Moonshot Goal 2

Progress Report 2025

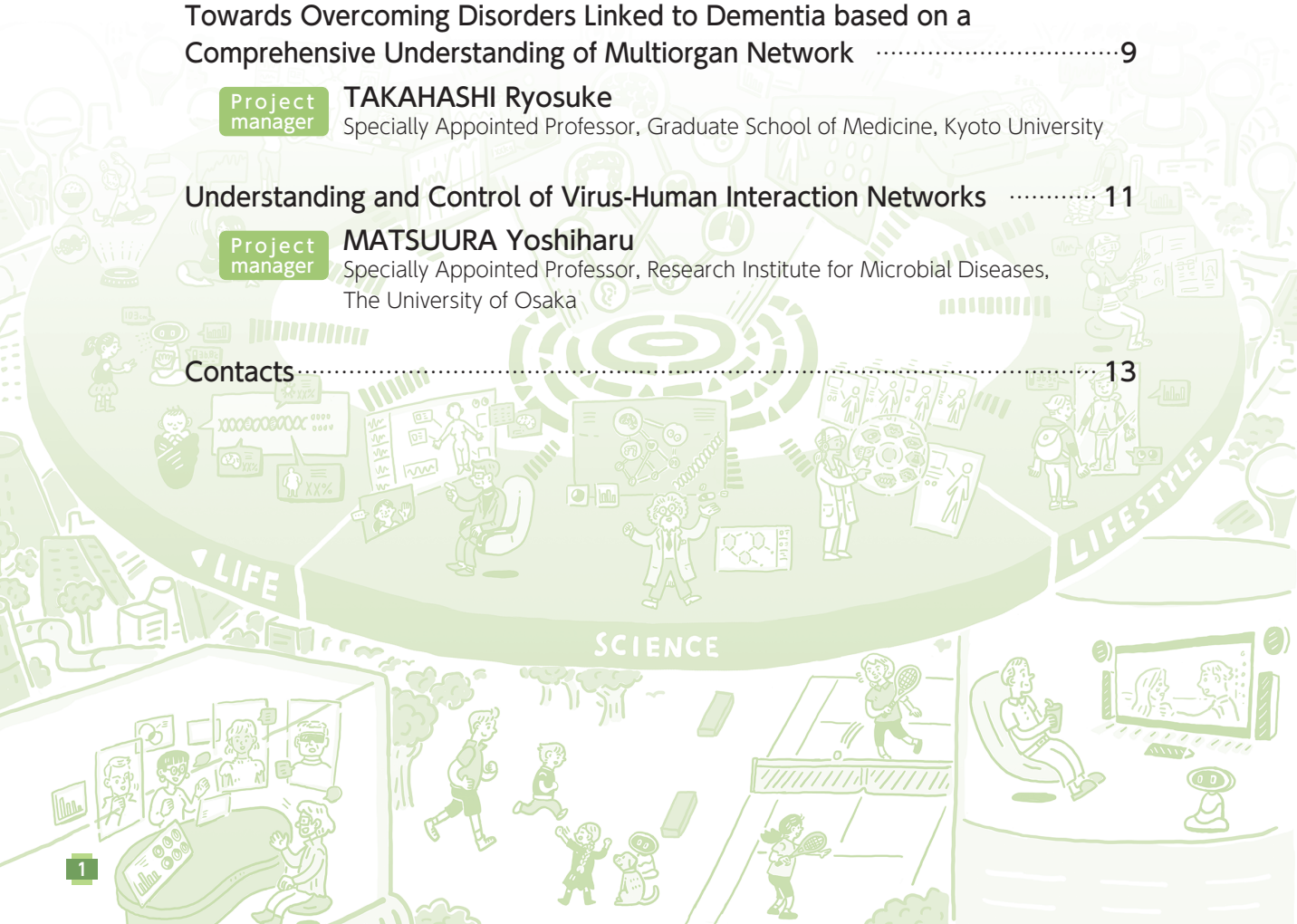
Realization of ultra-early disease prediction and intervention by 2050

MOONSHOT
RESEARCH & DEVELOPMENT PROGRAM

Goal 2

Contents

Moonshot Goal 2

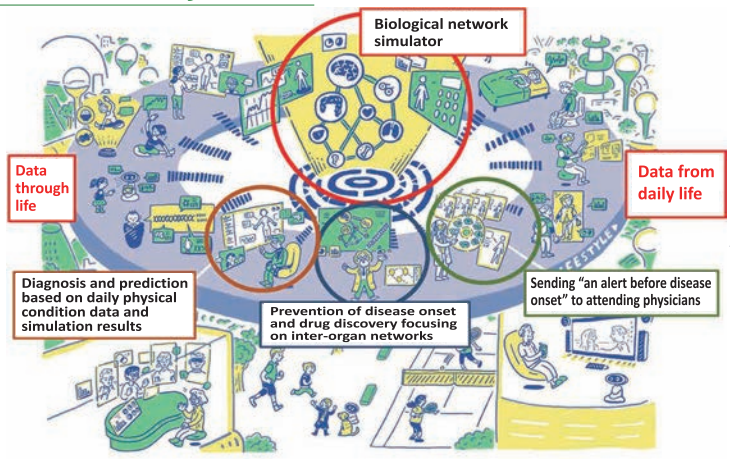


Moonshot R&D Goal 2

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

Program Director (PD)
SOBUE Gen
Chairperson,
Aichi Medical University

Vision of Society in 2050



A society where we can predict and prevent disease onset using lifetime and daily data

Until 2030, the 10th year of the program

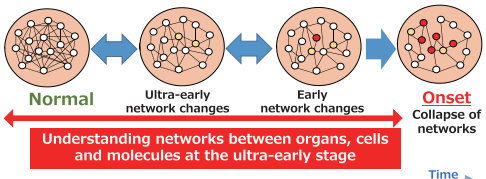
Milestone:
We will establish methods to identify precursors of refractory diseases such as cancer, dementia, diabetes, and viral infections and develop technologies to prevent them or restore the body to a normal state.

(Technological goals)
- Elemental technologies for ultra-early detection, prevention, and intervention of refractory diseases have been developed, and protocols for the prediction and evaluation of these diseases have been established.
- An integrated whole-body network database has been established.
- Mathematical analysis techniques to detect signs of disease and prevent it before onset have been developed.

Challenges to be addressed and our approach

Elucidation of ultra-early diseases associated with lifestyle conditions like cancer, dementia, and diabetes, and aging has yet to be solved.
Suppose there are reverse phases of diseases before the onset, referred to as ultra-early state

Current medical science primarily focuses on treatment after the onset of diseases.



Understanding networks between organs, cells and molecules at the ultra-early stage

Unexplained
Address changes in the networks at the ultra-early state

Develop interventions during the ultra-early stage

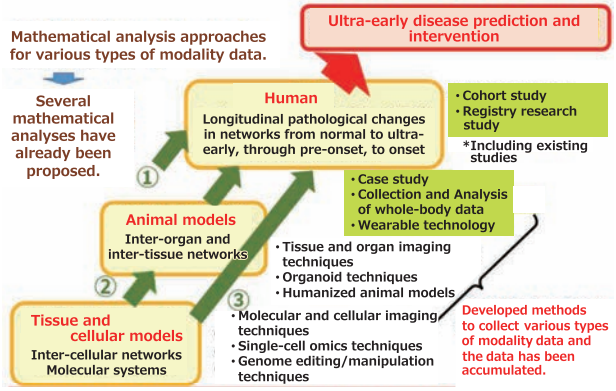
Integration of biological approach and mathematical approach
Comprehensive analysis of spatio-temporal measurement data is needed to understand complex life phenomena

Biological approach + Mathematical approach

Comprehensive elucidation of inter-organ/intercellular networks

Mathematical analysis approaches for various types of modality data.

Several mathematical analyses have already been proposed.



With the steady collection of various types of data and the development of techniques, longitudinal dataset includes ultra-early stages needs to be maintained.

Program structure


Program Director
SOBUE, Gen
Chairperson,
Aichi Medical University


Project Manager
AIHARA, Kazuyuki
University Professor,
The University of Tokyo


Project Manager
OHNO, Shigeo
Special Contract Professor,
Juntendo University


Project Manager
KATAGIRI, Hideki
Professor,
Tohoku University


Project Manager
TAKAHASHI, Ryosuke
Specially Appointed Professor,
Kyoto University

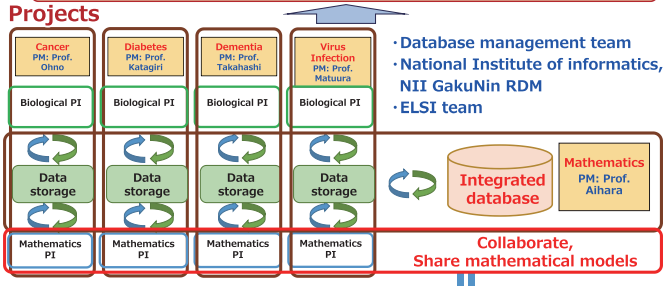

Project Manager
MATSUURA, Yoshiharu
Specially Appointed Professor,
The University of Osaka

MS2 researcher :
Total : 1,302 (PM・PI : 137)
Institution : 79

4 projects targeting disease with high unmet needs and 1 project focusing on mathematical platform

Society to predict and intervene diseases at the ultra-early stage

Comprehensive elucidation and simulation of inter-organ, inter-cellular, and inter-molecular networks at the ultra-early stage



Construct comprehensive database
Analyze with integrated data collected in the projects

Moonshot R&D

Goal 2, Mathematical Platform PJ

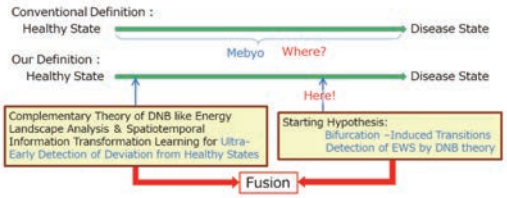
Comprehensive Mathematical Understanding of the Complex Control System between Organs and Challenge for Ultra-Early Precision Medicine

Project Manager (PM)

AIHARA Kazuyuki

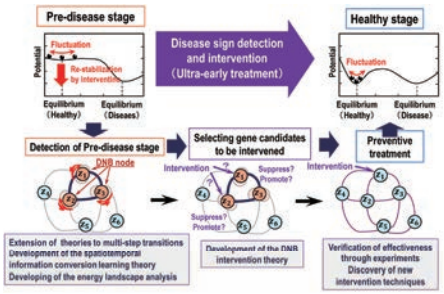
University Professor / Professor Emeritus, The University of Tokyo

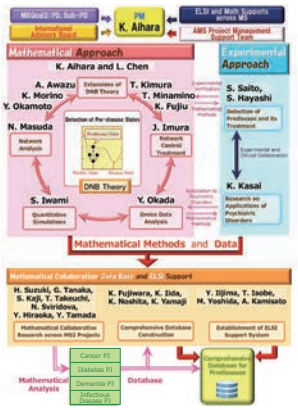
Project Outlook and Concept



Seamless Connection from Health Medicine through Preventive Medicine to Mebyo Medicine

Development of ultra-early disease detection and intervention methods by incorporating various mathematical theories around DNB theory
~Extensions and complements to this theory~

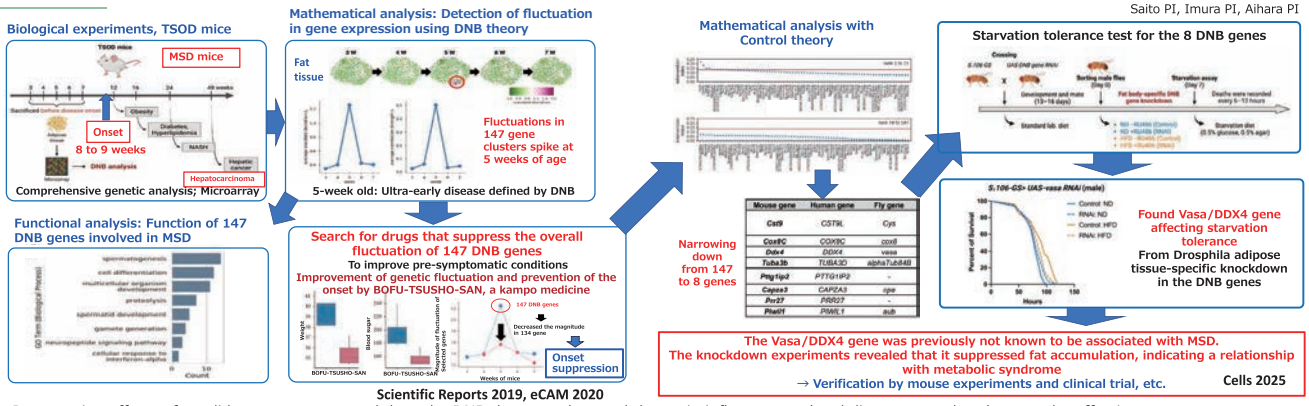




Results

Identification of disease-associated genes and refinement for intervention gene by DNB theory and Control theory; Ex. Metabolic syndrome disease, MSD

Saito PI, Imura PI, Aihara PI



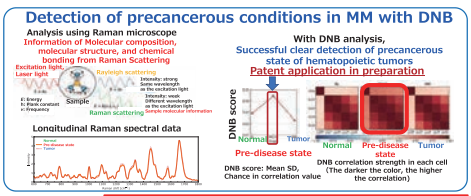
＊Intervention effects of candidate genes narrowed down by DNB theory and control theory in inflammatory bowel disease was also shown to be effective.

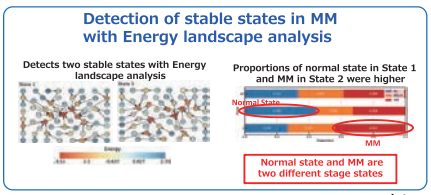
Hayashi PI, Saito PI, Imura PI, Aihara PI

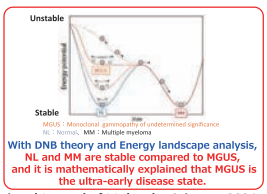
PATENT PENDING

Detection of disease progression process by DNB theory and Energy landscape analysis; Ex. Multiple myeloma, MM

Saito PI, Masuda PI







International Journal of Molecular Sciences 2024

Prototype machine under development with HORIBA, Ltd.

The other important results: Detection of multi-step transitions by DNB theory

Aihara PI

Lung cancer transformation from adenocarcinoma to squamous cell carcinoma, and peripheral blood differentiation with human ES cells

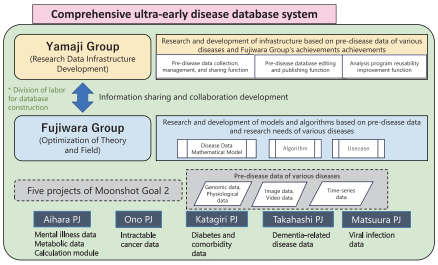
THE INNOVATION 2023

Signal Transduction and Targeted Therapy 2023

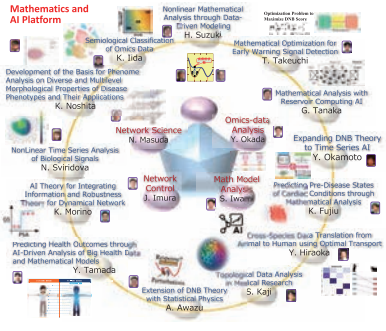
Database construction for smooth integrated analysis in ultra-early disease research

Large-scale ultra-early disease database system construction (National Institute of Informatics, NII, GakuNin RDM)

Project-wide, cross-sectional database for data sharing and mathematical collaboration in ultra-early disease research

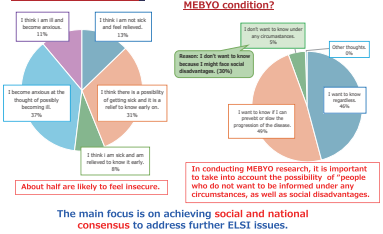


Mathematical analysis system for activation of mathematical collaboration



Examination of ELSI issues

Surveyed 1,020 individuals from the general public to assess awareness of the term "MEBYO," ultra-early disease condition



The main focus is on achieving social and national consensus to address further ELSI issues.

List of major papers

= AIHARA PJ =

Underlined: PM and/or PI

1. K. Aihara, R. Liu, K. Koizumi, X. Liu, and L. Chen: **Dynamical Network Biomarkers: Theory and Applications**, Gene, Vol.808, Article No.145997, pp.1-10, DOI: 10.1016/j.gene.2021.145997 (2022).
2. H. Namkoong, ⋯, Y. Okada: **DOCK2 Is Involved in the Host Genetics and Biology of Severe COVID-19**, Nature, Vol.609, pp.754-760, DOI: 10.1038/s41586-022-05163-5 (2022).
3. YD. Jeong, ⋯, K. Aihara, K. Shibuya, S. Iwami, AI. Bento, and M. Ajelli: **Designing Isolation Guidelines for COVID-19 Patients with Rapid Antigen Tests**, Nature Communications, Vol.13, Article No.4910, pp.1-9, DOI: 10.1038/s41467-022-32663-9 (2022).
4. C. Zuo, Y. Zhang, C. Cao, J. Feng, M. Jiao, and L. Chen: **Elucidating Tumor Heterogeneity from Spatially Resolved Transcriptomics Data by Multi-View Graph Collaborative Learning**, Nature Communications, Vol.13, Article No.5962, pp.1-14, DOI: 10.1038/s41467-022-33619-9 (2022).
5. Y. Okamoto, ⋯, and K. Aihara: **Early Dynamics of Chronic Myeloid Leukemia on Nilotinib Predicts Deep Molecular Response**, npj Systems Biology and Applications, Vol.8, Article No.39, pp.1-10, DOI: 10.1038/s41540-022-00248-3 (2022).
6. H. Tsuneki,et al.: **Food Odor Perception Promotes Systemic Lipid Utilization**, Nature Metabolism, Vol.4, pp.1514-1531, DOI: 10.1038/s42255-022-00673-y (2022).
7. K. Ishigaki, ⋯, Y. Okada, and S. Raychaudhuri: **Multi-Ancestry Genome-Wide Association Analyses Identify Novel Genetic Mechanisms in Rheumatoid Arthritis**, Nature Genetics, Vol.54, No.11, pp.1640-1651, DOI: 10.1038/s41588-022-01213-w (2022).
8. X. Shen, H. Sasahara, M. Morishita, J. Imura, M. Oku, and K. Aihara: **Model-free Dominant Pole Placement for Restabilizing High-Dimensional Network Systems via Small-Sample-Size Data**, IEEE Access, Vol.11, pp.45572-45585, DOI: 10.1109/ACCESS.2023.3274530 (2023).
9. M. Nishide, ⋯, Y. Okada, K. Hattori, M. Narazaki, and A. Kumanogoh: **Single-Cell Multi-Omics Analysis Identifies Two Distinct Phenotypes of Newly-Onset Microscopic Polyangiitis**, Nature Communications, Vol.14, Article No.5789, pp.1-14, DOI: 10.1038/s41467-023-41328-0 (2023).
10. S. Miyamoto, ⋯, S. Iwami, and T. Suzuki: **Infectious Virus Shedding Duration Reflects Secretory Iga Antibody Response Latency After Sars-Cov-2 Infection**, Proceedings of the National Academy of Sciences of the United States of America, Vol.120, No.52, e2314808120, pp.1-10, DOI: 10.1073/pnas.2314808120 (2023).
11. N. Masuda, K. Aihara, and NG. MacLaren: **Anticipating Regime Shifts by Mixing Early Warning Signals from Different Nodes**, Nature Communications, Vol.15, No.1, pp.1-15, DOI: 10.1038/s41467-024-45476-9 (2024).
12. F. Li, ⋯, L. Chen, F. Bai, and D. Gao: **Sex Differences Orchestrated by Androgens at Single-Cell Resolution**, Nature, Vol.629, pp.193-200, DOI: 10.1038/s41586-024-07291-6 (2024).
13. Xiaoshen Zhang, Kai Xiao, Yaokai Wen, Fengying Wu, Guanghui Gao, Luonan Chen, and Caicun Zhou: **Multi-Omics with Dynamic Network Biomarker Algorithm Prefigures Organ-Specific Metastasis of Lung Adenocarcinoma**, Nature Communications, Vol.15, No.1, Article No.9855, pp.19855-19819, DOI: 10.1038/s41467-024-53849-3 (2024).
14. M. Xu, T. Hosokawa, K. Tsutsui, and K. Aihara: **Dynamic Tuning of Neural Stability for Cognitive Control**, Proceedings of the National Academy of Sciences of the United States of America, Vol.121, No.49, e2409487121, pp.1-8, DOI: 10.1073/pnas.2409487121 (2024).
15. Yong Dam Jeong, Keisuke Ejima, Kwang Su Kim, Shoya Iwanami, William S Hart, Robin N Thompson, Il Hyo Jung, Shingo Iwami, Marco Ajelli, Kazuyuki Aihara: **A modeling study to define guidelines for antigen screening in schools and workplaces to mitigate COVID-19 outbreaks**, Communications Medicine, Vol.5, Article No.2, pp.1-13 DOI: 10.1038/s43856-024-00716-3 (2025).
16. X. Shen, H. Sasahara, J. Imura, M. Oku, K. Aihara: **Re-stabilizing Large-Scale Network Systems using High-Dimension Low-Sample-Size Data Analysis**, IEEE Transactions on Emerging Topics in Computational Intelligence, Vol.9, No.2, pp.1638-1649, DOI: 10.1109/TETCI.2024.3442824 (2025).

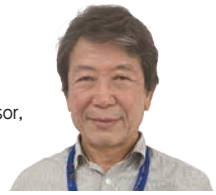
Moonshot R&D | Goal 2, Cancer PJ

Challenge toward the Control of Intractable Cancer through Understanding of Molecular, Cellular, and Interorgan Networks

Project Manager (PM)

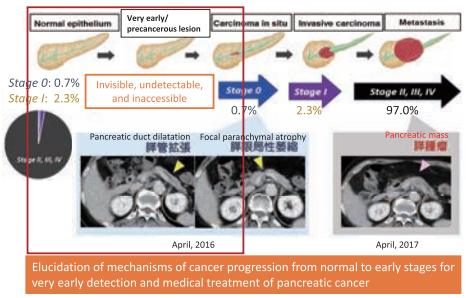
OHNO Shigeo

Special Contract Professor, Juntendo University

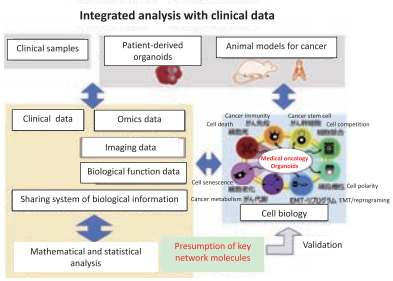


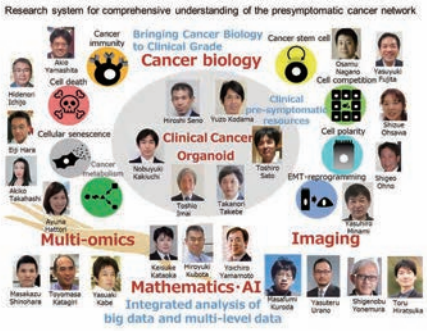
Project Overview and Concept

Target in our project (Refractory cancer: Pancreatic cancer)



Elucidation of mechanisms of cancer progression from normal to early stages for very early detection and medical treatment of pancreatic cancer

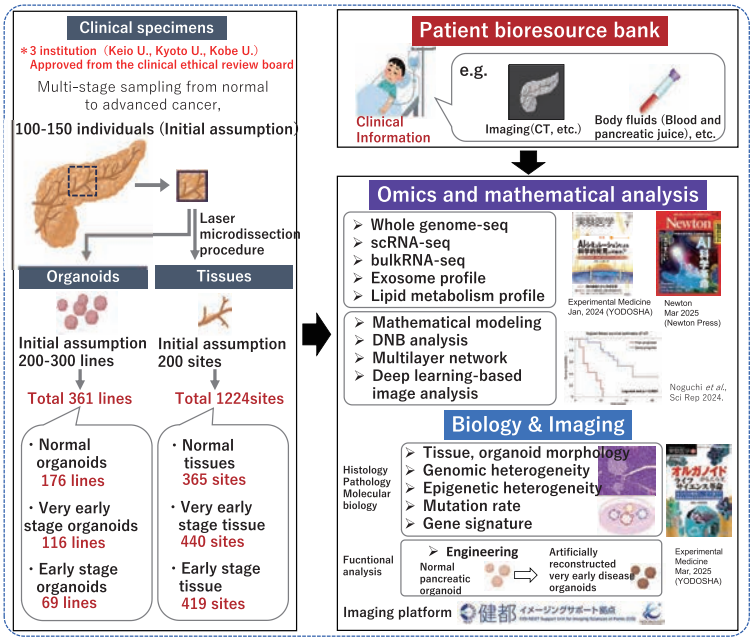




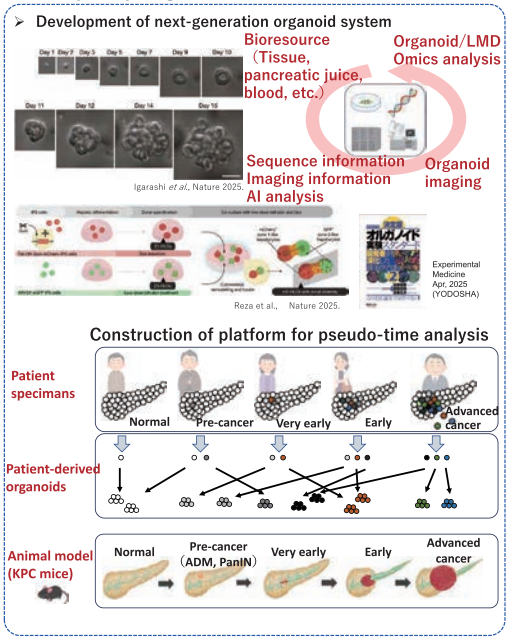
Results

Development of clinical resource of pancreatic cancer at very early stage

Establishment of research bases for collecting and analyzing clinical specimens



Platform for resource of human pancreatic cancer at very early stage

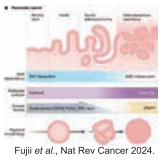


Challenge toward predication and treatment of very early/early cancer through understanding the natural history of cancer

Understanding natural history of cancer

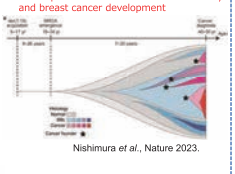
Natural history of pancreatic cancer progression and breast cancer onset

Molecules involved in pancreatic cancer progression and phenotypic evolution



Fujii *et al.*, Nat Rev Cancer 2024.

Phylogenic tree analysis revealed history of the acquisition of chromosomal abnormality and breast cancer development



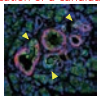
Nishimura *et al.*, Nature 2023.

Unraveling the natural history of cancer driven by the accumulation of genetic mutations and clonal evolution in normal tissues

Maeda and Kakiuchi., Cancer Sci 2024.

Identification of a novel marker for very early stage lesion

Identification of a candidate marker to detect very early pancreatic cancer



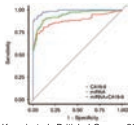
Marker X is overexpressed in human pre-cancerous lesion (ADM)

Pre-cancerous site

Novel technologies for prediction of very early stage cancer

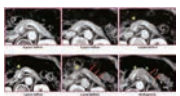
Diagnosis of very early cancer by blood tests and CT imaging

Toward Early Detection with Circulating miRNA and Artificial Intelligence



Kawai *et al.*, British J Cancer 2024.

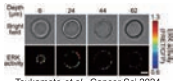
Abnormalities can be detected several years before onset



Gonda *et al.*, United Euro Gastroenterol J 2024.

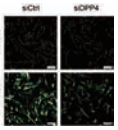
Development of biosensors and molecular probes

Deciphering ERK and AMPK activity dynamics in pancreatic cancer organoids using Biosensors



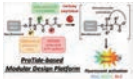
Tsukamoto *et al.*, Cancer Sci 2024.

Visualization of senescent cells using a DPP4-targeted fluorescent probe



Tanaka *et al.*, Cancer Sci 2024

Fluorescent probe targeting proteolytic enzymes enables detection of tumor protease activity



Kuriki *et al.*, J Am Chem Soc 2023.

Identification of novel therapeutic targets against very early cancer

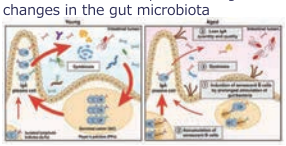
Epigenomic Alterations in the Malignant Progression of Pancreatic Cancer

EZH2 inhibition as a promising strategy for pancreatic cancer therapy, with epigenomic signatures enabling ultra-early detection

Tamagawa *et al.*, Nat Cell Biol 2024

Bacterial induction of senescence promotes age-related changes in the gut microbiota

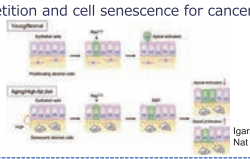
Identification of gut microbiota that promote tumorigenesis in senescent cells and their potential as targets for cancer prevention



Kawamoto *et al.*, Nat Cell Biol 2023

Cell competition and cell senescence for cancer onset

Uncovering the initiation mechanisms of ultra-early lesions involving cell competition and senescence, with predictive potential using a senescent cell imaging probe



Igarashi *et al.*, Nat Commun 2022

List of major papers

= OHNO PJ =

Underlined: PM or PI

1. **Early detection of pancreatic cancer by comprehensive serum miRNA sequencing with automated machine learning**
   Kawai M, Seno H, et al. (2024) British Journal of Cancer, 131 (7),1158-1168.
2. **Wnt-deficient and hypoxic environment orchestrates squamous reprogramming of human pancreatic ductal adenocarcinoma**
   Tamagawa H, Kodama Y, Kakiuchi N, Seno H, Sato T, et al. (2024) Nature Cell Biology, 26 (10), 1759-1772.
3. **Evolutionary histories of breast cancer and related clones**
   Nishimura T, Kakiuchi N, Sato T, et al. (2023) Nature, 620 (7974), 607-614.
4. **Generation of human adult hepatocyte organoids with metabolic functions**
   Igarashi R, Sato T, et al. (2025) Nature, 641 (8065),1248-1257.
5. **Multi-zonal liver organoids from human pluripotent stem cells**
   HA Reza,Takebe T, et al. (2025) Nature, 641 (8065),1258-1267.
6. **Self-organization of sinusoidal vessels in pluripotent stem cell-derived human liver bud organoids**
   Saiki N, Takebe T, et al. (2025) Nat Biomed Eng. doi: 10.1038/s41551-025-01416-6.
7. **Temporal progression of pancreatic cancer computed tomography findings until diagnosis: A large-scale multicenter study**
   Gonda M, Kodama Y, et al. (2024) United European Gastroenterol J, 12 (6),761-771.
8. **Quantitative live imaging reveals phase dependency of PDAC patient-derived organoids on ERK and AMPK activity**
   Tsukamoto S, Kakiuchi N, Seno H, Matsuda M, Hiratsuka T, et al. (2025) Cancer Science, 116 (3),724-735.
9. **Single-molecule oxidoreductase activity analysis for activity-based diagnosis based on proteoform alterations**
   Minoda M, Urano Y, et al. (2024) Journal of the American Chemical Society, 147 (6),4743-4751.
10. **Prognosis prediction of PDAC via detection of O-glycan altered extracellular vesicles in perioperative sera**
    Uemura S, Kabe Y, et al. (2024) Cancer Science, 115 (11), 3718-3728.
11. **Pan-cancer comparative and integrative analyses of driver alterations using Japanese and international genomic databases**
    Horie S, Kataoka K, et al. (2024) Cancer Discovery ,14 (5), 786-803.
12. **Deep learning predicts 1-year prognosis of pancreatic cancer patients using positive peritoneal washing cytology**
    Noguchi A, Yamamoto Y, et al. (2024) Scientific Reports ,14 (1),17059.
13. **Machine learning of histopathological images predicts recurrences of resected pancreatic ductal adenocarcinoma with adjuvant treatment**
    Yamaguchi R, Yamamoto Y, et al. (2024) Pancreas, 53 (2), e199-e204.
14. **Comparison of hepatic responses to glucose perturbation between healthy and obese mice based on the edge type of network structures**
    Ito Y, Kubota H, et al. (2023) Scientific Reports, 13(1), 4758.
15. **Dipeptidylpeptidase-4-targeted activatable fluorescent probes visualize senescent cells**
    Tanaka H, Urano Y, Takahashi A, et al. (2024) Cancer Science, 115 (8), 2762-2773.
16. **Mitochondrial fatty acid oxidation drives senescence**
    Yamauchi S, Takahashi A, Ichijo H, et al. (2024) Science Advances, 10 (43), eado5887.
17. **Bacterial induction of B cell senescence promotes age-related changes in the gut microbiota**
    Kawamoto S, Hara E, et al. (2023) Nature Cell Biology, 25 (6), 865-876
18. **mTOR-mediated p62/SQSTM1 stabilization confers a robust survival mechanism for ovarian cancer**
    Tamura T, Nagano O, et al. (2025) Cancer Letters, 616, 217565.
19. **Asymmetric cell division of ALDH1-positive cancer stem cells generates glycolytic metabolically diverse cell populations**
    Tamori S, Ohno S, et al. (2025) Scientific Reports, 15 (1), 13932.
20. **Macrophages promote tumor growth by phagocytosis-mediated cytokine amplification in *Drosophila***
    Hirooka E, Ohsawa S, et al. (2025) Current Biology, 35 (13), 3209-3227.

Moonshot R&D | Goal 2, Diabetes PJ

Challenge for Eradication of Diabetes and Comorbidities through Understanding and Manipulating Homeostatic Systems

Project Manager (PM)
KATAGIRI Hideki
Professor,
Tohoku University

Project Outlook and Concept

Project Structure

Project Manager (PM) : Hideki KATAGIRI

Representative Institution : Tohoku University
Assistant PM: Shinichi FUKUSHIGE

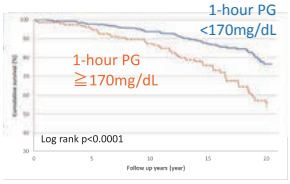
1. Inter-organ Network Elucidation and Control	2. Mechanism of Multi-organ Transformation	3. Human Biometric Data Acquisition and Data Analysis	4. Mathematical Model Analysis	5. Establishment of Pre-symptomatic Stage Database
Junken AOKI（Tokyo U）	Ichiro MANABE（Chiba U）	Katsuhito FUJIU（Tokyo U）	Hiroshi SUITO（Tohoku U）	Hideki KATAGIRI（Tohoku U）
Asuka INOUE（Kyoto U）	Kazuhiro SUZUKI（Osaka U）	Gen TAMIYA（Tohoku U）	Hayato CHIBA（Tohoku U）	Junken AOKI（Tokyo U）
Takayuki DOI（Tohoku U）	Kuniyasu NIIZUMA（Tohoku U）	Hideki KATAGIRI（Tohoku U）	Masaharu NAGAYAMA（Hokkaido U）	Ikuo KIMURA（Kyoto U）
Hideki KATAGIRI（Tohoku U）	Hideki KATAGIRI（Tohoku U）	Shojiro SAWADA（Tohoku Med Pha U）		Ichiro MANABE（Chiba U）
Kazuhiro NAKAMURA（Nagoya U）	Kazuto MASAMOTO（UEC）			Katsuhito FUJIU（Tokyo U）
Yoshiyuki KASAHARA（Tohoku U）	Shinji KUME（Shiga Med U）			Jun TAKAYAMA（Tohoku U）
Kuniyasu NIIZUMA（Tohoku U）	Katsuhiko MATSUMOTO（Tokyo U）			Yutaka HASEGAWA（Iwate Med U）
Ikuo KIMURA（Kyoto U）	Rikuhiro YAMADA（Kurume U）			Tetsuya YAMADA（Science Tokyo）
Toshiaki TERATANI（Keio U）				
Misa YOSHIMOTO（Nara W' U）				
Tetsuya YAMADA（Science Tokyo）				
Yukio NISHIMURA（TMIMS）				

Aihara/Takahashi Project
Shinji NAKAOKA（Hokkaido U）

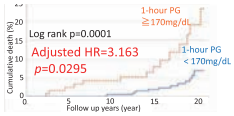
Why mibyo ?

Even in subjects with normal glucose tolerance, the 1-hour post-load plasma glucose shortens life expectancy, due to arteriosclerosis and cancer.

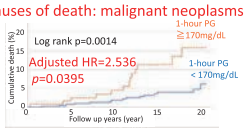
Survival Rates of NGT participants



Causes of death: cardio-vascular diseases



Causes of death: malignant neoplasms



Toward searching for markers of life expectancy

Toward discovering the determinants of life expectancy

PNAS Nexus 4:pgaf179, 2025

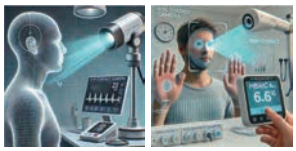
Results

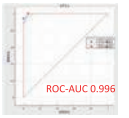
1. Development of simple detection (Challenge:Diabetes is asymptomatic)

Fujiu PI

Accurate prediction of prediabetes using still images of face

~Hyperspectral image~



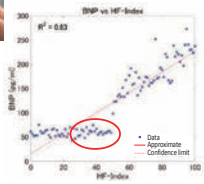


HbA1c≧6.5%,
Accuracy:81.8%
(At the present time)

Patent (U.S.) 2023/10/27, 63/545944

Detecting heart failure early with at-home ECG measurements

~AI algorithm~ Wearable device



The sensitivity for detecting heart failure is superior to that of BNP values measured in gold standard blood test.

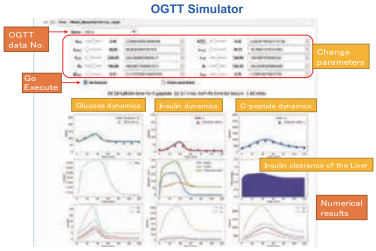
PCT pending

2. Elucidation of individual pathogenic mechanisms (Challenge:Diabetes has diverse pathogenic mechanisms)

Nagayama PI

Developing mathematical model simulator
～Visualization of metabolic states of each organ～

OGTT Simulator

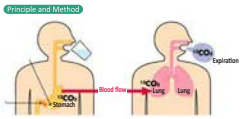


Determine the individual's mechanism of pathogenesis

Detecting liver glucose disposal capacity

Katagiri PI

^{13}C-glucose breath tests



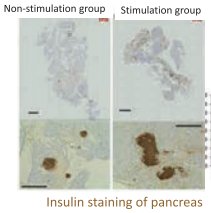
Determine ultra-early stages without drawing blood

Patented in Japan, U.S., and Europe

3. Development of interventions for each mechanism of pathogenesis (Challenge:Diabetes is progressive and incurable)

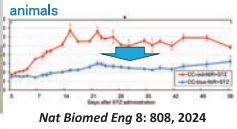
Katagiri PI

Succeeded in growing insulin-producing cells in mice



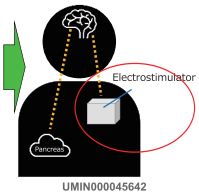
Insulin staining of pancreas

Vagus nerve stimulation increased insulin-producing cells and inhibited diabetes progression in model animals



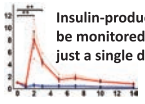
Nat Biomed Eng 8: 808, 2024

Currently in clinical trial



UMIN000045642

Developed a system that can monitor proliferation of insulin-producing cells



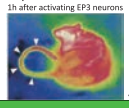
Insulin-producing cell growth can be monitored at any time using just a single drop of blood.

Nat Commun 14: 3253, 2023

Compound searching

Controlled energy consumption in the brain

Elucidated the mechanisms of body temperature and metabolism regulation

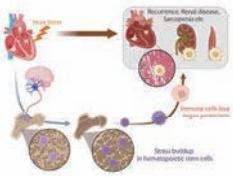


To develop technology to increase metabolism and prevent obesity

Sci Adv 8: eadd5463, 2022

Elucidated the multimorbidity mechanisms of heart failure

Manabe PI

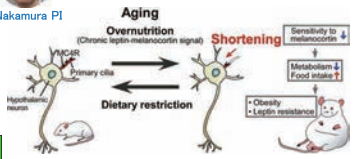


Fujiu PI

Sci Immunol 9:eade3814, 2024

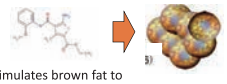
Nakamura PI

Elucidated mechanisms of middle-aged weight gain



Cell Metab 36:1044, 2024

Discovery of brown fat stimulants



Hasegawa PI

Stimulates brown fat to increase energy expenditure: To develop technologies to eat without weight gain

Obesity 32:324, 2024

Patented

List of major papers

= KATAGIRI PJ =

Underlined: PM and/or PI

1. **Redox-dependent liver gluconeogenesis impacts different-intensity exercise**
   Horiuchi T, Katagiri H, et al. *Nat. Metab.* in press
2. **Sex difference in BAT thermogenesis depends on PGC-1 α -mediated phospholipid synthesis in mice**
   Takeuchi A, Aoki J, Yamada T, et al. *Nat. Commun.* in press
3. **One-hour postload glucose levels predict mortality from cardiovascular diseases and malignant neoplasms in healthy subjects**
   Sato D, Katagiri H et al. *PNAS Nexus* **4**, pgaf179 (2025). DOI: 10.1093/pnasnexus/pgaf179
4. **Colonic inflammation triggers β cell proliferation during obesity development via a liver-to-pancreas interorgan mechanism**
   Kubo H, Katagiri H, et al. *JCI Insight* **10**, e183864 (2025). DOI: 10.1172/jci.insight.183864.
5. **Heart failure monitoring with a single-lead electrocardiogram at home**
   Hasumi E, Fujiu K, et al. *Int. J. Cardiol.* **432**,133203 (2025). DOI: 10.1016/j.ijcard.2025.133203.
6. **Sucrose-preferring gut microbes prevent host obesity by producing exopolysaccharides**
   Shimizu H, Kimura I, et al. *Nat. Commun.* **16**, 1145 (2025). DOI: 10.1038/s41467-025-56470-0
7. **Machine learning-based reproducible prediction of type 2 diabetes subtypes**
   Tanabe H, Katagiri H, Tamiya G, et al. *Diabetologia* **67**, 2446-2458 (2024). DOI: 10.1007/s00125-024-06248-8
8. **Heart failure promotes multimorbidity through innate immune memory**
   Nakayama Y, Fujiu K, Manabe I, et al. *Sci. Immunol.* **9**, eade3814 (2024). DOI: 10.1126/sciimmunol.ade3814
9. **Age-related ciliopathy: Obesogenic shortening of melanocortin-4 receptor-bearing neuronal primary cilia**
   Oya M, Nakamura K, et al. *Cell Metab.* **36**, 1044-1058 (2024). DOI: 10.1016/j.cmet.2024.02.010
10. **A newly identified compound activating UCP1 inhibits obesity and its related metabolic disorders**
    Onodera K, Hasegawa Y, Katagiri H, et al. *Obesity* **32**, 324-338 (2024). DOI: 10.1002/oby.23948
11. **Optogenetic stimulation of vagal nerves for enhanced glucose-stimulated insulin secretion and β cell proliferation**
    Kawana Y, Sawada S, Yamada T, Niizuma K, Katagiri H, et al. *Nat. Biomed. Eng.* **8**, 808-822 (2024). DOI: 10.1038/s41551-023-01113-2
12. **Phagocytosis by macrophages promotes pancreatic β cell mass reduction after parturition in mice**
    Endo A, Katagiri H, et al. *Dev. Cell* **58**, 1819-1829 (2023). DOI: 10.1016/j.devcel.2023.08.002
13. **A highly sensitive strategy for monitoring real-time proliferation of targeted cell types in vivo**
    Sugawara H, Sawada S, Katagiri H, et al. *Nat. Commun.* **14**, 3253 (2023). DOI: 10.1038/s41467-023-38897-5
14. **Inter-organ insulin-leptin signal crosstalk from the liver enhances survival during food shortages**
    Takahashi K, Yamada T, Sawada S, Katagiri H, et al. *Cell Rep.* **42**, 112415 (2023). DOI: 10.1016/j.celrep.2023.112415
15. **Celastrol suppresses humoral immune responses and autoimmunity by targeting the COMMD3/8 complex**
    Shirai T, Suzuki K, et al. *Sci. Immunol.* **8**, eadc9324 (2023). DOI: 10.1126/sciimmunol.adc9324
16. **Prostaglandin EP3 receptor-expressing preoptic neurons bidirectionally control body temperature via tonic GABAergic signaling**
    Nakamura Y, Nakamura K, et al. *Sci. Adv.* **8**, eadd5463 (2022). DOI: 10.1126/sciadv.add5463
17. **An oxytocinergic neural pathway that stimulates thermogenic and cardiac sympathetic outflows**
    Fukushima A, Kataoka N, Nakamura K. *Cell Rep.* **40**, 111380 (2022). DOI: 10.1016/j.celrep.2022.111380

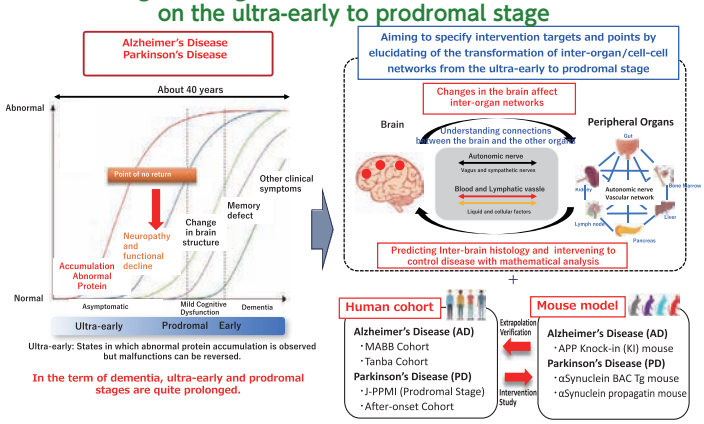
Moonshot R&D　Goal 2, ementia PJ

Towards Overcoming Disorders Linked to Dementia based on a Comprehensive Understanding of Multiorgan Network

Project Manager (PM)
TAKAHASHI Ryosuke
Specially Appointed Professor,
Kyoto University

Project Outlook and Concept

Elucidating inter-organ network transformations with a focus on the ultra-early to prodromal stage



Ultra-early: States in which abnormal protein accumulation is observed but malfunctions can be reversed.

In the term of dementia, ultra-early and prodromal stages are quite prolonged.

Basic Analysis and Basic Technology Development: Establishment of cutting-edge basic analysis technology and innovative fundamental technology
Supervisor: T. Ohtsuka, PI: R. Nitta, H. Hioki, A. Watabe, H. Hanafusa, H. Maruoka

Provide multi-modality data based on new technologies
Provide new technologies
Provide clinical samples and data
Validate with a mathematical model and provide feedback
Identify social issues for ultra-early prediction and intervention, and provide support or social implementation

ELSI Research: Collaboration through patient and citizen participation
Supervisor: K. Muto,

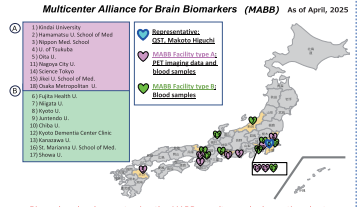
AI and Mathematical research: Integrated data management and development of mathematical models
Supervisor: N. Honda, PI: N. Okada, R. Kojima, T. Matsuda, S. Nakaoka, Y. Kondo

Disease Research: Examination of the effects between organs
Alzheimer's Diseases
Supervisor: K. Yamanaka, PI: T. Saito, T. Tomita, T. Satoh, M. Higuchi, M. Tsuda, H. Hibino, T. Furukawa
Vascular and Mixed Dementia
Supervisor: N. Mochizuki, PI: Y. Kubota, T. Maki, R. Matsumoto, K. Mizutani
Parkinson's Disease-Related Dementia
Supervisor: N. Hattori, PI: H. Yamakado, S. Miyake, H. Matsui, M. Kinoshita

Results

Cohort in the ultra-early stage dementia

Establishment of multi-center cohorts



Biomarker development using the *MABB*, an ultra-early dementia cohort.

Connection to J-PPMI

Prof. Yuji TAKAHAShI PI（J-PPMI Representative）

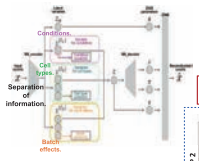
A prospective cohort study of RBD patients, a high-risk group for developing Parkinson's disease.

Elucidation of inter-organ networks

A new method developed to reduce batch effects in single-cell analysis.

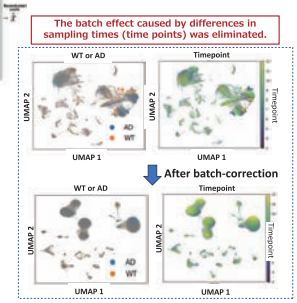
Honda PI

Kanade : A method utilizing deep generative models.



Separation and correction of batch effects using deep generative models.

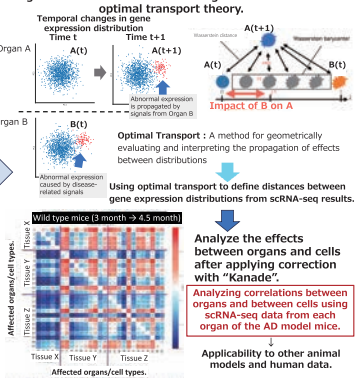
- bioRxiv, 2025
- Patent application. 2024-162597



Development of mathematical models for inter-organ transmission

Honda PI

Organomix : Estimation of inter-organ effects based on optimal transport theory.



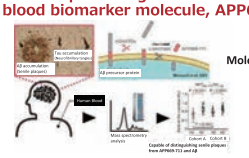
Observation and identification of Ultra-early dementia biomarkers

Search for Novel Biomarkers

Elucidated producing mechanism of early AD blood biomarker molecule, APP669-711

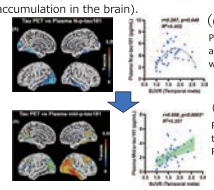
Tomita PI

Molecular Psychiatry 2023



Developing a novel, highly sensitive detection system for blood phosphorylated tau. Highchu PI

An AD biomarker correlated with tau PET (which reflects tau accumulation in the brain).



(**Conventional method**)
Plasma p-tau levels, especially in advanced stages, lost their correlation with tau accumulation observed by PET.

(**New Method**)
Plasma p-tau levels correlated with tau accumulation as measured by PET even in advanced stages.

Transl Neurodegener. 2024

Detection of immune alterations in predromal stages using blood from AD/PD mice. Satoh PI, Maki PI, Yamakado PI

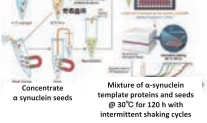
Aiming to develop preventive treatments, we are currently examining the changes in the peripheral blood of patients.

Development of abnormal protein identification

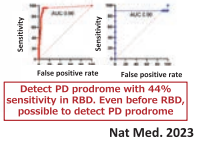
Measurement of few α-synuclein seed in serum

Hattori PI

Enable to measure With IP



Enable to identify with an AUC 0.9 and up.



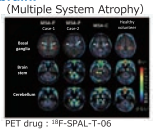
Detect PD prodrome with 44% sensitivity in RBD. Even before RBD, possible to detect PD prodrome

Nat Med. 2023

PET Imaging of α-synuclein seed

Higuchi PI

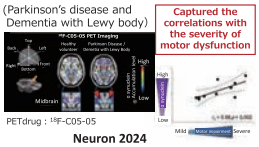
1st challenge: Successful visualization α-synuclein in a living brain.
(Multiple System Atrophy)



Mov Disord. 2022

2nd challenge: Successful visualization of diseases with low α-synuclein accumulation.
(Parkinson's disease and Dementia with Lewy body)

Captured the correlations with the severity of motor dysfunction

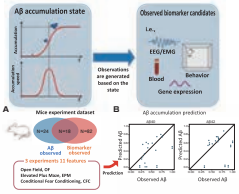


Neuron 2024

Prediction of abnormal protein accumulation in brain from blood sample or by non-invasive monitoring

Predicting Aβ accumulation from action data of AD mice.

Honda PI

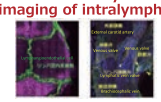


Predicting Aβ accumulation from cytokine in blood.

Yamanaka PI・Honda PI

High resolution imaging and functional imaging

Successful analysis of vascular structure and imaging of intralymphatic structure in transparent.



Mochizuki PI, Kubota PI, Maki PI

Extracerebral excretion of Aβ and abnormalities in lymphatic valves and cerebrospinal fluid annulation are under investigation

List of major papers

= TAKAHASHI PJ =

Underlined: PM and/or PI

1. **ADAMTS4 is involved in the production of the Alzheimer disease amyloid biomarker APP669-711**
   Matsuzaki M, Yokoyama M, Yoshizawa Y, Kaneko N, Naito H, Kobayashi H, Korenaga A, Sekiya S, Ikemura K, Opoku G, Hirohata S, Iwamoto S, Tanaka K, Tomita T.
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2. **Few-shot prediction of amyloid β accumulation from mainly unpaired data on biomarker candidates**
   Yada Y, Honda N.
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   Iga T, Kobayashi H, Kusumoto D, Sanosaka T, Fujita N, Tai-Nagara I, Ando T, Takahashi T, Matsuo K, Hozumi K, Ito K, Ema M, Miyamoto T, Matsumoto M, Nakamura M, Okano H, Shibata S, Kohyama J, Kim KK, Takubo K, Kubota Y.
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4. **High-Throughput CSF Proteomics and Machine Learning to Identify Proteomic Signatures for Parkinson Disease Development and Progression**
   Tsukita K, Sakamaki-Tsukita H, Kaiser S, Zhang L, Messa M, Serrano-Fernandez P, Takahashi R.
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5. **Propagative α -synuclein seeds as serum biomarkers for synucleinopathies**
   Okuzumi A, Hatano T, Matsumoto G, Nojiri S, Ueno SI, Imamichi-Tatano Y, Kimura H, Kakuta S, Kondo A, Fukuhara T, Li Y, Funayama M, Saiki S, Taniguchi D, Tsunemi T, McIntyre D, Gérardy JJ, Mittelbronn M, Kruger R, Uchiyama Y, Nukina N, Hattori N.
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6. **Imaging α -synuclein pathologies in animal models and patients with Parkinson's and related diseases**
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   Tagai K, Tatebe H, Matsuura S, Hong Z, Kokubo N, Matsuoka K, Endo H, Oyama A, Hirata K, Shinotoh H, Kataoka Y, Matsumoto H, Oya M, Kurose S, Takahata K, Ichihashi M, Kubota M, Seki C, Shimada H, Takado Y, Kawamura K, Zhang MR, Soeda Y, Takashima A, Higuchi M, Takahiko Tokuda.
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8. **Microglial cannabinoid receptor type II stimulation improves cognitive impairment and neuroinflammation in Alzheimer's disease mice by controlling astrocyte activation.**
   Sobue A, Komine O, Endo F, Kakimi C, Miyoshi Y, Kawade N, Watanabe S, Saito Y, Murayama S, Saido TC, Saito T, Koji Yamanaka.
   Cell Death Dis. 2024, 15, 858. doi: 10.1038/s41419-024-07249-6.

9. **α -Synuclein orchestrates Th17 responses as antigen and adjuvant in Parkinson's disease.**
   Furusawa-Nishii E, Solongo B, Rai K, Yoshikawa S, Chiba A, Okuzumi A, Ueno S, Hoshino Y, Imamichi-Tatano Y, Kimura H, Hatano T, Hattori N, Miyake S.
   J Neuroinflammation. 2025, 22, 38. doi: 10.1186/s12974-025-03359-w.

10. **A three dimensional immunolabeling method with peroxidase-fused nanobodies and fluorochromized tyramide-glucose oxidase signal amplification**
    Yamauchi K, Koike M, Hioki H.
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Moonshot R&D

Goal 2, Virus Infection PJ

Understanding and Control of Virus-Human Interaction Networks

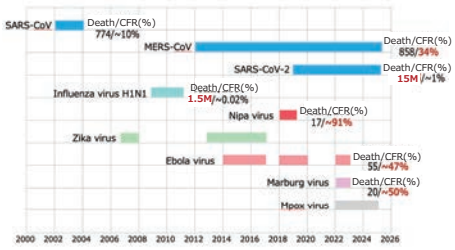
Project Manager (PM)

MATSUURA Yoshiharu

Specially Appointed Professor,
The University of Osaka

Project Outlook and Concept

Most major viral infectious diseases since 2000 are zoonoses

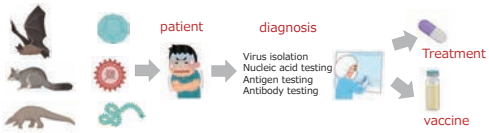


Viruses with high pandemic potential by NIH

Family/Order	Genome	Viral Disease
Coronavirus	RNA (+)	SARS, MERS, COVID-19
Bunyavirus	RNA (-)	Rift Valley fever, Hemorrhagic fever with renal syndrome Crimean-Congo hemorrhagic fever
Filoviruses	RNA (-)	Ebola hemorrhagic fever, Marburg hemorrhagic fever
Flaviviruses	RNA (+)	Yellow fever , Dengue fever , Zika virus infection
Paramyxoviruses	RNA (-)	Hendra virus infection Nipah virus infection
Picornaviruses	RNA (+)	Enterovirus A71/D68 Infection
Togavirus	RNA (+)	Chikungunya fever

No organism can survive without a healthy ecosystem

Countermeasures against viral infections



Predicting viral infections is difficult
It takes time to develop a vaccine or treatment

Infectious disease countermeasures are delayed, causing enormous damage to society

Against future pandemics
Preemptive measures need to be prepared

Classification of viruses based on host response patterns

Classification of viruses into patterns of network structures using the database of biological responses to viral infections

Develop therapeutics for each pattern

Rapid diagnosis and countermeasures

Project goals and outcomes

Characteristics of this project : Focus on virus

- Identification of target molecules involved in the progression of SARS-CoV-2
- Proof of therapeutic efficacy in intervention studies using mouse infection models
- Analyses of other viral infection models are also progressing smoothly
- Results are being achieved through collaboration between experimental science and mathematical science

Key Research Findings

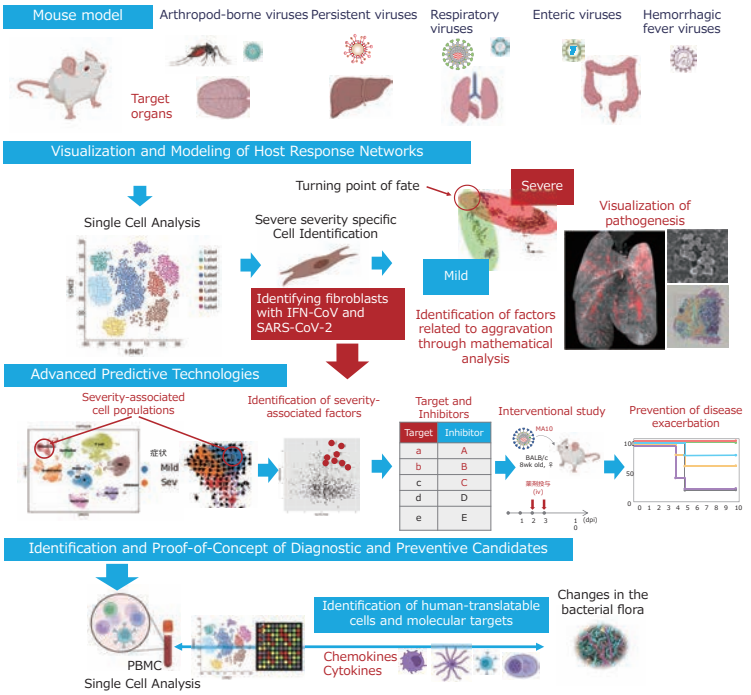
This project aims to elucidate the mechanisms of host responses that lead to the severity of viral infections and to establish a novel framework for prediction and prevention. Since its launch in 2020, the project has made significant progress in the following areas:

- **Visualization and Modeling of Host Response Networks**
  Comprehensive analysis of host immune response patterns in the early stages of infection has been conducted. Mathematical models have been developed to visualize these dynamics, enabling the identification of response patterns associated with high risk of severe disease.

- **Advanced Predictive Technologies**
  AI-based prediction algorithms have been developed through the integration of clinical human data and animal models. A highly accurate model for predicting severe viral infection outcomes (with ROC AUC above 0.85) is currently under construction.

- **Identification and Proof-of-Concept of Diagnostic and Preventive Candidates**
  Early infection biomarkers and host target factors have been successfully identified. Preclinical studies to verify the efficacy of preventive interventions targeting these factors are underway.

Through these achievements, the project is steadily progressing toward its 2030 goal: the control of infectious diseases through ultra-early prediction and prevention.



List of major papers

= MATSUURA PJ =

Underlined: PM and/or PI

1. **N-glycosylation of rotavirus NSP4 protein affects viral replication and pathogenesis**
   Jeffery A. Nurdin, Tomohiro Kotaki, Takahiro Kawagishi, Shintaro Sato, Moeko Yamasaki, Ryotaro Nouda, Shohei Minami, Yuta Kanai, Takeshi Kobayashi.
   Journal of Virology, 2023, DOI: 10.1128/jvi.01861-22

2. **Characterization of Sialic Acid-Independent Simian Rotavirus Mutants in Viral Infection and Pathogenesis**
   Moeko Yamasaki, Yuta Kanai, Yoshiki Wakamura, Tomohiro Kotaki, Shohei Minami, Ryotaro Nouda, Jeffery A Nurdin, Takeshi Kobayashi.
   Journal of Virology, 2023, DOI: 10.1128/jvi.01397-22

3. **A genetic method specifically delineates Th1-type Treg cells and their roles in tumor immunity.**
   Okamoto M, Sasai M, Kuratani A, Okuzaki D, Arai M, Wing JB, Sakaguchi S, Yamamoto M.
   Cell Reports, 2023, DOI: 10.1016/j.celrep.2023.112813

4. **Generation of single-round infectious rotavirus with a mutation in the intermediate capsid protein VP6**
   Tomohiro Kotaki, Yuta Kanai, Megumi Onishi, Shohei Minami, Zelin Chen, Ryotaro Nouda, Jeffery Nurdin, Moeko Yamasaki, and Takeshi Kobayashi.
   Journal of virology, 2024, 98(7.0), p.e00762-24 DOI: 10.1128/jvi.00762-24

5. **Tff1-expressing Tregs in lung prevent exacerbation of Bleomycin-induced pulmonary fibrosis.**
   Masaaki Okamoto, Ayumi Kuratani, Daisuke Okuzaki, Naganori Kamiyama, Takashi Kobayashi, Miwa Sasai, Masahiro Yamamoto.
   Frontiers in Immunology, 2024, 15 DOI: 10.3389/fimmu.2024.1440918

6. **Establishment of reverse genetics systems for Colorado tick fever virus**
   Shohei Minami, Ryotaro Nouda, Katsuhisa Hirai Zelin Chen, Tomohiro Kotaki, Yuta Kanai, Takeshi Kobayashi.
   PLOS Pathogens, 2025, 21(2.0), p.e1012921 DOI: 10.1371/journal.ppat.1012921

7. **Rapid production of recombinant rotaviruses by overexpression of NSP2 and NSP5 genes with modified nucleotide sequences.**
   Yuta Kanai, Tomohiro Kotaki, Satoko Sakai, Toshie Ishisaka, Kayoko Matsuo, Yukino Yoshida, Katsuhisa Hirai, Shohei Minami, Takeshi Kobayashi.
   Journal of virology, 2024, 98(12.0), p. e00996-24 DOI: 10.1128/jvi.00996-24

8. **Non-negative tensor factorization workflow for time series biomedical data**
   Koki Tsuyuzaki, Naoki Yoshida, Tetsuo Ishikawa, Yuki Goshima, Eiryo Kawakami.
   STAR Protocols, 2023, vol. 4(3.0), p.102318 DOI: 10.1016/j.xpro.2023.102318

9. **Monitoring of blood biochemical markers for periprosthetic joint infection using ensemble machine learning and UMAP embedding.**
   Eiryo Kawakami, Naomi Kobayashi, Yuichiro Ichihara, Tetsuo Ishikawa, Hyonmin Choe, Akito Tomoyama, and Yutaka Inaba.
   Archives of orthopaedic and trauma surgery, 2023, vol. 143, p.6057 DOI: 10.1007/s00402-023-04898-8

10. **Development of a robust predictive model for neutropenia after esophageal cancer chemotherapy using GLMMLasso.**
    Shuhei Sugaya, Masashi Uchida, Takaaki Suzuki, Eiryo Kawakami, Itsuko Ishii.
    International journal of clinical pharmacy, DOI: 10.1007/s11096-024-01836-5

11. **Prediction of cccDNA dynamics in hepatitis B patients by a combination of serum surrogate markers**
    Kwang Su Kim, Masashi Iwamoto, Kosaku Kitagawa, Hyeongki Park, Sanae Hayashi, Senko Tsukuda, Takeshi Matsui, Masanori Atsukawa, Kentaro Matsuura, Natthaya Chuaypen, Pisit Tangkijvanich, Lena Allweiss, Takara Nishiyama, Naotoshi Nakamura, Yasuhisa Fujita, Eiryo Kawakami, Shinji Nakaoka, Masamichi Muramatsu, Kazuyuki Aihara, Takaji Wakita, Alan S. Perelson, Maura Dandri, Koichi Watashi, Shingo Iwami, Yasuhito Tanaka.
    PLoS computational biology, 2025, 21(1.0), p.e1012615 DOI: 10.1371/journal.pcbi.1012615

Contacts

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

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Challenge toward the Control of Intractable Cancer through Understanding of Molecular, Cellular, and Interorgan Networks

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Challenge for Eradication of Diabetes and Comorbidities through Understanding and Manipulating Homeostatic Systems

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Towards Overcoming Disorders Linked to Dementia based on a Comprehensive Understanding of Multiorgan Network

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Understanding and Control of Virus-Human Interaction Networks

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Cabinet Office: About Moonshot Research and Development Program

Web site https://www8.cao.go.jp/cstp/english/moonshot/system_en.html

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Memo

Handout (Moonshot Goal2)

Booklet for BioJapan2025

https://www.jst.go.jp/moonshot/sympo/20251008/index.html

About Moonshot Goal2

https://www.jst.go.jp/moonshot/en/program/goal2/index.html

Progress Report

https://www.jst.go.jp/moonshot/en/program/report.html#MS2

Moonshot R&D/JST

https://www.jst.go.jp/moonshot/en/index.html

Moonshot R&D/Cabinet Office

https://www8.cao.go.jp/cstp/english/moonshot/top.html

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