed and which are consequences of a cascade of immunological events from progression of T1D. It is clear that T1D susceptibility is transferred in hematopoietic stem cells (HSCs) in both mouse and man, suggesting that intrinsic defects in hematopoietic cells contribute to development of autoimmunity. We have developed a humanized mouse model in which robust human immune systems are generated from adult bone marrow HSCs. The human T cells that develop in these mice are diverse, functional, self-tolerant, and enriched for naïve subsets compared to the donors. This "Personalized Immune" mouse model permits systematic analysis of immunoregulatory populations derived from healthy controls and individuals with T1DM. We hypothesize that the genetic predisposition to T1DM is associated with hematopoietic cell-intrinsic abnormalities affecting induction and maintenance of self-tolerance. We will use the Personalized Immune mouse transplanted with allogeneic human thymus and CD34+ HSCs from control and Type 1 diabetic subjects to analyze the evolution of two tolerogenic cell types implicated in the pathogenesis of T1D regulatory T cells and dendritic cells. In addition to monitoring development and peripheral reconstitution of these cells, we will assess (1) suppressive function of regulatory T cells, and (2) presentation/stimulation function of primary dendritic cells developed from control and T1DM-derived HSCs. We will also develop a model of autoimmune insulitis with the Personalized Immune mice (3). The objective of these studies is to gain insights into the intrinsic functional defects in regulatory T, and dendritic cells that differentiate from the HSCs of T1D patients. Identification of defects in the immunoregulatory populations analyzed here will help guide treatment strategies in T1D patients, and an individualized immune mouse model of autoimmune insulitis will provide a useful system in which to test the efficacy of new treatment strategies.