Dr. Megan Sykes

The study of autoimmune diseases such as Type 1 diabetes (T1D) has, until recently, been limited by the insufficiency of animal models and by the restriction of human patient samples to peripheral blood, which may not reflect immunity in the end organs. Moreover, patient populations are heterogeneous with respect to the duration of disease, treatments, comorbidities, genetic background and environmental exposures, making it difficult to identify pathophysiologic mechanisms. We have developed a "Personalized Immune" (PI) humanized mouse model that overcomes these limitations by allowing synchronized *de novo* development, in immunodeficient mice, of functional human immune systems from hematopoietic stem cells (HSCs) of Type 1 diabetic (T1D) patients and healthy controls (HCs). T cells develop in human thymus grafts from CD34+ HSCs in cohorts of mice generated from a small bedside bone marrow aspirate. We now propose to develop this model further as an individualized model of human T1D biology, incorporating complete immune systems and stem cell-derived β cells from the same T1D patient and healthy control donors. We have demonstrated *in vivo* function of β cells generated from iPSCs from skin fibroblasts of the same T1D patient and HC volunteers used to construct PI mice. We propose to further develop this model to induce β cell autoimmunity that attacks iPSC-derived β cells. We will:1) **Optimize the functionality of human immune systems generated from adult HSCs** by improving human APC repopulation and lymphoid structure and generating autologous thymic epithelial cells (TECs) from iPSCs derived from adult donors. Generation of TECs from iPSCs will provide autologous HLA/peptide complexes for positive selection of T cells that optimally interact with autologous APCs in the periphery. Readouts of immune function in all studies will include antibody, proliferative and cytokine responses to antigens used for immunization and ability to control EBV infections; 2) **Optimize the use of iPSC-derived β cells as a target for autoimmunity in PI mice and compare the immunogenicity of T1D- vs HC-derived iPSC-derived β cells and of "natural" β cells**. We will develop methods of enhancing the purity of iPSC-derived endocrine cells, optimize implantation methods and sites and characterize the immunogenicity of iPSC-derived endocrine cells that mature *in vivo* in comparison to adult human pancreatic islet β cells from T1D and HC subjects; 3) **Develop an insulitis/diabetes model in PI mice**. We will attempt to induce insulitis against the native pancreas and autologous iPSC-derived β cells in PI mice using a variety of manipulations. This optimized PI mouse will serve as a "gold standard" baseline in which to apply improvements in the ability to generate iPSC-derived β cells and HSCs, visualize immune interactions that initiate and drive T1D and assess environmental precipitants of disease. Through the Consortium, the model will allow analyses of both early and late events involved in T1D pathogenesis, and serve as a model to build upon as methods of expanding or generating HSCs from iPSCs and other technologies advance.