Here begins our new MIRAI
MOONSHOT RESEARCH & DEVELOPMENT PROGRAM

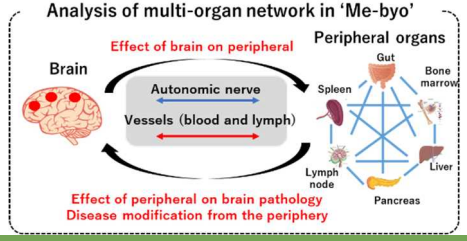
R&D Theme

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

Progress until FY2022

1. Outline of the project

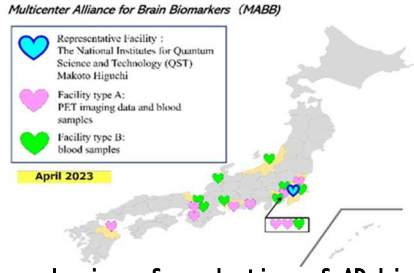
Alzheimer's disease, vascular dementia, and Parkinson's disease dementia are the three major dementias. We aim to elucidate the multi-organ network by mathematical analysis using novel mouse models and human cohorts to develop risk prediction and prevention methods. We will use a model in which the causative 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

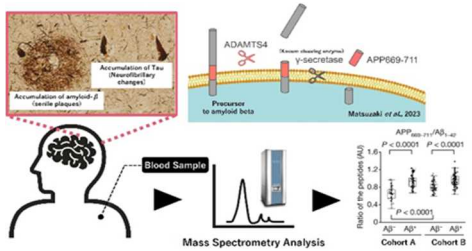
1. A multicenter cohort of 'Me-byo' for dementia

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.



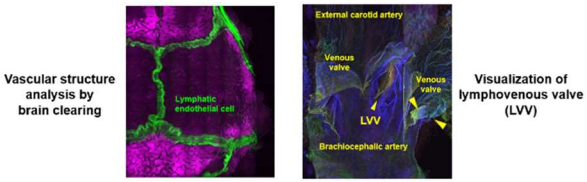
2. The mechanism of production of AD biomarkers

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.



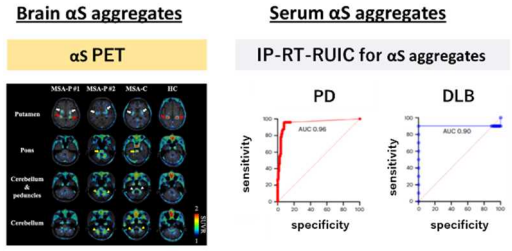
3. High-resolution and functional imaging of vascular structures entering and exiting the brain

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.

国立研究開発法人 科学技術振興機構 Japan Science and Technology Agency

R&D Theme

Development and application of novel imaging, measurement, and manipulation techniques for ultra-early detection of network transformations

Progress until FY2022

1. Outline of the project

To study the early stages of diseases and understand their underlying mechanisms, it is crucial to develop advanced technologies that can accurately capture and analyze changes in interconnected organ networks at a highly precise level. We will analyze synaptic structures involved in neuronal communication, explore the network between the entire body and organs, examine the synthesis and release mechanism of extracellular vesicles implicated in inter-organ communication, and investigate physiological and behavioral changes within the interconnected network. Our goal is to identify a wide range of biomarkers capable of detecting early alterations in inter-organ networks. By measuring and analyzing these inter-organ networks, we aim to discover ultra-early disease markers and develop intervention technologies that can target these networks. This interdisciplinary approach will contribute to advancing our knowledge of neurodegenerative diseases and inter-organ communication.

Fundamental Analysis and Foundational Technology Development Group
(Supervisor:Ohtsuka)

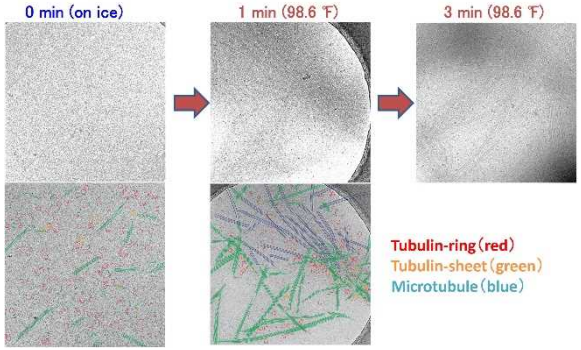
Development Project 4:
Development and Application of Novel Imaging, Measurement, and Manipulation Techniques Enabling Early Detection of Network Remodeling

2. Outcome so far

Nita et al. from Kobe University have presented two notable findings in the field of imaging technology using cryo-electron microscopy techniques.

(1) Time-lapse cryo-microscopic analysis to capture continuous changes in cells at the microscopic level

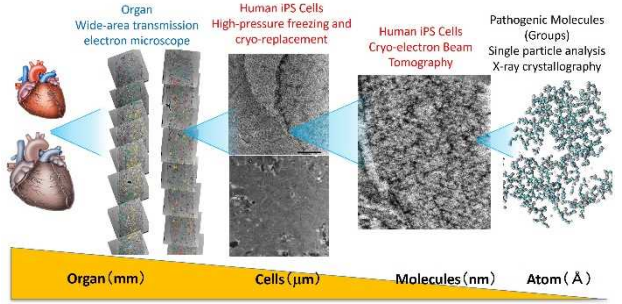
We have developed a new method called time-lapse cryo-microscopic analysis to capture continuous changes inside cells. This technique allows us to observe the process of proteins called tubulin overlapping and forming microtubule structures (*ELife, 2022*). By applying this method to proteins like amyloid beta, tau, and alpha-synuclein, which are implicated in dementia, we can investigate how these proteins come together and create aggregates. In simpler terms, by watching these crucial cellular processes like a video, we hope to uncover insights into the mechanisms underlying dementia.



(2) Cross-scale structural analysis from organs to molecules

Cross-scale cryo-EM analysis

We developed a new method for studying structures at different levels, ranging from organs to tissues, cells, and molecules (*Sci. Adv, 2023*). We initially focused on analyzing the detailed structure of the heart, starting from the entire organ and going down to the tissue, cell, and molecular levels. In the future, we plan to explore the application of this technique to the central nervous system to observe structural changes in its healthy state. The goal is to capture structural alterations occurring in the central nervous system prior to the onset of disease (“Me-byo”).



3. Future plans

We will focus on developing advanced imaging techniques and searching new molecules and biomarkers that can identify “Me-byo”. By collaborating with the AI/Mathematics Group, we aim to establish foundational technologies for ultra-early diagnosis and prevention.

R&D Theme

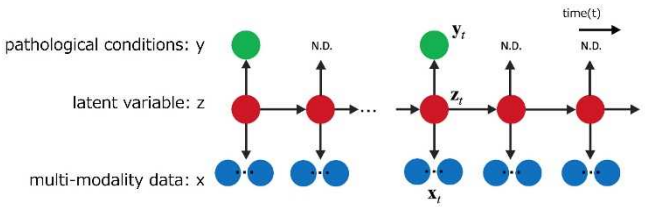
Elucidation of Inter-Organ Networks by AI and Mathematical Research

Progress until FY2022

1. Outline of the project

Our aim is to understand inter-organ networks by constructing data-driven mathematical models in animal models combined with human data. In the data linkage system, AI and machine learning techniques will be used to make effective use of the limited data we have collected from living organisms, which enable us to remove noise from the data and fill in missing values.

By integrating mathematical models with human data, we will develop machine learning algorithms that can estimate the condition of each organ and identify the early stages of dementia using non-invasive and cost-effective measurements in the preclinical 'ME-BYO' conditions.



$$z_{k,t+1}=F(z_{k,t})+\eta_{k,t} \quad x_{n,t}=Uz_{k,t}+u+\varepsilon_{n,t} \quad y_{k,t}=Vz_{k,t}+v+\xi_{k,t}$$

U, V: weight matrix
u, v: bias
ε, ξ, η_k: noise

2. Outcome so far

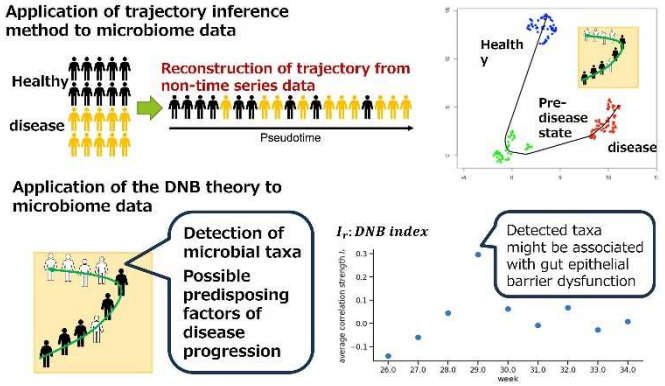
(1) Deep Input-Output Stable dynamics (DIOS), a deep learning technique for learning dynamics from data

Kojima et al. at Kyoto University have developed a novel deep learning technique to learn the dynamics of biological motion from data while maintaining input-output stability, an important property of biological motion. The study focused on input-output stable systems that are robust against unexpected stimuli and noise. We then realized a method for learning neural network systems to guarantee input-output stability.

(2) Development of the pseudo-time reconstruction method from non-time series data

The pseudo-time reconstruction method is a technique that estimates the growth and differentiation processes of individual cells. Although this method is usually applied to single-cell RNA-seq data, Nakaoka and his research team in Hokkaido Univ. has developed a method to apply this technique to gut microbiome data.

Recently, the relationship between central nervous system disorders including Parkinson's disease-related dementia and gut bacteria has been attracting attention (gut-brain interaction). They plan to utilize their developed method to analyze data on gut bacteria in preclinical 'ME-BYO' individuals to identify gut bacteria associated with the onset and progression of disease based on gut-brain interaction. In addition, a mathematical analysis called dynamic network biomarker (DNB) theory was applied to identify factors that can be used to identify conditions before the onset of the disease. As a result, they succeeded in detecting predictors before the changes of composition of the gut microbiota in attention-deficit/hyperactivity disorder and autism spectrum disorder. They will conduct further research to apply DNB-based analysis not only to gut microbiota data, but also to data related to dementia more broadly.



3. Future plans

we will construct data-driven mathematical models for multiple parameters obtained from animal models and preclinical human 'ME-BYO' cohorts to elucidate the transformation of the inter-organ network. We will also apply this to the achievement of prediction and prevention methods for dementia based on brain-organ interactions.

国立研究開発法人 科学技術振興機構
Japan Science and Technology Agency