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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.