Development of T1D in Humanized Mice Engrafted with Tissues from Autoimmune Donors

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Purpose: Our understanding of type 1 diabetes (T1D) pathogenesis has been advanced greatly by rodent model studies. However, rodents are not humans. Further, current imperfect assays for the analysis of human diabetogenic T cell populations *in vivo* have limited our capabilities to elucidate human T1D pathogenesis, and to test immunotherapies without placing individuals at risk. The availability of spleen, bone marrow, and thymus tissues from T1D and islet autoantibody-positive cadaveric donors as well as the availability of peripheral blood mononuclear cells (PBLs) from living T1D donors provides a unique opportunity to analyze the diabetogenic function of these cell populations following engraftment in newly developed "humanized" mouse models.

Methods: We have developed several novel NOD-scid IL2rnull (NSG) HLA-transgenic humanized models optimized for human hematolymphoid engraftment. These mice support high levels of engraftment with human hematopoietic stem cells (HSC) and mature human lymphoid cells. We have observed that transplanting human spleen cells or PBLs from T1D donors into HLA-class I-matched recipients can induce insulitis, but not overt diabetes. One constraint is the short duration of these experiments due to the development of xeno-GVHD, as the engrafted human T cells respond to murine MHC. Another constraint is the lack of HLA matching between the donor cells and the recipient's HLA class II alleles. To further refine the NSG model, we have recently developed strains of NSG mice that express human MHC (HLA) class I but are deficient in murine MHC class I. We also have developed NSG-HLA-class II transgenic mice that are deficient in murine MHC class II. These NSG mice deficient in murine MHC class I or class II expression display reduced xeno-GVHD responses following human T cell engraftment, permitting longer experimental observation periods.

Summary of Results: We are currently matching the lymphocytes obtained from T1D donors and NSG mouse recipients at both HLA class I and class II alleles in combination with knocking out the mouse MHC class I or class II alleles to determine whether the insulitis will progress to overt diabetes in these recipients. In addition, we have initiated experiments using hematopoietic stem cells from T1D donors engrafted into optimized NSG-HLA transgenic mice matched with the donor's HLA class I and class II alleles.

Conclusions: Based on the induction of insulitis when using HLA Class I matched PBLs from T1D donors, the use of these newly developed mouse strains may permit the recapitulation of human T1D where actions of potential therapies can be examined and manipulated.