Form 2-3

Japan-U.S. Brain Research Cooperation Program
Group Joint Study Project Program FY2020 - FY2022: Report

Field: 4

1. Principal Researcher
   Name: Sanae Ishii
   Title: Associate Professor at Kyorin University
   Affiliation: Faculty of Health Sciences, Pathology Research Team

2. Research Title:
   Nasal inflammation-induced depression-like behavior via dual routes: degeneration of olfactory neurocircuit and activation of meningeal immunity

3. Japanese Group Organization
   Principal Researcher
   Name: Sanae Ishii
   Title and Affiliation: Associate professor at Kyorin University
   Collaborating Researcher
   Name: Yuko Mishima
   Title and Affiliation: Lecturer at Kyorin University
   Collaborating Researcher
   Name: Hinami Asano
   Title and Affiliation: Student at Department of Medical technology, Faculty of Health Sciences of Kyorin University (master course)

4. U.S. Group Organization
   Principal Researcher
   Name: Geoffroy Laumet
   Title and Affiliation: Assistant Professor at Michigan State University, College of Natural Science, Neuroscience Program, East Lansing, MI, 48824, USA
   Collaborating Researcher
   Name: Robert Dantzer
   Title and Affiliation: Professor at MD Anderson Cancer Center, Department of Symptom Research, Division of Internal Medicine, Houston, TX, 77030, USA

5. Research Period, from/to (yyyy/mm/dd) and total number of years.
   From 2020/04/01 to 2023/03/31 (3 years)

6. Abstract, Results, and Research Significance (300 words):

Olfactory system is a unique pathway that can affect the brain by bypassing the blood brain barrier, since the olfactory sensory neurons (OSNs) project their axons to the olfactory bulb (OB). Our previous studies indicate that chronic nasal inflammation causes loss of OSNs, neuroinflammation and synaptic loss in the OB within 3 weeks, and degeneration of projection neurons and atrophy of the OB within 10 weeks, indicating that nasal inflammation affected the OB through the olfactory pathway. In addition, nasal cavity connects to the subarachnoid space via olfactory nerves, so that the nasal inflammation may affect the meningeal immunity. In this study, we aimed 1) to determine the changes in the meningeal immunity and OB microenvironment following nasal inflammation by immunohistochemistry, real time RT-PCR, and spectral flow cytometry. The other aim was 2) to determine whether nasal inflammation triggers sickness and/or depression-like behavior. U.S. group taught us the experimental techniques for examining meningeal immunity and for behavioral studies and performed spectral flow cytometry of the OB and meninges after nasal inflammation.

Histological and spectral flow cytometric analyses indicated that a variety of peripheral immune cells transiently infiltrated the OB and the ratio of peripheral immune cells in the OB increased at 24 hours after intranasal LPS administration, however, the ratio did not change in the meninges. Real time RT-PCR indicated that pro-inflammatory cytokines were upregulated in the OB and meninges, and anti-inflammatory cytokines were upregulated only in the OB. At 24 hours after intranasal administration, food and water intake and the body weight decreased in LPS-treated mice, but the immobility time of tail suspension test and forced swim test was not different in saline- and LPS-treated mice, suggesting that acute nasal inflammation caused sickness behavior, but not depression-like behavior.

7. Other (Research-related concerns, particular points of note):
It is very sorry that we could not visit US group during the first 2 years because of the pandemic of corona virus.

*Please attach any reference materials as necessary.