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Regulatory T Cell Function in a Mouse Model of Sjögren’s Syndrome
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Lay Abstract
Sjögren’s syndrome is a devastating autoimmune disease that is characterized by lymphocyte-mediated inflammation of lacrimal and salivary glands, resulting in dry mouth and dry eyes. The etiology of Sjögren’s syndrome is complex and likely involves multiple immune cell types including T cells. We have discovered that mice whose T cells lack an enzyme called PI3K spontaneously develop several pathological hallmarks of Sjögren’s syndrome. This mouse model represents a novel tool for studying the pathogenesis of Sjögren’s syndrome. In this proposal we hypothesize that T cell dysfunction, in particular defects of immunosuppressive regulatory T cells, are an important causative factor in the autoimmune phenotype in these mice. We propose a series of experiments that will test regulatory T cell function and development in our model.

Scientific Abstract
Phosphoinositide 3-kinase (PI3K) plays a complex role in T cell development and function, as both augmented and diminished PI3K signaling results in autoimmunity. We have shown previously that TdKO mice, which lack class IA PI3K activity specifically in T cells, develop autoimmune exocrinopathy that resembles the human disease Sjögren’s syndrome (SS). TdKO mice have impaired peripheral tolerance with reduced CD4+CD25+FoxP3+ regulatory T cell (Treg) populations in the periphery despite normal numbers in the thymus. Preliminary data show that naïve CD4+ TdKO T cells have reduced Treg differentiation in vitro while displaying normal Th17 differentiation, suggesting that Treg induction in the periphery is impaired. Furthermore, TdKO Tregs have reduced suppressive function in vitro. In this proposal we will further characterize Treg function and look at differentiation of Treg, Th9, and Th17 cells to delineate the T cell-dependent mechanisms that are mediating the autoimmune phenotype in this novel model of SS.