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*“Receptor-mediated siRNA delivery in Sjögren's Syndrome”*

***Recipient of Research Grant Award***

**LAY ABSTRACT:**

Sjögren’s Syndrome (SjS) is characterized by dry mouth and dry eyes. Research indicates that dryness in SjS is mediated by cytotoxic immune cells and autoantibodies. Interestingly, our studies on the salivary glands suggest that pathological changes in the glands occur even before immune cells are found in the glands, which appears to be critical for vulnerability of salivary glands to immune cell attack. To disrupt the pathological changes in the glands, we propose to utilize the latest breakthrough in therapeutics called siRNA (short-interfering-RNA), which silences problematic genes inside of cells. We will specifically investigate if ligands for muscarinic receptor (MR) on fluid secreting cells, such as carbachol or a clinically-proven Evoxac®, can deliver siRNA into the cells. If this is proven to be successful, it will become possible that taking Evoxac® capsules can alter gene profiles to make epithelial cells more resistant to pathological stimuli, restoring secretory dysfunction in SjS.

**SCIENTIFIC ABSTRACT AND RESEARCH PROPOSAL:**

During recent years, research interests in Sjögren’s Syndrome (SjS) have focused on strategies of immune modulation by altering adaptive immune responses. Our studies utilizing animal models indicate disrupted glandular homeostasis in the salivary glands precedes SjS-like disease onset, subjecting the salivary glands to immune cell infiltration and subsequently loss of secretory function. Based on our expertise on muscarinic type-3- receptor (M3R), we hypothesize that ligands specific for MR can deliver siRNA into cells via receptor-mediated endocytosis, altering epithelial cell responses to external cues such as pro-inflammatory or death signals. To investigate our innovative hypothesis, we propose 3 specific aims. Specific Aim 1: Test if a MR agonist, carbachol, delivers siRNA via M3R internalization. Specific Aim 2: Test if a clinically proven agonist for MR, cevimeline, delivers siRNA. Specific Aim 3: Investigate if a carbachol (or cevimeline): streptavidin: caspase-3 siRNA conjugate can reduce cytokine-induced cell death of HSG cells in vitro.