R&D Theme

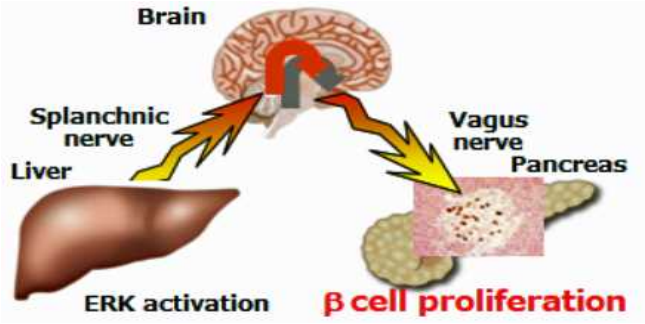
Elucidation of homeostatic mechanisms by inter-organ communication and development of therapeutic and diagnostic methods

Progress until FY2022

1. Outline of the project

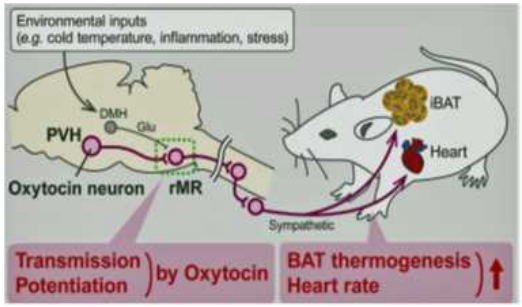
This R&D theme is responsible for the project's themes of (i) elucidating the inter-organ network mechanisms (See figure below) that maintain metabolic and circulatory homeostasis, and (ii) developing new prevention, diagnosis, and treatment methods for diabetes and its co-morbidities based on these mechanisms.

To achieve this goal, we are tackling this challenging theme by conducting detailed analyses to elucidate the molecules involved in the signaling of afferent, central, and efferent nerves connecting organs and their regulatory mechanisms. With the idea of developing preventive, diagnostic, and therapeutic methods for diabetes using inter-organ networks through the nervous system, which is completely different from conventional methods, we are working on this project using single cell RNA sequencing, optogenetics, fMRI, artificial nerve connections, plasma lipidomics, and other techniques.



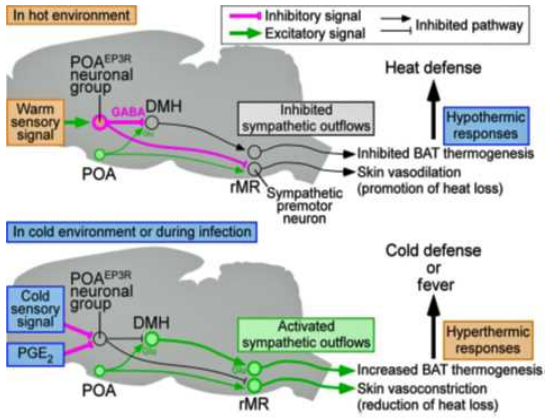
2. Outcome so far

(1) Vagus nerve stimulation of the pancreas leads to proliferation of pancreatic β cells and suppresses the onset of diabetes in model mice (lower left figure)
(2) Successful single-cell RNA sequencing of ganglia
(3) Discovery of the oxytocin nervous system in the hypothalamus, which is linked from emotion to heat metabolism (lower figure)
(4) Identification of master EP3 neurons that regulate energy metabolism (right figure)
(5) Simultaneous measurement of vagal and sympathetic activity in rats
(6) Establishment of fMRI method to measure activity of human hypothalamus brainstem system and discovery of activity during muscle exertion
(7) Transient control of heart rate and blood pressure by magnetic stimulation of the thoracic spinal cord
(8) Discovery of neural signals from intestinal bacteria and the intestinal tract that regulate sugar preference



Press Release with Nagoya University and JST (2022.9.21)

In the above, (1) is an important finding for POC when considering human applications. (3) will lead to the development of a new treatment for obesity caused by dysfunction of oxytocin neurons. (4) will lead to the development of techniques for obesity prevention and therapeutic intervention in the pre-symptomatic stage.



Press Release with Nagoya University and JST (2022.12.24)

3. Future plans

In the future, to verify the results of vagus nerve stimulation obtained in mice, we will try to perform vagus nerve stimulation in monkeys and analysis of glucose metabolism in epilepsy patients with implanted human vagus nerve stimulators. This will lead to the development of methods to prevent and treat diabetes using vagus nerve stimulation.

In addition, we will search for receptors and ligands to elucidate the molecular mechanisms of afferent nerve signaling involved in the inter-organ network. This will lead to the development of prevention and treatment of diabetes and its co-morbidities by controlling the inter-organ network.

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

R&D Theme

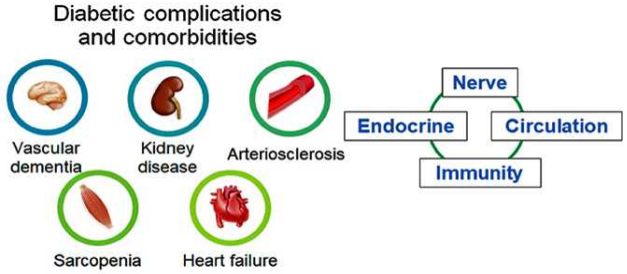
Elucidation and control of the mechanism of multi-organ transformation in diabetes mellitus

Progress until FY2022

1. Outline of the project

This R&D theme is responsible for research within the project to elucidate the mechanisms of multi-organ transformation in diabetes (See figure below) and to develop control methods.

To achieve this goal, we are working on challenging themes in organs such as heart, liver, brain, and kidney, as well as blood vessels, where we must analyze organ transformation from both functional and morphological perspectives. Based on the idea that close interactions are involved between concomitant diseases, which is completely different from the conventional approach, we are working on this project using techniques such as single cell RNA sequencing, flow cytometry, two-photon microscopy, scanning electron microscopy, light sheet microscopy, and tissue transparency techniques.



https://www.moonshot-katagiri.proj.med.tohoku.ac.jp/research-e.html

2. Outcome so far

(1) Discovery that sympathetic neuropathy caused by heart failure deteriorates hematopoietic stem cell differentiation

(2) Discovery that bone marrow transplantation of mentally stressed mice induces heart failure and increases stress vulnerability in kidney and skeletal muscle

(3) Discovery of the presence of plasmablasts in adipose tissue

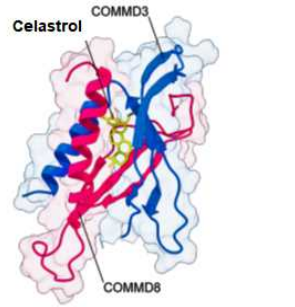
(4) Establishment of a spatiotemporal analysis method for the flow of red blood cells and plasma in the cerebral microcirculation

(5) Elucidation of the mechanism from the liver that survives starvation and protects life (right figure)

(6) Elucidate the role of ketone body production by the proximal tubule in maintaining renal function

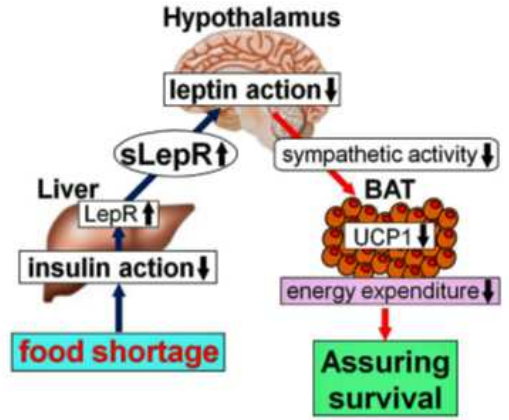
(7) Creation of a multi-organ whole-cell atlas and quantification of the degree of organ damage

In the above, (1) is a discovery that leads to the elucidation of the mechanism by which bone marrow transplantation in heart failure mice causes heart failure and multi-organ damage. (3) will lead to the elucidation of new mechanisms of metabolic deterioration caused by obesity. A control agent (Celastrol) has already been identified (left figure). (5) discovered a life-preserving mechanism in which the liver plays a key role by reducing calorie consumption beyond what is necessary during starvation and increasing appetite. It has been reported that increased appetite tends to occur when blood glucose levels are elevated, and this finding may be one of the reasons for this, and is expected to lead to applications to methods to prevent diabetic patients from overeating.



Osaka University Press Release (2023.3.22)

Inter-organ insulin-leptin signal crosstalk



Tohoku University Press Release (2023.4.24)

3. Future plans

In the future, we will analyze cell-cell interactions in the heart to elucidate the mechanism of homeostasis by macrophages and how the alteration of macrophage function induces pathological conditions such as heart failure. This will lead to the development of diagnostic and preventive methods.

In addition, to elucidate the role of the fenestrae of hepatic sinusoidal endothelial cells, we will analyze the porosity of the fenestrae in more detail and elucidate its regulatory mechanism. This will allow us to clarify whether the porosity of the fenestrae is involved in the mechanism that determines blood glucose levels in the early phase after glucose loading.

R&D Theme

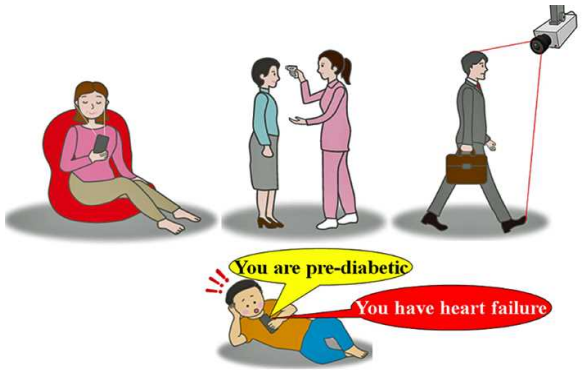
Development of technology for easy acquisition of biometric data in humans and analysis of human data

Progress until FY2022

1. Outline of the project

This R&D theme is responsible for the development and social implementation of a method to detect and predict the early stages of diabetes and its co-morbidities as simply and non-invasively as possible based on the analysis of biological information, genome, and hepatic glucose uptake capacity using contact and non-contact devices (See figure below).

To achieve this, we are working on creating a highly accurate early diabetes detection algorithm, improving the accuracy of the diabetes omnigenic model, and collecting data from the $^{13}CO_2$ breath test as challenging themes. We are working on the concept of early detection of diabetes and heart failure from non-invasive devices only, which is completely different from conventional methods, using high-speed spectral cameras, AI, cohort data analysis, and other methods.



https://www.moonshot-katagiri.proj.med.tohoku.ac.jp/research-e.html

2. Outcome so far

(1) Establishment of a system that displays the degree of heart failure over time using a contact device (lower figure)

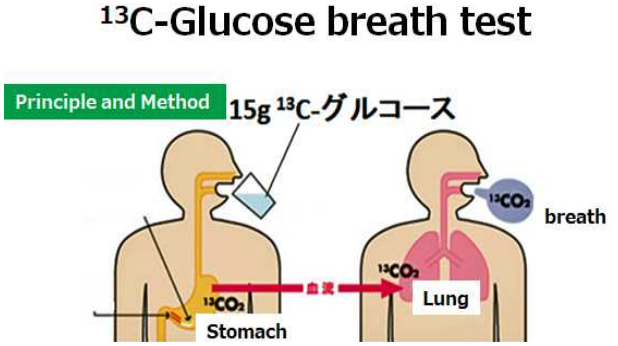
(2) Development of an algorithm (HF-index) that can be used to estimate blood BNP levels from electrocardiograms obtained with a contact device and use them for alerts

(3) Non-contact detection of blood pressure from mouse skin using a spectral camera

(4) Detecting high polygenic risk scores by measuring risk prediction performance using large-scale genomic data

(5) Cohort study found a correlation between 1-hour post-glucose tolerance and subsequent life expectancy and a cutoff value of 170 mg/dL in human normal glucose-tolerant subjects

(6) Elucidated the cause of death in human normal glucose-tolerant subjects with postprandial glucose intolerance >170 mg/dL



(7) Proved the importance of hepatic glucose uptake capacity in determining postprandial blood glucose in humans (upper figure)

In the above, (1) is in the process of being IP-enabled. (2) is in the process of filing for IP and conducting clinical trials. In (7), the ^{13}C-glucose breath test, a simple test for glucose uptake by the liver, has patented as an intellectual property.

3. Future plans

In order to enable early detection of hypertension and diabetes by non-invasive devices, we will acquire data from 200 to 300 patients and healthy subjects, and try to create and evaluate algorithms. This will enable the evaluation of diabetes and its concomitant diseases in the human condition using non-invasive biometric devices.

For the $^{13}CO_2$ breath test, we will also try to accumulate data on a 75 g ^{13}C -glucose load in order to link it to the data related to life expectancy obtained in the Ohasama cohort. This will allow us to examine the relationship between sugar processing and glycoxidation by the $^{13}CO_2$ breath test and to estimate its relationship to the prognostic impact of the cohort.

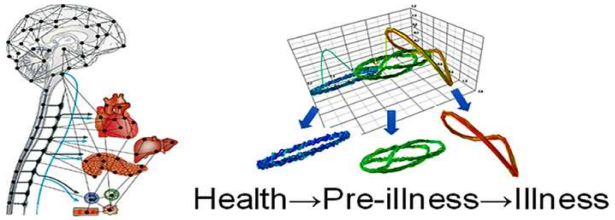
R&D Theme

Understanding homeostasis through mathematical model analysis and its applications, Understanding the pre-symptomatic stage of diabetes and its complications and building a database

Progress until FY2022

1. Outline of the project

The two R&D themes (Themes 4 and 5) play two roles in the project: (i) to collect various data over time on the transition from the normal or pre-symptomatic stage to the diseased state, focusing on type 2 diabetes and its concomitant disease, heart failure (Theme 5), and (ii) to use these animal experimental data and human biological data to advance mathematical model analysis to extract key elements for a comprehensive understanding (Theme 4, see figure below).



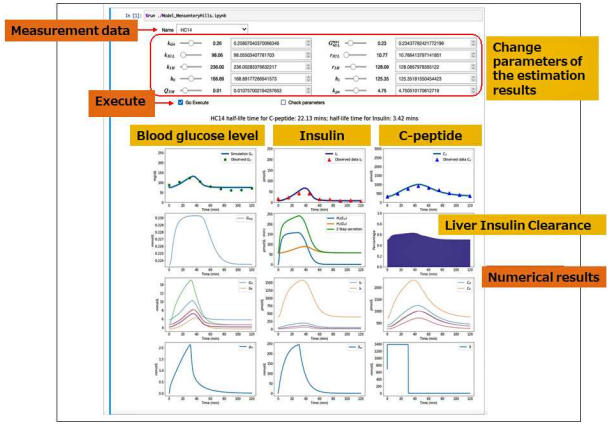
https://www.moonshot-katagiri.proj.med.tohoku.ac.jp/research-e.html

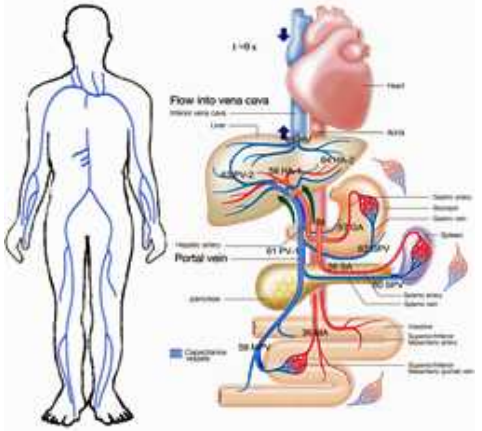
To achieve this, close collaboration between mathematical scientists and medical biologists is a challenge, and we are working on this as a challenging theme. We are working on the concept of linking experiments/data acquisition with model analysis, which is completely different from the conventional approach, using various methods such as biochemistry, gene expression analysis, epigenomics, metabolomics, organ-specific functional analysis, and mathematical model analysis.

2. Outcome so far

(1) Proceed with mathematical model analysis using glucose tolerance test data from healthy subjects, and estimate half-lives of insulin and C-peptide using a 9-organ compartment model
(2) Implementation of a glucose tolerance test simulator (see figure below)
(3) Construction of a circulatory system model using time series data of flow rate obtained as a result of blood circulation simulation (right figure)
(4) Start of mouse data acquisition for time-series analysis of pre-symptomatic states

In (2), we were able to visualize changes in blood glucose and insulin concentrations and the metabolic state of the whole body by changing various parameters. In (3), we constructed a 1D + 0D coupled model of the whole-body circulatory system and completed a prototype of a whole-body circulatory network model (upper right figure). (4) will lead to the clarification of key phenomena through the refinement of mathematical models and simulators.





3. Future plans

In the future, to extend the inter-organ network model (compartment model) to a mathematical model corresponding to a normal diet, we will construct a mathematical model that enables us to understand the dynamic homeostasis of glucose metabolism. By applying the 9-compartment model to the same individual mouse data that transitions from healthy to diabetic, we will identify the parameters that change specifically for diabetes and clarify the mechanism of diabetes onset from a mathematical science perspective.

In addition, we will select effective time points for analysis from the pre-symptomatic stage to the diabetic state as an analysis in order to consider building a database by adding the effects of aging and sex differences. In this way, we will construct a pre-symptomatic disease database and share the obtained data with mathematical scientists from time to time to combine the estimation of mechanisms obtained from mathematical model analysis with molecular analysis in experiments.