2019Joint Usage and Research Report

Title of Research Project		Role of AKT and the lysosome regulation in the induction of lymphoma in Sjogren's syndrome patients
Applicant	Institution	National Institute of Dental and Craniofacial Research,
	Job title and name	Senior Investigator
Visiting researcher	Name	John Chiorini
Purpose of the Research Project (approx. 250 words)		A major problem facing medicine today is defining the mechanism associated with the onset and symptoms of disease and developing treatment for them. With the reported increase in the prevalence and incidence of autoimmune diseases this group of diseases represents a major health concern. Sjögren's syndrome is the second most common autoimmune disease and is estimated to affect over 35 million individuals worldwide. This disease is characterized by a poor quality of life due to secretory epithelial cell dysfunction with dry mouth and dry eyes, lymphocytic infiltration within the affected salivary gland tissue, development of autoantibodies, and a 30 fold increased risk of developing lymphoma. Several viruses have been associated with inducing a Sjögren's syndrome like condition including HTLV-1, HIV, and HCV. Currently, no effective treatment exists for Sjögren's syndrome and our understanding of the mechanism associated with the increased risk of lymphoma is not clear. The purpose of this research project is to investigate the molecule changes that occur in Sjögren's associated lymphomas and identify target therapies for intervention.
Development of the Research Project and Results (approx.. 850 words)		Our approach to understand the underlying mechanism of SS has been to first, dissect the transcriptome of minor salivary gland (MSG) from patients (*e.g.*, SS and non-SS) that are routinely collected for SS clinical evaluation. We have reported that altered expression of the cytokine bone morphogenetic protein (BMP6) is likely associated with the most common symptom of primary SS (pSS), the loss of salivary gland function in some patients. These results have suggested a novel therapy to restore gland function in these individuals. Through a collaboration with Professor Atsumi in the Hokkaido medical school, we have expanded our analyzes of the transcriptomes from a diverse group of SS patients that present with different sets of symptoms. We are presently examining network changes that may explain characteristics of this disease, primarily pathways associated with endoplasmic reticulum (ER) stress and constitutive activation of the unfolded protein response (UPR). This proposal will focus on one marker of this pathway, LAMP3, which is upregulated in the MSG of pSS patients and in our preliminary experiments can induce a change in Akt and mTOR phosphorylation suggestive of a change in cellular state (*e.g.*, induction of apoptosis and autophagy). The goal of this grant proposal is to: 1) Characterize LAMP3 expression in the salivary glands of pSS and non-pSS patients and understand the correlation between LAMP3 expression and the patient characteristics, 2) study the relationship between LAMP3 expression and ER stress response, and 3) role of LAMP3 in salivary gland exocytosis. Correspondingly Dr. Noguchi' s laboratory has discovered by means of yeast two hybrid screening using full-length Akt as a bait and RNA aptamer technology, a connection with critical proteins and regulatory

	RNA molecules in the activation of the lysosome and autophagy. Dr Noguchi's lab recently identified RNA aptamer specifically recognize PI3P, which inhibits autophagy. The collaborative work with Dr. Noguchi's laboratory should clarify the role of Akt and autophagy in the induction of lymphoma in Sjogren's syndrome patients. In this research proposal, we will use recombinant DNA experiments as well as animal studies. This research is part of an international effort to understand the transcriptome of Sjogren's syndrome and how it results in the complex set of phenotypes associated with Sjogren's syndrome and lymphoma. The role of LAMP3 in lysosomal function has not been as well studied as that of other LAMP protein and its increased expression in Sjogren's syndrome suggests an important role in autoimmunity and the cell death associated with the SS. The work by Drs. Chiorini and Noguchi provides new insight into what this role might be as a regulator of cellular state by modulating Akt and mTOR activity. The proposed project will expand on this as well as explore LAMP3's role in autoantigen presentation and developing animal models of altered LAMP3 expression. It is likely that these new concepts will influence global research on other forms of autoimmunity. Over the past 25 years, our understanding of the biochemical mechanisms underlying cell death has expanded greatly. However, the connections between the signal for cell death, survival, and the initiation of disease are not clear. LAMP3 and lysosomal function has not been previously understood as a possible key regulator of this activity. The innovation in our project is to link autophagy/apoptosis and the lysosome with autoimmunity.
Publication *Enter the names of conference or journal and its vol. No. where the above work was presented.	【Conference, symposium, workshop etc.】 An abstract on this joint project will be presented at the upcoming International Sjogren's syndrome meeting Dr. Chiorini and Prof. Noguchi both presented seminars at Chiba University and agreed to collaborate with Prof. Nakajima on the role of autophagy in autoimmune disease.
	【Journals】 A manuscript is in revision for Science Reports (Tanaka et al. Lamp3 induces Stall autophagy and apoptosis in Sjogren's Syndrome Patients). Prof Atsumi and Noguchi (Hokkaido University) and Tsutomu Tanaka (former Post Doc from Prof Noguchi's lab , and Toshio Odani (former Post Doc from Prof Atsumi's lab) both from Hokkaido University are co-investigators on this project. A review is accepted for Cell Death and Disease (Noguchi et al. Autophagy as a modulator for the cell death machinery). This is a collaboration that came about from the visit with Prof. Nakajima at Chiba University. A review article was accepted for Modern Rheumatology (Odani et al. Targeting primary Sjögren's syndrome). Odani (former Post Doc from Prof Atsumi's lab) is from Hokkaido University and co-investigators on this project. A manuscript was accepted for Biochem Biophys Res Commun. (Donia et al. Identification of RNA aptamer which specifically interacts with PtdIns(3)P)). Prof Noguchi (Hokkaido University) and Tsutomu Tanaka (former Post Doc from Prof Noguchi's lab is from Hokkaido University and co-investigators on this project.