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*“B cell-expressed COX-2 and Sjögren’s syndrome development”*

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**LAY ABSTRACT:**

Sjögren’s Syndrome is an autoimmune disease which targets glands producing saliva and tears. Locally activated B lymphocytes are responsible for producing autoantibodies that block glandular function and lead to dry mouth and eyes. For reasons that have not yet become clear, B cells in the affected glands have a heightened risk of developing into malignant lymphoma. This project will begin to analyze whether the capacity of dividing B cells to produce an enzyme, COX-2, and its product, prostaglandin E2, is critical both for the production of the disease-inducing auto-antibodies and lymphoma. Evidence that this is the case would validate the use of new therapies for this disabling disease.

**SCIENTIFIC ABSTRACT AND RESEARCH PROPOSAL:**

Sjögren’s syndrome (SS) is an autoimmune disease primarily targeting the salivary and lacrimal glands. B lymphocytes play a major role in this condition, at least in part, by generating the pathogenic autoantibodies that lead to gland dysfunction. Additionally, the chronic in situ B cell activation leads to a significantly greater than normal risk for B cell lymphoma. The proposed project is based on this laboratory’s working hypothesis that prostaglandin E2 (PGE2) produced by replicating B cells is critical to the pathology associated with SS. On the basis of several recent findings, it is highly suspected that PGE2-mediated phosphorylation (activation) of activation-induced cytosine deaminase (AID) may contribute both to the development of somatically mutated, pathogenic IgG autoantibodies and to the development of lymphoma. In order to critically examine whether B cell PGE2 production contributes to SS, an in vivo model is most important. The project’s immediate goal is to use the Cre/LoxP recombination system to specifically inactivate the rate limiting enzyme for PGE2 synthesis, i.e. COX-2, within B cells of mice with a known predisposition to SS. A newly generated floxed COX-2 transgene and well-described CD19-Cre transgene will be backcrossed onto the NOD.B10 background. Subsequent breeding steps will generate experimental mice with COX-2 selectively inactivated in the B cell lineage from the pro-B cell stage onward. Completion of this project is an essential step to generating an important mouse model for understanding SS development in humans.