Here begins our new MIRAI
MOONSHOT RESEARCH & DEVELOPMENT PROGRAM

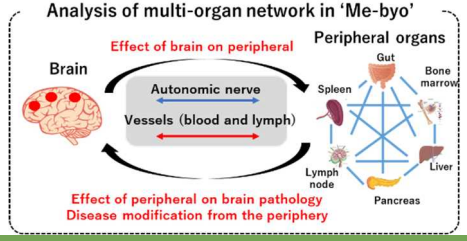
R&D Theme

Brain and multi-organ network in Alzheimer's disease, vascular dementia and Parkinson's disease dementia

Progress until FY2022

1. Outline of the project

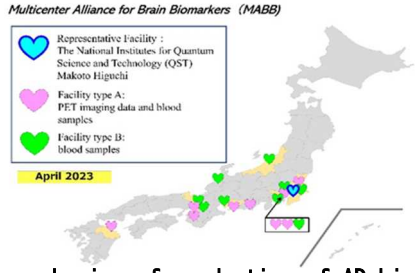
Alzheimer's disease, vascular dementia, and Parkinson's disease dementia are the three major dementias. We aim to elucidate the multi-organ network by mathematical analysis using novel mouse models and human cohorts to develop risk prediction and prevention methods. We will use a model in which the causative protein starts to accumulate in "Me-byo" state and symptoms develop later, enabling us to analyze the preclinical stages of various pathological conditions. We are also conducting human cohorts in preclinical conditions.



2. Outcome so far

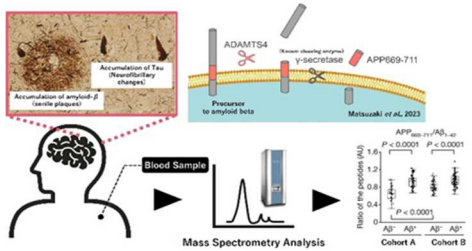
1. A multicenter cohort of 'Me-byo' for dementia

The MABB (multicenter alliance for brain biomarkers) 'Me-byo' cohort, in which 18 institutions are currently participating, is a multicenter alliance that promotes the development of imaging and blood biomarkers. The MABB research is characterized by the availability of secondary use of data and samples from other clinical studies, which will accelerate validation of biomarkers.



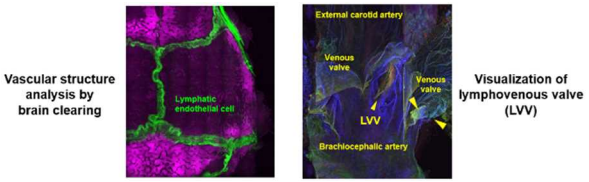
2. The mechanism of production of AD biomarkers

The causative protein amyloid β (Aβ) accumulates in the brain long before the onset of the disease. Using biomarker APP669-711 in blood, we can estimate the amount of Aβ accumulation in the brain, but its mechanism of production remained unknown. Professor Tomita at the University of Tokyo demonstrated that the proteinase ADAMTS4 is involved in the production of APP669-711 (Mol Psychiatry, 2022). This discovery will lead to the accurate estimation of brain AD pathology based on the brain-peripheral interaction.



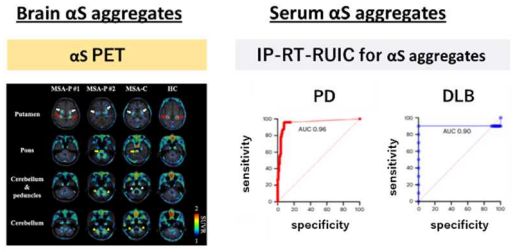
3. High-resolution and functional imaging of vascular structures entering and exiting the brain

We are performing 3D imaging of vessels draining into and from the brain using the transparent brain of mice with visualization of lymphatic endothelial cells as well as mice and humans with visualization of intralymphatic venous valves.



4. Visualization of α-synuclein (αS) in the brain and its detection in blood

Dr. Higuchi at the QST have succeeded in imaging of accumulation of disease-causing protein "αS" using PET, and Dr. Hattori at Juntendo University have succeeded in detecting pathologically structured αS aggregates in blood, world-leading achievements that will greatly contribute to establishing accurate diagnostic procedures in dementia.



Mov Disord, 2022 *Nat Med*, 2023

3. Future plans

Various types of data will be collected from original disease models and dementia "Me-byo" cohorts. Furthermore, we will identify candidate biomarkers that contribute to early diagnosis through data-driven analysis of multi-organ networks, and try to predict and prevent the development of dementia based on the brain-peripheral interactions.

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