Form 1-3

Japan-U.S. Brain Research Cooperation Program
Researchers Dispatched to the U.S. Program FY2023: Report

Field: Neurobiology of disease

1. Researcher

Name: Rei Yasuda
Title: Assistant Professor
Affiliation: Department of Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

2. Research Title:
Identification of causative genes and development of therapy for undiagnosed and rare neurological diseases using *Drosophila* models

3. U.S. Joint Researchers/Institutes
Please give the name, title and affiliation.

Name: Shinya Yamamoto, DVM, PhD
Title: Assistant Professor
Affiliation: Department of Molecular & Human Genetics, Baylor College of Medicine

4. Research Period, from/to (yyyy/mm/dd): 2023/5/1 to 2024/3/15

5. Abstract, Results, and Research Significance (300 Words):

There are many undiagnosed or rare genetic diseases in the field of neurology. In the USA, the national research program, the Undiagnosed Disease Network (UDN), was organized to solve undiagnosed or rare diseases. In this project, the Model Organisms Screening Center (MOSC) has conducted functional analysis and pathogenicity evaluation of candidate genes using model organisms, which has contributed to the identification of causative genes and the development of therapy. We focused on a rare genetic disease, *LAMB1*-related leukoencephalopathy. Although nonsense, missense, and late-truncating variants in *LAMB1* are associated with a diverse severity of symptoms, the functional consequences of these variants are largely unknown. In addition, while the function of *LAMB1* orthologs has been studied during development in various model organisms, the role of this gene in the mature nervous system has been ill-defined. We aimed to generate and evaluate the *Drosophila melanogaste*r (fruit fly) model of *LAMB1*-related leukoencephalopathy and to study the role of the fly ortholog in the post-developmental nervous system.

Drosophila LanB1 is orthologous to all four human *LAMB* family genes. First, we found that fly *LanB1* is expressed in a subset of glial cells in developing and mature fly brains. Second, we found that biallelic knockout of *LanB1* causes lethality, and wing-specific knockdown of *LanB1* causes abnormal morphology, both of which were not rescued by human *LAMB1*. Third, human transgenic LAMB1 protein was not localized to the basement membrane upon expression in fly salivary gland cells.

These data suggest that while fly *LanB1* is an essential gene that is expressed in the nervous system during development and post-development, human *LAMB1* may lack the ability to replace the function of the fly gene. We are now pursuing experiments in *LanB1* transgenic flies to understand the mechanisms of human *LAMB1*-related disorders.

6. Other (Research-related concerns, particular points to note):
There are no research-related concerns. I'm very thankful for the generous support from the Japan-U.S. Brain Research Cooperation Program.

*Please attach any reference materials as necessary.