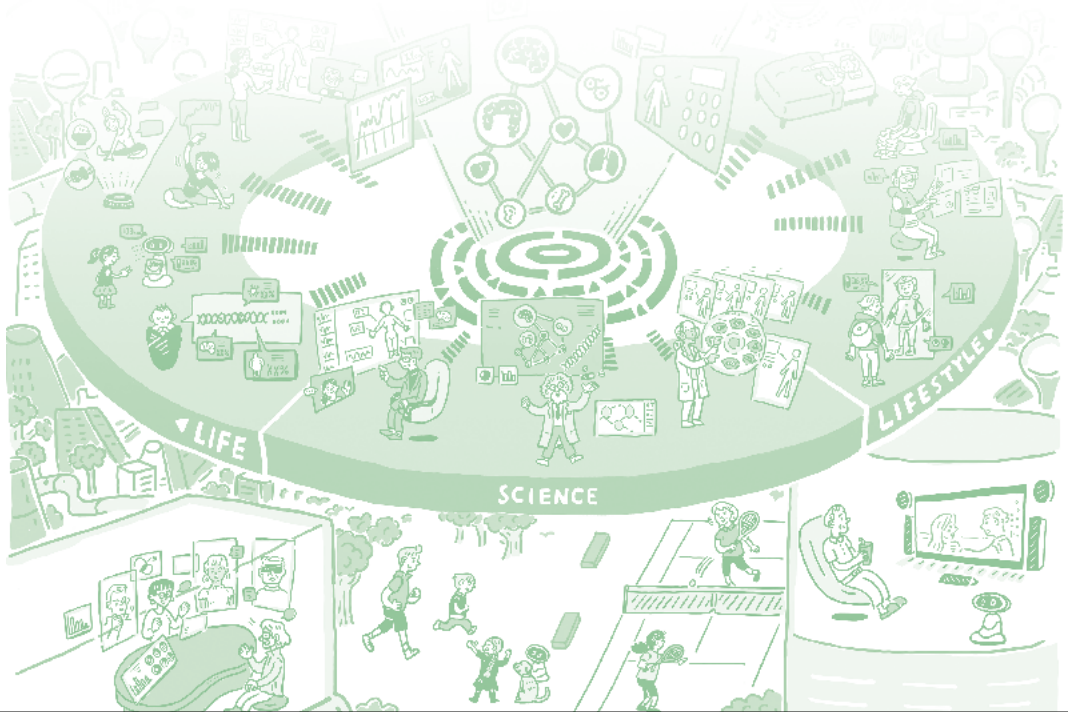
Moonshot Goal 2

Progress Report 2024

Realization of ultra-early disease prediction and intervention by 2050

MOONSHOT
RESEARCH & DEVELOPMENT PROGRAM

Contents

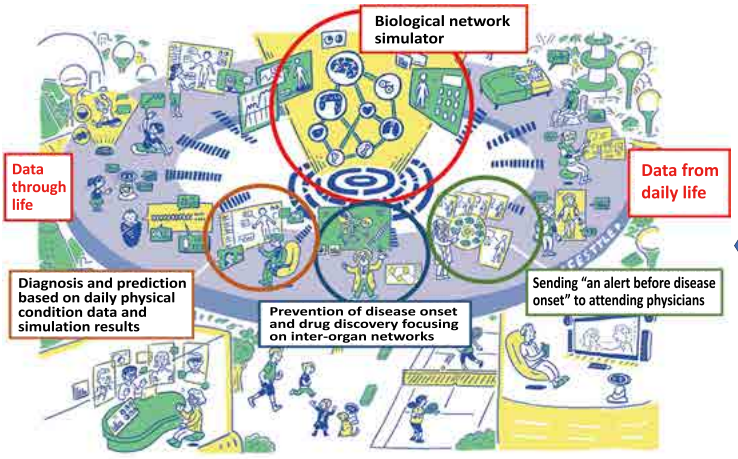


Moonshot R&D Goal 2

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

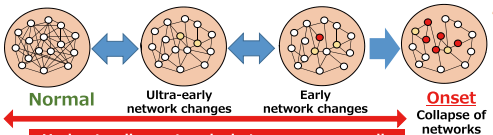
Milestone:
We will establish methods to identify precursors of refractory diseases such as cancer, dementia, diabetes, and viral infections and develop technologies to prevent them or restore the body to a normal state.

(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.

Ultra-early disease prediction and intervention

Human
Longitudinal pathological changes in networks from normal to ultra-early, through pre-onset, to onset
- Cohort study
- Registry research study

*Including existing studies

Animal models
Inter-organ and inter-tissue networks
- Case study
- Collection and Analysis of whole-body data
- Wearable technology

Tissue and cellular models
Inter-cellular networks
Molecular systems
- Tissue and organ imaging techniques
- Organoid techniques
- Humanized animal models
- Molecular and cellular imaging techniques
- Single-cell omics techniques
- Genome editing/manipulation techniques

Developed methods to collect various types of modality data and the data has been accumulated.

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

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

Program Manager
OHNO, Hideo
Special Contract Professor,
Juntendo University

Program Manager
KATAGIRI, Hideki
Professor,
Tohoku University

Program Manager
TAKAHASHI, Ryosuke
Specially Appointed Professor,
Kyoto University

Program Manager
MATSUURA, Yoshiharu
Specially Appointed Professor,
Osaka University

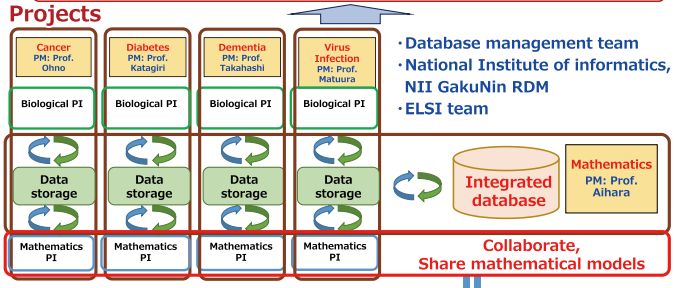
MS2 researcher :
Total : 1224 (PM・PI : 137)
Institution : 67

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

Projects



- Database management team
- National Institute of informatics, NII GakuNin RDM
- ELSI team

Collaborate, Share mathematical models

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

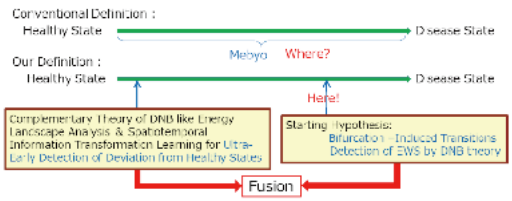
Project manager (PM)

AIHARA Kazuyuki

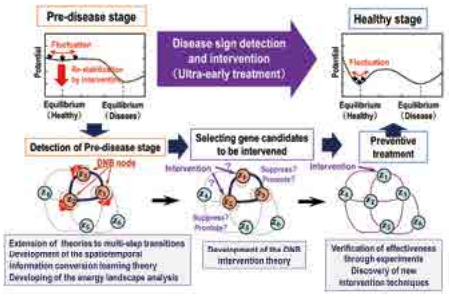
University Professor/
Professor Emeritus,
The University of Tokyo

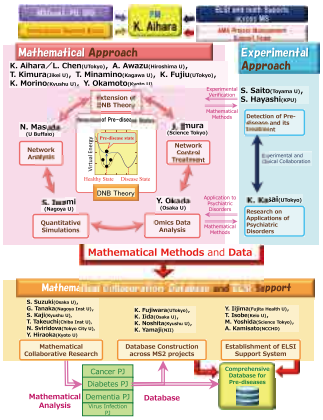
Project Outlook and Concept

DNB, Dynamic Network Biomarkers
: Mathematical theory focusing on fluctuations in biological signals



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



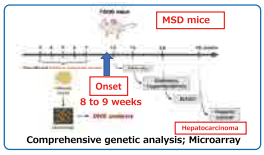


Results

Development of ultra-early disease detection and intervention methods by combining mathematical and biological approaches

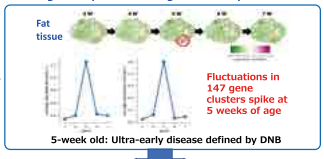
Identification of diseaes-associated genes and refinement for intervention gene by DNB theory and Control theory; Ex. Metabolic syndrome disease, MSD Saito PI, Imura PI, Aihara PI

Biological experiments, TSOD mice



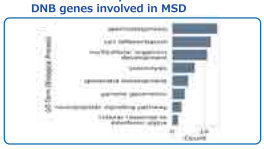
Comprehensive genetic analysis; Microarray

Mathematical anaysis: Detection of fluctuation in gene expression using DNB theory

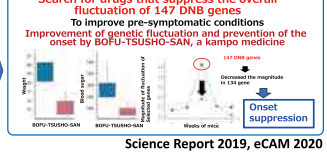


5-week old: Ultra-early disease defined by DNB

Functional analysis: Function of 147 DNB genes involved in MSD

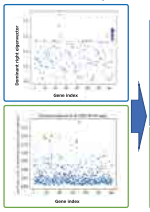


Search for drugs that suppress the overall fluctuation of 147 DNB genes
To improve pre-symptomatic conditions
Improvement of genetic fluctuation and prevention of the onset by BOFU-TSUSHO-SAN, a kampo medicine

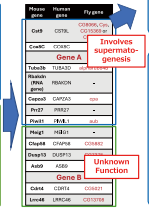


Science Report 2019, eCAM 2020

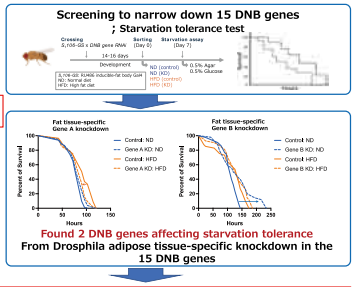
Mathematical analysis with Control theory



Narrowing down 15 to 2 DNB genes



Screening to narrow down 15 DNB genes
; Starvation tolerance test



Found 2 DNB genes affecting starvation tolerance
From Drosphila adipose tissue-specific knockdown in the 15 DNB genes

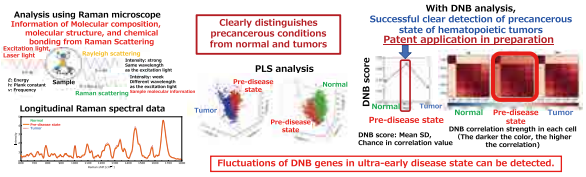
The 2 genes were previously not known to be associated with MSD.
The knockdown experiments revealed that Gene A suppressed fat accumulation and Gene B increased fat accumulation, indicating a relationship with metabolic syndrome
→ Verification by mouse experiments and clinical trial, etc.

PATENT PENDING

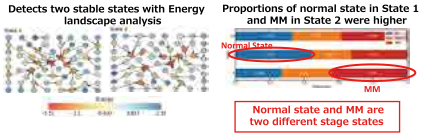
*Intervention effects of candidate genes narrowed down by DNB theory and Control theory in inflammatory bowl disease was also shown to be effective. Hayashi PI, Saitou PI, Imura PI, Aihara PI

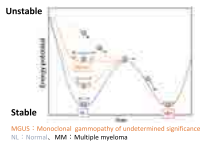
Detection of diseae progression process by DNB theory and Energy landscape anaysis; Ex. Multiple myeloma, MM Saitou PI, Masuda PI

Detection of precancerous conditions in MM with DNB



Detection of stable states in MM with Energy landscape analysis





With DNB theory and Energy landscape analysis, NL and MM are stable compared to MGUS, and it is mathematically explained that MGUS is the ultra-early disease state.

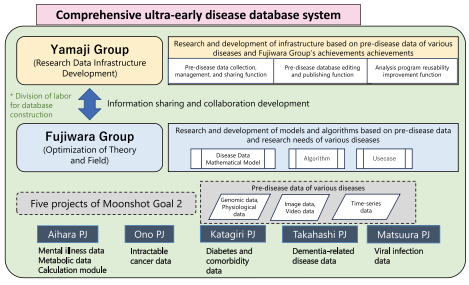
International Journal of Molecular Science 2024

The other important results: Detection of multi-step transitions by DNB therory
Lang cancer transformation from adenocarcinoma to squamous cell carcinoma, and peripheral blood differentiation with human ES cells Aihara PI
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



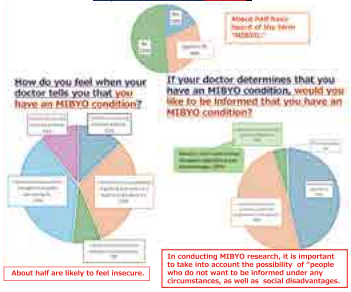
Mathematical analysis system for activation of mathematical collaboration
(Active collaboration of mathematical researchers and young researchers)

New PI participation

- **Keita Iida, Associate Professor, Osaka University**
  Mathematical Studies for Semiological Classification of Omics Data
- **Koji Noshita, Assistant Professor, Kyushu University**
  Development of the basis for phenome analysis on diverse and multilevelmorphological properties of disease phenotypes and their applications
- **Hideyuki Suzuki, Professor, Osaka University**
  Nonlinear Mathematical Analysis through Data-Driven Modeling
- **Tomoya Takeuchi, Chiba Institute of Technology**
  Mathematics of Disease Prediction
- **Shizuo Kaji, Professor, Kyushu University**
  Topological Data Analysis in Medical Research
- **Gohei Tanaka, Professor, Nagoya Institute of Technology**
  Mathematical Analysis with Reservoir Computing AI
- **Nina Sviridova, Lecturer, Tokyo City University**
  Non-Linear Time Series Analysis of Biological Signals
- **Shusaku Hayashi, Associate Professor, Kyoto Pharmaceutical University**
  Pathophysiological Significance of DNB Genes in Inflammatory Bowel Disease
- **Katsuhito Fujiu, Project Professor, The University of Tokyo**
  Predicting Pre-Disease States of Cardiac Conditions through Mathematical Analysis
- **Akinori Awazu, Associate Professor, Hiroshima University**
  Extension of DNB Theory with Statistical Physics
- **Yasuaki Hiraoka, Professor, Kyoto University**
  Transformation theory of animal data to human data using optimal transport theory
- **Yuji Okamoto, Program-Specific Assistant Professor, Kyoto University**
  Expansion of DNB theory to longitudinal data and longitudinal application of generative AI
- **Kai Morino, Associate Professor, Kyushu University**
  AI theory for integrating information and robustness theory for dynamical network

Examination of ELSI issues

Surveyed 1,020 individuals from the general public to assess awareness of the term "MIBYO," 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 or PI

1. T. Inagaki, K. Inaba, T. Leleu, T. Honjo, T. Ikuta, K. Enbutsu, T. Umeki, R. Kasahara, K. Aihara, and H. Takesue: **Collective and Synchronous Dynamics of Photonic Spiking Neurons**, Nature Communications, Vol.12, Article No.2325, pp.1-8, DOI: 10.1038/s41467-021-22576-4 (2021).
2. 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).
3. 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).
4. 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).
5. 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).
6. 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).
7. 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).
8. A. Nawaz, et al.: **Depletion of CD206+ M2-like Macrophages Induces Fibro-adipogenic Progenitors Activation and Muscle Regeneration**, Nature Communications, Vol.13, Article No.7058, pp.1-12 (2022).
9. 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).
10. 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).
11. Y. Tong, R. Hong, Z. Zhang, K. Aihara, P. Chen, R. Liu, and L. Chen: **Earthquake Alerting based on Spatial Geodetic Data by Spatiotemporal Information Transformation Learning**, Proceedings of the National Academy of Sciences of the United States of America, Vol.120, No.37, e2302275120, pp.1-12, DOI: 10.1073/pnas.2302275120 (2023).
12. WS. Harta, H. Park, YD. Jeong, KS. Kim, R. Yoshimura, R.N. Thompson, and S. Iwami: **Analysis of the Risk and Pre-emptive Control of Viral Outbreaks Accounting for Within-Host Dynamics: Sars-Cov-2 as a Case Study**, Proceedings of the National Academy of Sciences of the United States of America, Vol.120, No.41, e2305451120, pp.1-10, DOI: 10.1073/pnas.2305451120 (2023).
13. 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).
14. 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).
15. X. Shen, N. Shimada, H. Sasahara, and J. Imura: **Ultra-Early Medical Treatment-Oriented System Identification Using High-Dimension Low-Sample-Size Data**, IFAC Journal of Systems and Control, Vol.27, Article No.100245, pp.1-11, DOI: 10.1016/j.ifacsc.2024.100245 (2024).
16. 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).
17. 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).

Moonshot R&D　Goal 2, Cancer PJ

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

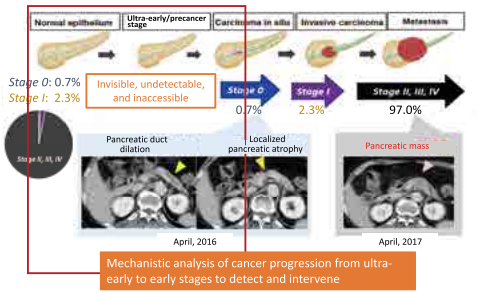
Project manager (PM)

OHNO Shigeo

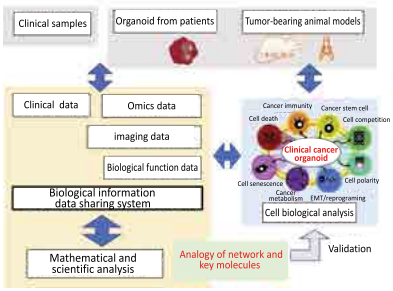
Special Contract Professor,
School of Medicine,
Juntendo University

Project Outlook and Concept

Project Target (Refractory cancer: Pancreatic cancer)

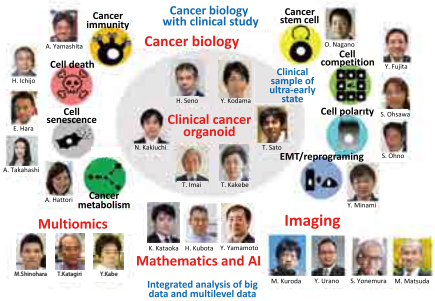


Integrated analysis with clinical data



A society where cancer can be predicted and prevented

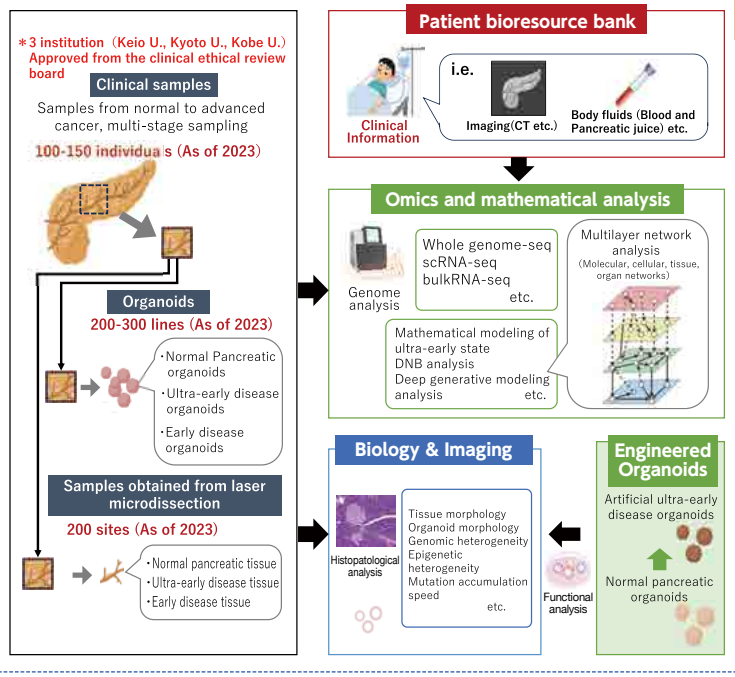
Research group for comprehensive understanding of ultra-early cancer networks



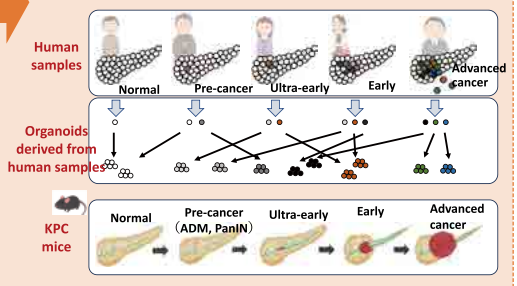
Results

Clinical pancreatic cancer resource development from the ultra-early stage

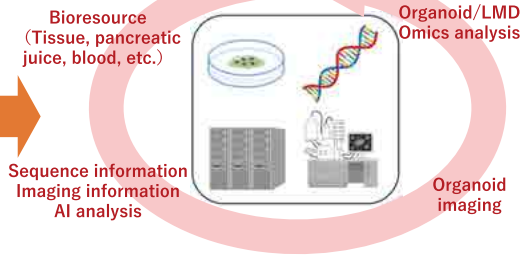
Establishing systems to collect samples from the same patients and the same tissue for analysis



Construction of pseudo-time analysis platform



Human pancreatic ultra-early resource platform



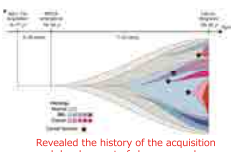
Challenges in ultra-early and early cancer predication and intervention by understanding the natural history of cancer

Understanding natural history of cancer

Natural history of pancreatic cancer progression and breast cancer onset

Investigated pancreatic cancer molecules and morphological evolution

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



Revealed the history of the acquisition and development of chromosomal aberrations from phylogenic tree analysis

Nishimura *et al.*, Nature 2023.

Specifying novel makers for ultra-early detection

Marker X
α-catenin
Hoechst

Marker X overexpressed in human precancer state, ADM

▷ Pre-cancer state

Identified a human pancreatic ultra-early marker candidate

Developing novel technologies for ultra-early cancer prediction

Blood tests and imaging for ultra-early cancer detection

Nucleic acids and protein in blood + AI analysis

For ultra-early or early cancer
Sensitivity >80%
Specificity >90%

Past CT imaging + AI analysis

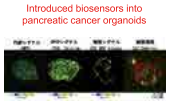
Localized pancreatic atrophy

Pancreatic duct dilation

Capable of detecting abnormalities several years before onset

Developing cancer biosensors and probes

Introduced biosensors into pancreatic cancer organoids

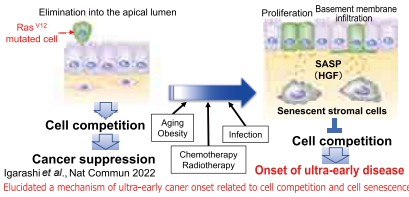


Kuriki *et al.*, J Am Chem Soc 2023.

Building an imaging analysis platform to develop biosensors, probes and related technologies

Identifying novel targets for ultra-early cancer intervention

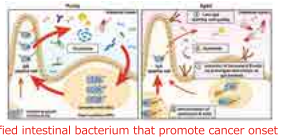
Cell competition and senescence, and cancer onset



Igarashi *et al.*, Nat Commun 2022

Elucidated a mechanism of ultra-early caner onset related to cell competition and cell senescence

Disturbance of the intestinal microflora in senescent cells and cancer onset



Identified intestinal bacterium that promote cancer onset in senescent cells

List of major papers

= OHNO PJ =

Underlined: PM or PI

1. **Decoding the basis of histological variation in human cancer**
   Fujii M, Sekine S, Sato T. (2024) Nat Rev Cancer,24(2),141-158.
2. **Evolutionary histories of breast cancer and related clones**
   Nishimura T, Kakiuchi N, Sato T, et al. (2023) Nature, 620 (7974), 607-614.
3. **Cell-matrix interface regulates dormancy in human colon cancer stem cells**
   Ohta Y, Sato T, et al. (2022) Nature, 608 (7924), 784-794.
4. **Building consensus on definition and nomenclature of hepatic, pancreatic, and biliary organoids**
   Marsee A, Takebe T, et al. (2021) Cell Stem Cell, 28 (5), 816-832.
5. **Visualization of stem cell activity in pancreatic cancer expansion by direct lineage tracing with live imaging**
   Maruno T, Seno H, et al. (2021) eLife, 10, e55117.
6. **Characterization of the interface between normal and transformed epithelial cells**
   Hogan C, Fujita Y, et al. (2009) Nature Cell Biology, 11 (4), 460-467.
7. **Mitochondrial defect drives non-autonomous tumour progression through Hippo signalling in Drosophila**
   Ohsawa S, et al. (2012) Nature, 490, 547-551.
8. **Cell competition with normal epithelial cells promotes apical extrusion of transformed cells through metabolic changes**
   Kon S, Sato T, Fujita Y, et al. (2017) Nature Cell Biology, 19 (5), 530-541.
9. **FGF21 Induced by the ASK1-p38 Pathway Promotes Mechanical Cell Competition by Attracting Cells**
   Ogawa M, Fujita Y, Ichijo H, et al. (2021) Current Biology, 31 (5), 1048-1057.
10. **Hepatocyte growth factor derived from senescent cells attenuates cell competition-induced apical elimination of oncogenic cells**
    Igarashi N, Fujita Y, Takahashi A, et al. (2022) Nature Communications, 13 (1), 4157.
11. **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
12. **A data-driven ultrasound approach discriminates pathological high grade prostate cancer**
    Akatsuka J, Yamamoto Y, et al. (2022) Sci Rep, 12(1), 860.
13. **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) Sci Rep, 13(1), 4758.
14. **Benefits of pancreatic parenchymal endoscopic ultrasonography in predicting microscopic precancerous lesions of pancreatic cancer**
    Yamakawa K, Kodama Y, et al. (2023) Sci Rep, 13 (1), 12052.
15. **Frequent mutations that converge on the NFKBIZ pathway in ulcerative colitis**
    Kakiuchi N, Kataoka K, Seno H, Ogawa S, et al. (2020) Nature, 577 (7789), 260-265.
16. **A feedback loop between lamellipodial extension and HGF-ERK signaling specifies leader cells during collective cell migration**
    Hino N, Matsuda M, et al. (2022) Dev Cell, 57, 2290-2304.
17. **Functional visualization of NK cell-mediated killing of metastatic single tumor cells**
    Ichise H, Matsuda M, et al. (2022) eLife, 11, e76269.
18. **Development of a fluorescent probe library enabling efficient screening of tumour-imaging probes based on discovery of biomarker enzymatic activities**
    Kuriki Y, Urano Y, et al. (2022) Chem Sci, 13, 4474-4481.

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 Graduate School of Medicine

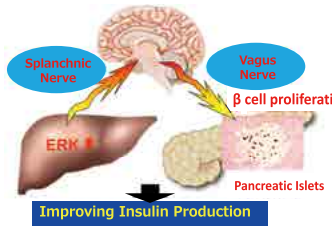
Project Outlook and Concept

Elucidation and Control of the Neural Network of the Liver-Brain-Pancreas

Neural Network is important for Onset and Control of Diabetes (*Science* 2008 etc.)

Improvement of Insulin Production

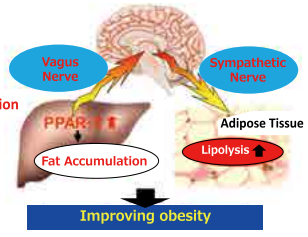
Improve Function and Quantity of Pancreatic β cells



Science 322: 1250 2008
Nat Commun 8:1930, 2017

Improvement of Insulin Resistance

Burn Fat



Science 312: 1656, 2006
Cell Metab 16: 825, 2012

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 (Tohoku 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 (RIKEN)			Yutaka HASEGAWA (Iwate Med U)
Ikuo KIMURA (Kyoto U)	Rikuhiro YAMADA (RIKEN)			Tetsuya YAMADA (Science Tokyo)
Toshiaki TERATANI (Keio U)				
Misa YOSHIMOTO (Nara W U)				
Tetsuya YAMADA (Science Tokyo)				
Yukio NISHIMURA (TMIMS)				

Aihara Project
Shinji NAKAOKA (Hokkaido U)

Results

Development of simple detection
(Challenge:Diabetes is asymptomatic)

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

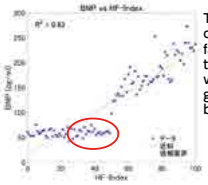
Fujiu PI

~AI algorithm~

Grip to start measurement

Wearable device

AppleWatch®



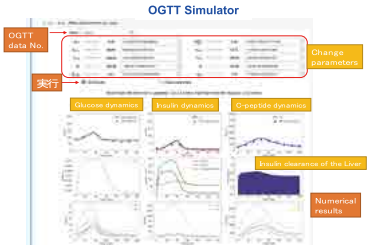
The sensitivity for detecting heart failure is superior to that of BNP values measured in gold standard blood test.

PCT pending

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

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

Nagayama PI

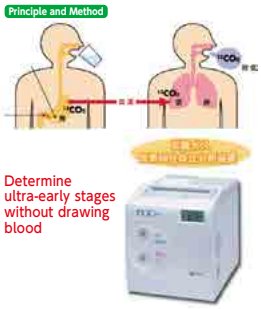


Determine the individual's mechanism of pathogenesis.

Detecting liver glucose disposal capacity

Katagiri PI

^{13}C- glucose breath tests



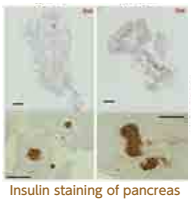
Determine ultra-early stages without drawing blood

Patented in Japan, U.S., and Europe

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

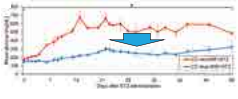
Succeeded in growing insulin-producing cells in mice

Katagiri PI



Insulin staining of pancreas

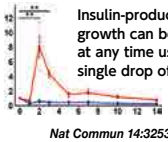
Vagus nerve stimulation increased insulin-producing cells and inhibited diabetes progression in model animals.



Nat Biomed Eng 8:808 / 2024

Currently in clinical trial

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



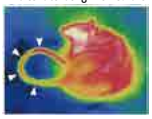
Insulin-producing cell growth can be monitored at any time using just a single drop of blood.

Nat Commun 14:3253 / 2023

Compound searching

Controlled energy consumption in the brain

1h. after activating EP3 neurons

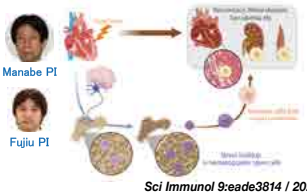


Elucidated the mechanisms of body temperature and metabolism regulation

To develop technology to increase metabolism and prevent obesity

Sci Adv 8: eadd5463 / 2022

Elucidated the multimorbidity mechanisms of heart failure



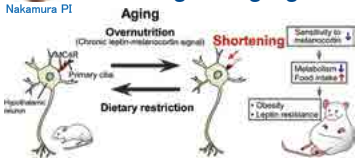
Manabe PI

Fujiu PI

Sci Immunol 9:eade3814 / 2024

Elucidated mechanisms of middle-aged weight gain

Nakamura PI



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 or PI

1. **Machine learning-based reproducible prediction of type 2 diabetes subtypes**
   Tanabe H, Sato M, Miyake A, Shimajiri Y, Ojima T, Narita A, Saito H, Tanaka K, Masuzaki H, Kazama JJ, Katagiri H, Tamiya G, Kawakami E, Shimabukuro M.
   Diabetologia in press

2. **Heart failure promotes multimorbidity through innate immune memory**
   Nakayama Y, Fujiu K, Oshima T, Matsuda J, Sugita J, Matsubara TJ, Liu Y, Goto K, Kani K, Uchida R, Takeda N, Morita H, Xiao Y, Hayashi M, Maru Y, Hasumi E, Kojima T, Ishiguro S, Kijima Y, Yachie N, Yamazaki S, Yamamoto R, Kudo F, Nakanishi M, Iwama A, Fujiki R, Kaneda A, Ohara O, Nagai R, Manabe I, Komuro I.
   Sci. Immunol. **9**, eade3814 (2024). DOI: 10.1126/sciimmunol.ade3814

3. **Age-related ciliopathy: Obesogenic shortening of melanocortin-4 receptor-bearing neuronal primary cilia**
   Oya M, Miyasaka Y, Nakamura Y, Tanaka M, Suganami T, Mashimo T, Nakamura K.
   Cell Metab. **36**, 1044-1058 (2024). DOI: 10.1016/j.cmet.2024.02.010

4. **A newly identified compound activating UCP1 inhibits obesity and its related metabolic disorders**
   Onodera K, Hasegawa Y, Yokota N, Tamura S, Kinno H, Takahashi I, Chiba H, Kojima H, Katagiri H, Nata K, Ishigaki Y.
   Obesity **32**, 324-338 (2024). DOI: 10.1002/oby.23948

5. **Optogenetic stimulation of vagal nerves for enhanced glucose-stimulated insulin secretion and β cell proliferation**
   Kawana Y, Imai J, Morizawa YM, Ikoma Y, Kohata M, Komamura H, Sato T, Izumi T, Yamamoto J, Endo A, Sugawara H, Kubo H, Hosaka S, Munakata Y, Asai Y, Kodama S, Takahashi K, Kaneko K, Sawada S, Yamada T, Ito A, Niizuma K, Tominaga T, Yamanaka A, Matsui K, Katagiri H.
   Nat. Biomed. Eng. Online ahead of print (2023). DOI: 10.1038/s41551-023-01113-2

6. **Phagocytosis by macrophages promotes pancreatic β cell mass reduction after parturition in mice**
   Endo A, Imai J, Izumi T, Kawana Y, Sugawara H, Kohata M, Seike J, Kubo H, Komamura H, Sato T, Asai Y, Hosaka S, Kodama S, Takahashi K, Kaneko K, Katagiri H.
   Dev. Cell **58**, 1819-1829 (2023). DOI: 10.1016/j.devcel.2023.08.002

7. **A highly sensitive strategy for monitoring real-time proliferation of targeted cell types in vivo**
   Sugawara H, Imai J, Yamamoto J, Izumi T, Kawana Y, Endo A, Kohata M, Seike J, Kubo H, Komamura H, Munakata Y, Asai Y, Hosaka S, Sawada S, Kodama S, Takahashi K, Kaneko K, Katagiri H.
   Nat. Commun. **14**, 3253 (2023). DOI: 10.1038/s41467-023-38897-5

8. **Inter-organ insulin-leptin signal crosstalk from the liver enhances survival during food shortages**
   Takahashi K, Yamada T, Hosaka S, Kaneko K, Asai Y, Munakata Y, Seike J, Horiuchi T, Kodama S, Izumi T, Sawada S, Hoshikawa K, Inoue J, Masamune A, Ueno Y, Imai J, Katagiri H.
   Cell Rep. **42**, 112415 (2023). DOI: 10.1016/j.celrep.2023.112415

9. **Celastrol suppresses humoral immune responses and autoimmunity by targeting the COMMD3/8 complex**
   Shirai T, Nakai A, Ando E, Fujimoto J, Leach S, Arimori T, Higo D, van Eerden FJ, Tulyeu J, Liu YC, Okuzaki D, Murayama MA, Miyata H, Nunomura K, Lin B, Tani A, Kumanogoh A, Ikawa M, Wing JB, Standley DM, Takagi J, Suzuki K.
   Sci. Immunol. **8**, eadc9324 (2023). DOI: 10.1126/sciimmunol.adc9324

10. **Prostaglandin EP3 receptor-expressing preoptic neurons bidirectionally control body temperature via tonic GABAergic signaling**
    Nakamura Y, Yahiro T, Fukushima A, Kataoka N, Hioki H, Nakamura K.
    Sci. Adv. **8**, eadd5463 (2022). DOI: 10.1126/sciadv.add5463

11. **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, Dementia PJ

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

Project manager (PM)

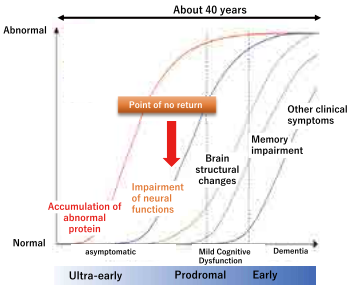
TAKAHASHI Ryosuke

Specially Appointed Professor,
Kyoto University Graduate School of Medicine

Project Outlook and Concept

Elucidating changes in the inter-organ network with a focus on the ultra-early to prodromal stages

Alzheimer's Disease
Parkinson's Disease

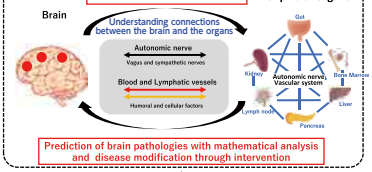


Ultra-early stage: A state where abnormal proteins accumulate, but functional deficit is reversible."

In dementia, ultra-early and prodromal stages are extremely prolonged.

Aiming to specify intervention targets and points by elucidating the changes in inter-organ/cell-cell networks from the ultra-early to prodromal stages

Changes in the brain influence inter-organ networks



Prediction of brain pathologies with mathematical analysis and disease modification through intervention

Human cohort – **Mouse model**

Human cohort		Mouse model
Alzheimer's Disease (AD) ・MABB Cohort ・Tamba Cohort	Extrapolation Verification	Alzheimer's Disease (AD) ・APP Knock-in (KI) mouse
Parkinson's Disease (PD) ・J-PPMI (Prodromal Stage) ・After-onset Cohort	Intervention	Parkinson's Disease (PD) ・αSynuclein BAC Tg mouse ・αSynuclein propagation mouse

Development of Basic Technologies:
Establishment of cutting-edge and innovative fundamental techn ologies
Team leader: T. Ohtsuka, PI: R. Nitta, H. Hioki, A. Watabe, H. Hanafusa, H. Maruoka

Provide multi-modality data achieved through novel technologies

Provide novel technologies

Identify social issues necessary for ultra-early prediction and intervention, and provide support for real-world application

Provide clinical samples and data

ELSI Research:
Collaboration with patients and citizens
Team leader: K. Muto,

Validate with a mathematical model and provide feedback

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

Disease research: investigation of inter-organ networks in animal models and human cohorts

Alzheimer's Diseases
Team leader: K. Yamanaka, PI: T. Saito, T. Tomita, T. Satoh, M. Higuchi, M. Tsuda, H. Hibino, T. Furukawa

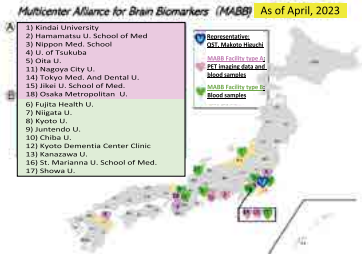
Vascular and Mixed Dementia
Team leader: N. Mochizuki, PI: Y. Kubota, T. Maki, R. Matsumoto, K. Mizutani

Parkinson's Disease-Related Dementia
Team leader: N. Hattori, PI: H. Yamakado, S. Miyake, H. Matsui, M. Kinoshita, Y. Takahashi

Results

Cohorts in the ultra-early stages

Establishment of multi-center dementia cohorts

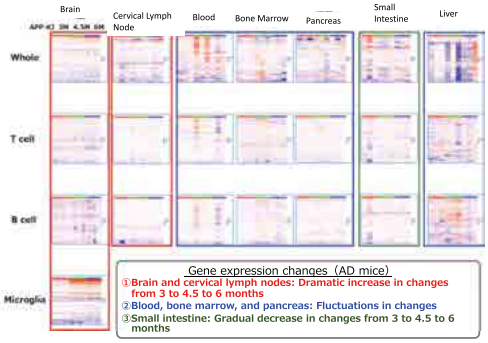


Collaboration with J-PPMI cohort

PI: Y. Takahashi (J-PPMI Representative)

Elucidation of inter-organ networks

Analysis of the propagation of inter-organ networks in the ultra-early stage

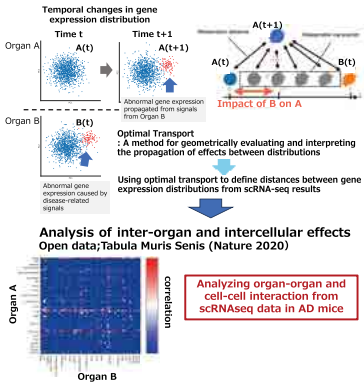


Gene expression changes (AD mice)
①Brain and cervical lymph nodes: Dramatic increase in changes from 3 to 4.5 to 6 months
②Blood, bone marrow, and pancreas: Fluctuations in changes
③Small intestine: Gradual decrease in changes from 3 to 4.5 to 6 months

Examination of the sequential changes in gene expression across different organs through a scRNA-seq

Development of mathematical models for inter-organ propagation

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



Analysis of inter-organ and intercellular effects
Open data;Tabula Muris Senis (Nature 2020)

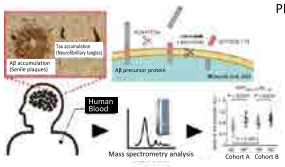
Analyzing organ-organ and cell-cell interaction from scRNAseq data in AD mice

Identification of biomarkers in the ultra-early stage of dementia

Search for Novel Biomarkers

Elucidating the mechanism of production of APP669-711, an early blood biomarker of AD

PI: T. Tomita



Molecular Psychiatry 2023

Capable of identifying senile plaques based on the levels of APP669-711 and Aβ in the blood

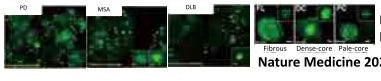
Discovery of novel phosphorylation site of α-synuclein

PI: H. Matsui

PNAS 2023

Identification of α-synuclein seeds highly specific to PD

PI: N. Hattori



Nature Medicine 2023

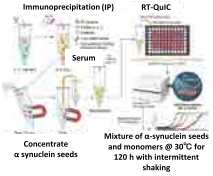
Liver-derived factors as a potential AD biomarker
(Paper in preparation) PIs: K. Yamanaka・T. Maki・H. Yamakado

Development of novel technology to detect abnormal proteins

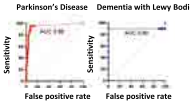
Measurement of trace amounts of α-synuclein seeds in serum

PI: N. Hattori

Combination of IP and RT-QuIC



AUC >0.9



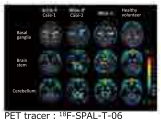
Detection in the prodromal stage of PD (RBD) with 44% sensitivity. Potential for earlier detection than with RBD

Nature Medicine 2023

PET Imaging of α-synclein deposition

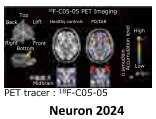
PI: M. Higuchi

Successful imaging of α-synuclein deposition in human (Multiple System Atrophy)

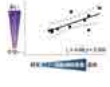


Movement Disorders 2022

Successful imaging of fewer α-synuclein deposition (Parkinson's disease and Lewy body dementia)



Correlations with the severity of motor dysfunction

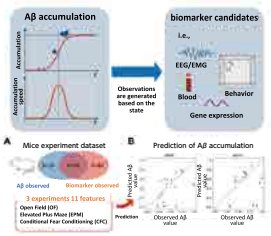


Neuron 2024

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

Predicting Aβ accumulation from serum cytokine levels of AD mice

PI: N. Honda



Predicting Aβ accumulation from behavioral data of AD mice

PIs: K. Yamanaka, N. Honda

High resolution and functional imaging

Successful analysis of vascular structure with cleaning technology and imaging of intra-lymphatic structure

PIs: N.Mochizuki, Y.Kubota and T. Maki

Investigating the relationship between Aβ clearance from the brain and abnormalities in lymphatic valves and cerebrospinal fluid flow.

List of major papers

= TAKAHASHI PJ =

Underlined: PM or PI

1. **Neurodegenerative processes accelerated by protein malnutrition and decelerated by essential amino acids in a tauopathy mouse model**
   Sato H, Takado Y, Toyoda S, Tsukamoto-Yasui M, Minatohara K, Takuwa H, Urushihata T, Takahashi M, Shimojo M, Ono M, Maeda J, Orihara A, Sahara N, Aoki I, Karakawa S, Isokawa M, Kawasaki N, Kawasaki M, Ueno S, Kanda M, Nishimura M, Suzuki K, Mitsui A, Nagao K, Kitamura A, Higuchi M.
   Sci Adv, 2021, 7:eabd5046. doi: 10.1126/sciadv.abd5046.

2. **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.
   Mol Psychiatry. 2023, 28, 1802-1812. doi: 10.1038/s41380-023-01946-y

3. **A spinal microglia population involved in remitting and relapsing neuropathic pain**
   Kohno K, Shirasaka R, Yoshihara K, Mikuriya S, Tanaka K, Takanami K, Inoue K, Sakamoto H, Ohkawa Y, Masuda T, Tsuda M.
   Science, 2022, 376:86-90. doi: 10.1126/science.abf6805

4. **A Machine Learning-Based Approach to Discrimination of Tauopathies Using [18 F]PM-PBB3 PET Images**
   Endo H, Tagai K, Ono M, Ikoma Y, Oyama A, Matsuoka K, Kokubo N, Hirata K, Sano Y, Oya M, Matsumoto H, Kurose S, Seki C, Shimizu H, Kakita A, Takahata K, Shinotoh H, Shimada H, Tokuda T, Kawamura K, Zhang MR, Oishi K, Mori S, Takado Y, Higuchi M.
   Mov Disord, 2022, 37:2236-2246. doi: 10.1002/mds.29173.

5. **High-Contrast Imaging of α-Synuclein Pathologies in Living Patients with Multiple System Atrophy**
   Matsuoka K, Ono M, Takado Y, Hirata K, Endo H, Ohfusa T, Kojima T, Yamamoto T, Onishi T, Orihara A, Tagai K, Takahata K, Seki C, Shinotoh H, Kawamura K, Shimizu H, Shimada H, Kakita A, Zhang MR, Suhara T, Higuchi M.
   Mov Disord, 2022, 37:2159-2161. doi: 10.1002/mds.29186.

6. **Idiopathic rapid eye movement sleep behavior disorder in Japan: An observational study**
   Nishikawa N, Murata M, Hatano T, Mukai Y, Saitoh Y, Sakamoto T, Hanakawa T, Kamei Y, Tachimori H, Hatano K, Matsuda H, Taruno Y, Sawamoto N, Kajiyama Y, Ikenaka K, Kawabata K, Nakamura T, Iwaki H, Kadotani H, Sumi Y, Inoue Y, Hayashi T, Ikeuchi T, Shimo Y, Mochizuki H, Watanabe H, Hattori N, Takahashi Y, Takahashi R; Japan Parkinson's Progression
   Markers Initiative (J-PPMI) study group.
   Parkinsonism Relat Disord, 2022, 103:129-135. doi: 10.1016/j.parkreldis.2022.08.011

7. **Few-shot prediction of amyloid β accumulation from mainly unpaired data on biomarker candidates**
   Yada Y, Honda N.
   NPJ Syst Biol Appl, 2023, 9:59. doi: 10.1038/s41540-023-00321-5.

8. **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.
   Nat Med, 2023, 29:1448-1455. doi: 10.1038/s41591-023-02358-9.

9. **Imaging α-synuclein pathologies in animal models and patients with Parkinson's and related diseases**
   Endo H, Ono M, Takado Y, Matsuoka K, Takahashi M, Tagai K, Kataoka Y, Hirata K, Takahata K, Seki C, Kokubo N, Fujinaga M, Mori W, Nagai Y, Mimura K, Kumata K, Kikuchi T, Shimozawa A, Mishra SK, Yamaguchi Y, Shimizu H, Kakita A, Takuwa H, Shinotoh H, Shimada H, Kimura Y, Ichise M, Suhara T, Minamimoto T, Sahara N, Kawamura K, Zhang MR, Hasegawa M, Higuchi M.
   Neuron, 2024 May 27:S0896-6273(24)00332-5. doi: 10.1016/j.neuron.2024.05.006

Moonshot R&D | Goal 2, Virus Infection PJ

Understanding and Control of Virus-Human Interaction Networks

Project manager (PM)

MATSUURA Yoshiharu

Specially Appointed Professor,
Research Insbtute for
Microbial Diseases,
Osaka University

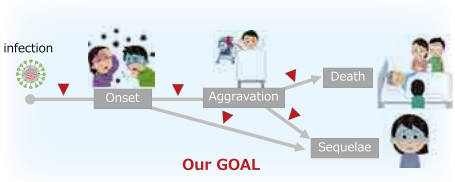
Project Outlook and Concept

MIBYO in viral infectious diseases

MIBYO : the state of the body and mind between health and illness

Viral infection begins with the entry of viruses into host cells, therefore, the concept of **MIBYO** is different from diseases such as cancer, dementia, and diabetes

State before a serious change occurs → Appropriate intervention at this stage can prevent serious changes



Comprehensive analysis of host response to viral infection to understand MIBYO

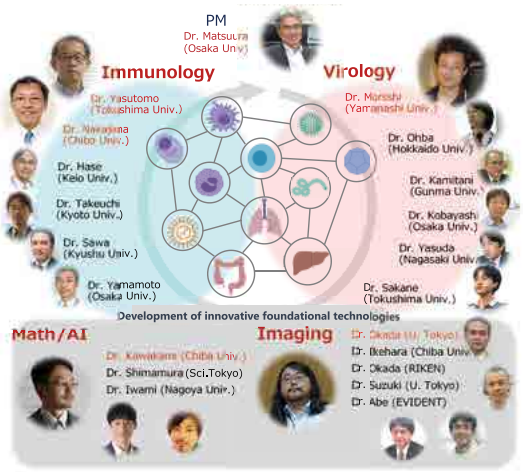
Classification of viruses based on host response patterns

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

Develop diagnosis and therapeutics for each pattern

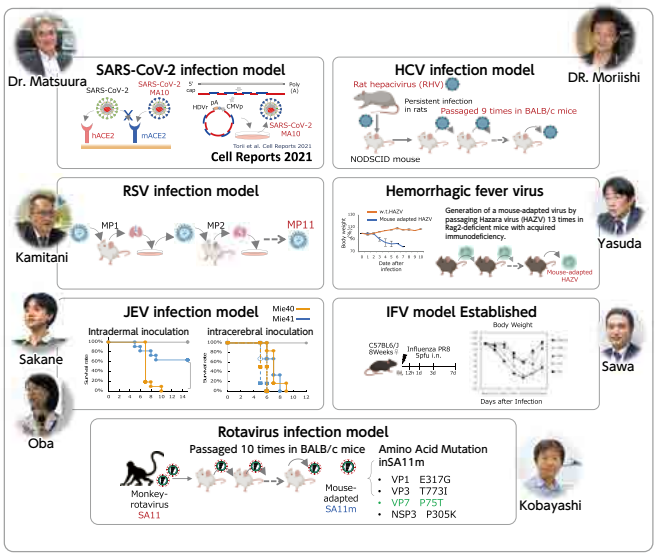
Rapid diagnosis and countermeasures

Research Flamework

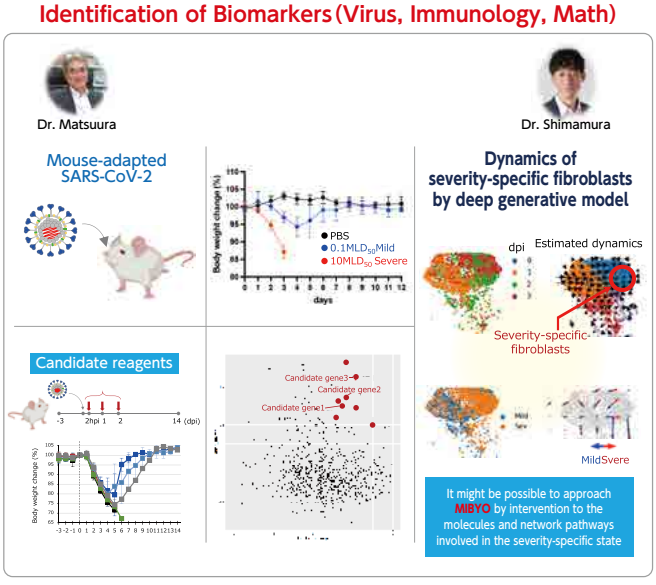


Results

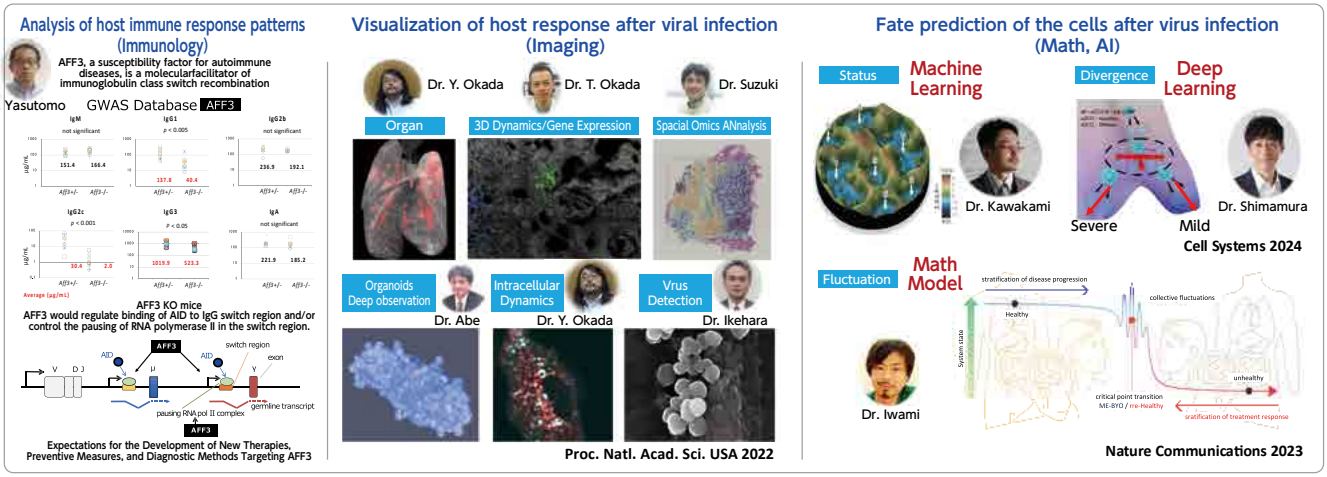
Mouse Models (Virus)



Identification of Biomarkers (Virus, Immunology, Math)



Patterning of virus-host interactions



List of major papers

= MATSUURA PJ =

Underlined: PM or PI

1. **Establishment of a reverse genetics system for SARS- CoV-2 using circular polymerase extension reaction.**
   Torii S, Matsuura Y. et al., Cell Rep. 2021 Apr 20;35(3):109014.
2. **Detection of significant antiviral drug effects on COVID-19 with reasonable sample sizes in randomized controlled trials: A modeling study.**
   Iwanami S, Iwami S, et al.,
   PLoS Med. 2021 Jul 6;18(7):e1003660. doi: 10.1371/journal.pmed.1003660.
3. **Revisiting the guidelines for ending isolation for COVID-19 patients.**
   Jeong YD, Iwami S, et al.,
   Elife. 2021 Jul 27;10:e69340. doi: 10.7554/eLife.69340.
4. **A mixture-of-experts deep generative model for integrated analysis of single-cell multiomics data.**
   Minoura K, Shimamura T, et al.
   Cell Rep Methods. 2021 Sep 15;1(5):100071. doi: 10.1016/j.crmeth.2021.100071.
5. **Elevated Myl9 reflects the Myl9-containing microthrombi in SARS-CoV-2-induced lung exudative vasculitis and predicts COVID-19 severity.**
   Iwamura C, Ikehara Y, Nakajima H, et al.,
   Proc Natl Acad Sci U S A. 2022 Aug 16;119(33):e2203437119. doi: 10.1073/pnas.2203437119.
6. **Detecting time-evolving phenotypic components of adverse reactions against BNT162b2 SARS-CoV-2 vaccine via non-negative tensor factorization.**
   Ikeda K, Nakajima H, Kawakami E, et al.,
   iScience. 2022 Oct 21;25(10):105237. doi: 10.1016/j.isci.2022.105237.
7. **Designing isolation guidelines for COVID-19 patients with rapid antigen tests.**
   Jeong YD, Iwami S, et al.,
   Nat Commun. 2022 Aug 20;13(1):4910. doi: 10.1038/s41467-022-32663-9.
8. **AFF3, a susceptibility factor for autoimmune diseases, is a molecular facilitator of immunoglobulin class switch recombination.**
   Tsukumo SI, Yasutomo K, et al.
   Sci Adv. 2022 Aug 26;8(34) doi: 10.1126/sciadv.abq0008.
9. **Analysis of the risk and pre-emptive control of viral outbreaks accounting for within-host dynamics: SARS-CoV-2 as a case study.**
   Hart WS, Iwami S, et al.,
   Proc Natl Acad Sci U S A. 2023 Oct 10;120(41) doi: 10.1073/pnas.2305451120.
10. **Single-cell colocalization analysis using a deep generative model.**
    Kojima Y, Shimamura S, et al.,
    Cell Syst. 2024 Feb 21;15(2):180-192.e7. doi: 10.1016/j.cels.2024.01.007.

Contacts

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

Project manager AIHARA Kazuyuki

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

Project manager OHNO Shigeo

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e-mail ms2cancer@juntendo.ac.jp

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

Project manager KATAGIRI Hideki

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e-mail ms2-katagiri@g-mail.tohoku-university.jp

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

Project manager TAKAHASHI Ryosuke

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Understanding and Control of Virus-Human Interaction Networks

Project manager MATSUURA Yoshiharu

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Cabinet Office: About Moonshot Research and Development Program

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

Go to Website

Department of Moonshot Research and Development Program, Japan Science and Technology Agency

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

Goal 2 Secretariat

e-mail moonshot-goal2@jst.go.jp

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Handout (Moonshot Goal2)

Booklet for BioJapan2024

https://www.jst.go.jp/moonshot/sympo/20241009/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

Explore

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

X

https://x.com/JST_Moonshot

note

https://note-moonshot.jst.go.jp/m/m9889bcfdc9db

YouTube

https://www.youtube.com/channel/UCc70P11qREXTJlk5aw5wL8A

"Body-monitoring": through life, through each day

More data means more accuracy

From genome information at birth to the state of growth and development in childhood, it is important to keep monitoring physical condition at healthy (pre-illness) times. Collecting a large amount of data for whole body network simulators will not only improve the accuracy of predicting diseases from genomic information and trends in various data, but will also be useful in developing drugs and preventive methods. By 2050 people will be able to extend their healthy life expectancy, spending 100 years in good health through the daily exchange of information with their whole body network simulator.

Everyday objects will become sensors

We now know that diseases are affected not only by blood pressure, body temperature and blood components, but also by sleep quality and the type of flora in our intestines. In the society of 2050, sensors will be installed in the things we wear, in furniture and toilets, and data on the body will be collected daily for whole body network simulators. In addition, home appliances that work with your simulator will advise you on proper exercise and eating habits according to your physical condition, and automatically adjust lighting and music to help you feel better when you are stressed or have poor sleep quality.

Japan Science and Technology Agency

QRコード

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