Dr. Robert Winchester

Recently an advance in modeling the human immune system in mice was reported, involving thymic maturation of human bone marrow hematopoietic stem cells in immunodeficient mice receiving partially HLA-matched human fetal thymic tissues to recreate the donor‘s individualized functional T and B cell repertoires. The functional and diverse human T cell repertoire of these mice resemble the donor repertoire in tolerance of self and non-self recognition, but is distinguished by being recreated at an earlier period of development, predominantly consisting of naïve phenotype T cells. Intriguingly, T1D patient stem cells engender a similarly diverse T cell repertoire, but which exhibits much more maturation towards memory-effector phenotype. This suggests T1D susceptibility genes contained in the stem cells foster the development of autoimmunity. We propose an exploratory study to examine the feasibility of applying this methodology to recreate in the mouse the T and B cell repertoires of RA patients at a stage prior to the development of autoimmunity and disease that will enable determining the role of susceptibility genes on abnormalities in lymphocyte development, selection and regulation underlying the development of RA. This will provide an experimental model of RA based on the human RA immune system and its determinative genes that can be subsequently studied with all of the technology of murine genetics and experimental immunology, and using interventions that would not be possible in a patient. In Aim1 of this preliminary project we will determine the feasibility of reconstituting the RA patient’s immune system in a state antecedent to development of disease, and acquire preliminary data on the differing immunologic character of the reconstituted immune systems as a function of the contribution of MHC susceptibility genes and the rate and extent to which the individual reconstituted RA immune systems progress to self-reactivity and autoimmunity. In Aim2 we explore the potential of immunization with adjuvant or citrullinated proteins and administration of cultured fibroblastoid synovial lining cells to accelerate the progression of autoimmune manifestations, and determine whether dominant donor CD4+CD28null subset clonotypes are recreated in the reconstituted immune system.
