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The study of autoimmune diseases such as Type 1 diabetes (T1D) has been limited by the incomplete fidelity of animal models. Studies in patients have been limited by lack of access to lymphocytes from disease sites and by patient heterogeneity with respect to disease duration, treatments, genetic backgrounds and environmental triggers. Thus, high levels of "scatter" are seen in immunologic assays and underlying pathophysiologic mechanisms remain obscure. We have developed a "Personalized Immune" (PI) humanized mouse model that overcomes these limitations by allowing synchronized *de novo* development, in immunodeficient mice, of highly functional human immune systems from hematopoietic stem cells (HSCs) of T1D patients and healthy controls. T cells develop, from progenitors in patient CD34+ cells, in T cell-depleted, partially HLA-matched human fetal thymus tissue grafts. We now propose to develop this model further to explore the potential for stem cell-derived β cell islet replacement therapy in the context of an autoimmune T1D-derived human immune system. Induced pluripotent stem cell (iPSC)-derived β cells could potentially allow autologous islet replacement in diabetic patients and also have utility in modeling T1D in humanized mice. However, there is currently no information about the potential immunogenicity of these cells compared to normal adult pancreatic islet β cells in the presence of autoimmunity. T1D-associated genetic polymorphisms expressed by β cells themselves may contribute to disease susceptibility. We will develop a model comparing immunogenicity of healthy control-derived and T1D-derived β cells in the presence of an autoimmune autologous immune system. Moreover, stem cell-derived β cells may also have utility as an "off-the-shelf" product for allogeneic transplantation, necessitating exploration of their immunogenicity in an allogeneic context. Additionally, the impact of autoimmunity on rejection of allogeneic natural or stem cell-derived β cells requires assessment. We have now generated iPSCs and differentiated β cells from skin fibroblasts of the same T1D patient and healthy control volunteers donating bone marrow for construction of PI mice. We propose to: 1) Further develop this model to induce β cell autoimmunity; and 2) Use this model to compare the immunogenicity of iPSC-derived β cells vs "natural" β cells used as islet replacement therapy in the context of both anti-β cell autoimmunity and alloimmunity. These studies will establish important models for understanding T1D pathogenesis, using stem cell-derived β cells to model immunotherapies and optimizing the potential of stem cell-derived β cell therapy to replace islets in T1D.