Goal2 Realization of ultra-early disease prediction and intervention by 2050.

Comprehensive Mathematical Understanding of the Complex Control System between Organs and Challenge for Ultra-Early Precision Medicine

Here begins our new MIRAI

MOONSHOT RESEARCH & DEVELOPMENT PROGRAM

R&D Theme

Experimental Approach to Complex Control System between Organs

Progress until FY2022

1. Outline of the project

Our R&D theme has the following three objectives:

1. We are promoting the project by applying mathematical methods to our health science research on the pre-disease state **in collaboration with the Mathematical Approaches Team within the project**.

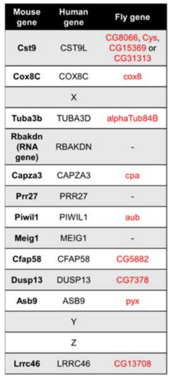
2. Based on the results of our studies, we are leading the realization of ultra-early precision medicine through **medical intervention in the pre-disease state**.

3. To elucidate and detect the pre-disease state, we are providing to a Mebyo database by acquiring temporal and comprehensive biological information of **multiple organs in animal models and in humans**.

Specifically, we are conducting validation of mathematical methods such as **dynamical network biomarkers (DNB) analysis** applied for health sciences using animal models (e.g., **metabolic syndrome model**), clinical samples (e.g., **gestational hypertension, hematopoietic tumor**), and data of **mental diseases**. Furthermore, we are providing the acquired biological information (pre-disease datasets) to GakuNin RDM **through the Mathematical Collaboration Team (Fujiwara Group, the University of Tokyo)** within the project for utilization throughout the project.

2. Outcome so far

① Ranking of the importance of DNB genes and elucidation of their functions through collaborative research within the project



Mouse gene	Human gene	Fly gene
Cst9	CST9L	CG8066, Cys, CG15369 or CG31313
Cox8C	COX8C	cox8
	X	
Tuba3b	TUBA3D	alphaTub84B
Rbakdn (RNA gene)	RBAKDN	-
Capza3	CAPZA3	cpa
Prr27	PRR27	-
Piwil1	PIWIL1	aub
Meig1	MEIG1	-
Cfap58	CFAP58	CG5882
Dusp13	DUSP13	CG7378
Asb9	ASB9	pyx
	Y	
	Z	
Lrrc46	LRRC46	CG13708

Table 1

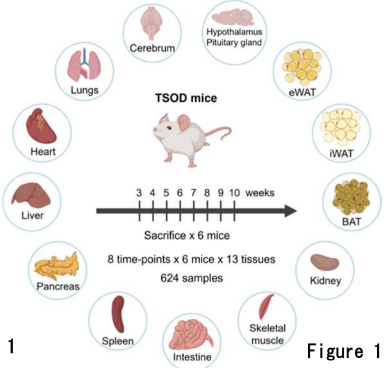


Figure 1

From 147 DNB genes in adipose tissue of spontaneously developing metabolic mice (TSOD mice), we selected 15 DNB genes (Table 1) that we considered important **from the viewpoint of Systems and Control Theory in collaboration with the Mathematical Approach Team (Tokyo Institute of Technology)**. Then at the University of Toyama, taking advantage of the genetics of Drosophila as a model organism, we conducted a rapid and comprehensive evaluation of DNB gene functions and found that **three DNB genes** (X, Y, Z) in Table 1 are involved in lipid metabolism.

② Pre-disease datasets to elucidate the inter-organ networks in metabolic syndrome mice

To detect changes in each organ that are thought to be induced before the onset of metabolic syndrome using **DNB analysis**, we obtained comprehensive gene expression information of **13 organs including adipose tissue, brain, intestine, liver, and muscle at 8 time points** from before to after the onset in TSOD mice as shown in Figure 1, and further performed DNB analysis and **detected pre-disease states in each organ**.

③ Detection of precancerous state (pre-disease state) of hematopoietic tumors using Raman microscopy

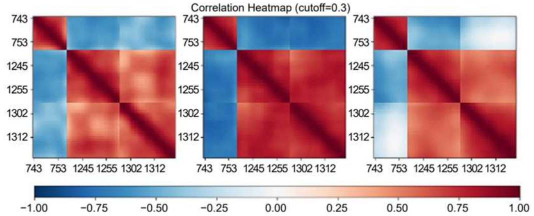


Figure 2

We are analyzing cells collected from bone marrow of patients with **hematopoietic tumors** by measuring their spectra using **Raman microscopy**. It was possible to clearly distinguish between cells from patients with hematopoietic tumors and cells from patients in precancerous states. Furthermore, **DNB analysis of Raman spectral data** showed that the DNB score of cells from patients with precancerous conditions (Figure 2 middle) was higher than that of cells from normal cases (Figure 2 left) and cells from hematopoietic tumor patients (Figure 2 right), indicating **an increased fluctuations in the cells from patients with precancerous conditions**. On the other hand, **mathematical analysis of the brain data** like mental diseases and Tokyo Teen Cohort are also progressing.

3. Future plans

We are working on more detailed single cell analysis and intercellular network analysis of visceral adipose tissues from **high-fat diet-induced metabolic syndrome mice and humans**. **We are also improving the Raman microscope** for developing a clinical examination device that can be applied to detect the pre-disease state of human hematopoietic tumors.

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