2016Joint Usage and Research Report

Title of Research Project		Role of LAMP3 in autoimmunity
Applicant	Institution	National Institutes of Health (USA)
	Job title and name	Principal Investigator
Visiting researcher	Name	John Chiorini
Purpose of the Research Project (approx. 250 words)		We are collaborating with the University of Hokkaido to identify the mechanism of cell death in Sjogren's Syndrome patients and its connection to autoimmunity as well as characterize the changes in cellular gene expression.
Development of the Research Project and Results (approx.. 850 words)		Primary Sjögren's Syndrome (pSS) is a systemic autoimmune disorder that affects an estimated 1% of the American population with a strong gender bias of 9:1 toward females. pSS is characterized by exocrine gland lymphocytic infiltration and dysfunction, as well as autoantibody formation. The conventional explanation of salivary gland dysfunction assumes an important role of autoimmune inflammation in salivary gland (SG) and lacrimal gland (LG). However, in many patients the correlation between the focus score (FS) on SG biopsy (a measure of lymphocytic infiltration) and decreased saliva production is limited. This suggests a critical role of other non-immunological factors such as gender, environment, and genetics in this disease. To date, little is understood regarding the changes in the epithelia associated with the loss of gland activity. We hypothesized that changes in the acinar and ductal cells might be key determinants of SG dysfunction. Our analysis suggests a change in network pathways associated with ER stress, autophagy, and the unfolded protein response. Because of their high secretory activity, salivary glands exhibit a high basal level of ER stress and consequently activation of the unfolded protein response. Markers of this change in state (specifically LAMP3 and LC3) show a statistically significant correlation with the level of autoimmune activity in the patients as well as colocalization and an increase in enlarged vesicles. We have carefully examined these pathways and in contrast to

	reports in the literature, our *in vitro* studies of these pathways and transcriptome-associated changes associated with Sjögren's syndrome suggest that, instead of enhanced autophagy in salivary glands of pSS patients, we observe stalled autophagy. Our hypothesis is the stalling in autophagy results in the aberrant release of neoantigens resulting in the creation of autoantibodies. Our ongoing work in this project (a collaboration with the Noguchi and Atsumi laboratories at Hokkaido University in Sapporo Japan) will examine the question of what is driving this change in autophagy, the mechanism of action, as well as develop strategies that could be used to restore a balance between autophagy and ER stress in patients. Understanding this aspect of Sjögren's syndrome will identify novel therapeutic targets that may be helpful in controlling systemic complications of this disease and will lead to a broader understanding of autoantibody development.
Publication *Enter the names of conference or journal and its vol. No. where the above work was presented.	【Conference, symposium, workshop etc.】
	【Journals】