Mohsen Khosravi Maharlooei, MD

Cloning and sequencing of T cells and their receptors from blood, islets and pancreatic lymph nodes of Type 1 Diabetes (T1D) patients has led to the discovery of “public” (i.e., shared) T cell receptors and new specificities of human islet antigen-reactive T cells. Some of these clones recognize peptides endogenously produced from proinsulin (“Type A” clones), whereas others recognize only insulin peptides but not proinsulin protein (“Type B” clones). Others are specific for peptide fusions derived from insulin and other proteins (hybrid insulin peptides, HIPs). Using humanized (HU) HLA-transgenic (Tg) mice constructed with human thymic tissues expressing risk-associated HLA and a human TCR transgene, we have demonstrated the diabetes-initiating capacity of a Type B insulin-reactive TCR. This model provides an opportunity to assess the diabetogenic properties of autoreactive TCRs in the absence of graft-versus-host reactivity and allows temporal assessment of the evolution of epitope spreading and insulitis. Using this model, the ability of known and newly-identified Type A, Type B and HIP-specific human insulin-specific TCRs and of HLA-A2-restricted islet antigen TCRs to initiate diabetes will be investigated. The temporal evolution of insulitis, including the TCR repertoire of islet-infiltrating T cell populations harvested from the islets at various times will be evaluated. Together, these studies will integrate data from a humanized mouse model of autoimmune diabetes with data from T1D donors, providing new insights into T1D pathogenesis, a new pipeline for the identification and functional analysis of islet-reactive T cells, and a new platform for testing novel immunotherapies for T1D.