Form 2-3

Japan-U.S. Brain Research Cooperation Program
Group Joint Study Project Program FY2022 - FY2024: Report

Field: Cellular/Molecular

1. Principal Researcher
   Name: Haruhisa Inoue
   Title: Professor
   Affiliation: Center for iPS Cell Research and Application (CiRA), Kyoto University

2. Research Title: Decoding human specific genetic network using brain organoids generated from patient-specific iPSC

3. Japanese Group Organization
   Names, Titles and Affiliations of the Principal Researcher and Collaborating Researchers
   Principal Researcher
   Haruhisa Inoue, Professor: Center for iPS Cell Research and Application (CiRA), Kyoto University | Team-leader: RIKEN BioResource Research Center, iPSC-based Drug Discovery and Development Team
   Collaborating Researcher
   Tomohisa Kato, Lecturer: Division of iPS Cell Applied Medicine, Department of Advanced Medicine, Medical Research Institute, Kanazawa Medical University | Visiting researcher: RIKEN BioResource Research Center, iPSC-based Drug Discovery and Development Team

4. U.S. Group Organization
   Names, Titles and Affiliations of the Principal Researcher and Collaborating Researchers
   Principal Researcher
   Alysson R. Muotri, Professor: Department of Pediatrics and Department of Cellular & Molecular Medicine, School of Medicine, University of California, San Diego; Center for Academic Research and Training in Anthropogeny and Archealization, University of California, San Diego | Director: Sanford Integrated Space Stem Cell Orbital Research Center (ISSCOR)
   Collaborating Researcher
   Pinar Mesci, Assistant Project Scientist: Department of Pediatrics and Department of Cellular & Molecular Medicine, School of Medicine, University of California, San Diego

5. Research Period, from/to (yyyy/mm/dd) and total number of years.
   From 2022/04/01 to 2025/03/31 (3 years)

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

Cockayne syndrome (CS), UV-sensitive syndrome (UVSS), and xeroderma pigmentosum (XP) are rare photosensitive human disorders caused by mutations in DNA repair genes. CS and UVSS are associated with defects in the transcription-coupled nucleotide excision repair (TC-NER) pathway, while XP involves impairment in the global genome nucleotide excision repair (GG-NER) pathway. Notably, patients with CS and XP exhibit progressive neurodegeneration, whereas those with UVSS do not show neurological symptoms, despite sharing the same defective TC-NER pathway as CS. This unique difference provides an important opportunity to explore the molecular basis of human-specific neural circuit development and degeneration.

To investigate these syndromes, we utilized patient-derived induced pluripotent stem cells (iPSCs) to

generate human brain organoids, which mimic key features of brain development and disease. iPSCs from CS patients, provided by our collaborator Dr. Muotri (UC San Diego), along with those from healthy individuals and XP patients, were used to create cerebral organoids. Single-cell RNA sequencing analysis revealed overlapping cellular and molecular phenotypes between CS and XP organoids, highlighting shared mechanisms of neurodegeneration in these progeroid disorders. These findings were presented at the 54th International Symposium of the National Institute for Physiological Sciences and are being prepared for publication.

For UVSS, iPSCs have been successfully generated from patient-derived fibroblasts. In the next phase, cerebral brain organoids will be derived from these cells, followed by comparative analysis with CS and XP models. The goal is to identify the cellular and epigenetic mechanisms that may account for the absence of neurodegeneration in UVSS, despite similar DNA repair deficiencies.

This research demonstrates the power of brain organoids in modeling human neurological diseases and provides valuable insight into the genetic networks that govern human brain-specific development, aging, and resilience to DNA damage.

7. Other (Research-related concerns, particular points of note):

None.

*Please attach any reference materials as necessary.