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*Epigenetic Profiling of Multiple Cell and Tissue Types in Sjögren’s Syndrome*  
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**Lay Abstract**  
Although the cause of Sjögren’s Syndrome (SS) remains unknown, it is clearly complex with important contributions from both genetic and environmental factors. New molecular genetic assays offer an extraordinary opportunity to accelerate progress in the identification of epigenetic mechanisms for complex human autoimmune diseases such as SS. Epigenetic modifications, such as methylation of the 5’ carbon of cytosine which occurs in the context of CpG dinucleotides, do not affect the genetic sequence; however, they do play a critical role in gene regulation. Methylation of DNA can be detected on a large scale basis using recently developed high-throughput technologies. We propose to apply these assays to a very well characterized collection of SS cases and controls developed by the Sjögren’s International Collaborative Clinical Alliance. The identification of unique epigenetic profiles in SS will significantly transform our understanding of SS etiology, and may lead to more effective approaches to prevention, diagnosis and treatment.

**Scientific Abstract**  
Epigenetic modifications, such as DNA methylation, do not affect the genetic sequence; however, they do play a critical role in transcriptional regulation of genes and subsequent gene expression. Methylation of DNA can be detected on a large scale basis using recently developed high-throughput technologies. We propose to perform a comprehensive screen of 27,578 highly informative CpG sites spanning 14,495 genes across the genome using DNA derived from peripheral blood mononuclear cells (PBMCs), saliva and labial salivary gland biopsy tissue from 30 Sjögren’s Syndrome cases and 30 controls to identify epigenetic profiles associated with disease susceptibility (Aim 1). We will also collect fresh blood samples to perform epigenetic studies in specific cell types following utilization of sophisticated cell sorting techniques (Aim 2). The identification of unique epigenetic profiles in Sjögren’s Syndrome will significantly transform our understanding of disease etiology, and may lead to more effective approaches to prevention, diagnosis and treatment.