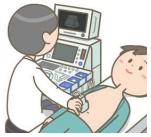
R&D item

1． Development of technologies for collecting patient biospecimens and data for the realization of optimal medicine (My Medicine)

Progress until FY2023

1.Outline of the project

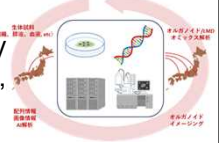
Since many intractable cancers are found as advanced cancers, clinical data and biological data derived from patients are limited, which is a major obstacle to elucidating the onset factors. In addition, the technology for acquiring various biological data from minute amounts of specimens and the mechanism for accumulating and sharing data are immature.



In this theme, we are collecting clinical specimens (blood and cancer tissue, nearby normal tissue), clinical data (blood biochemical data, images, etc.), blood, body fluids, feces, etc.

In parallel, we are establishing and accumulating organoids from the patient tissue samples. Patient organoids can be used for various experiments that are not possible with patient samples only. They are an innovative technology that opens up great possibilities for understanding developmental processes of cancer.

ヒト膵がん未病生体リソースプラットフォーム

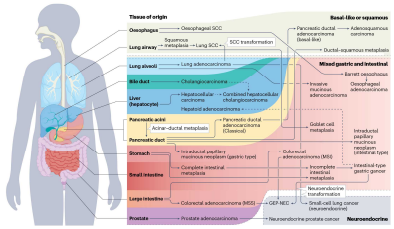


We are building a database by acquiring various biological data, including genomes, from the patient tissue samples.

2. Outcome so far

Building a patient biospecimen bank:

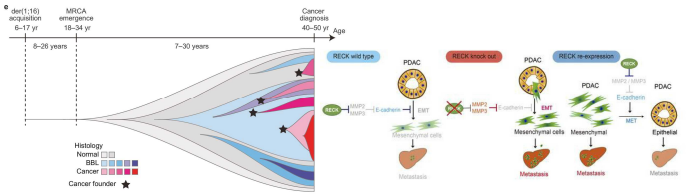
We have obtained approval from the ethics committee for common efforts at Keio University, Kyoto University, and Kobe University. Surplus residual specimens obtained by various methods (endoscopy, surgery, etc.) are accumulated at each facility. Furthermore, we have been establishing organoids and their omics are underway.



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

Construction of the organoid culture platform:

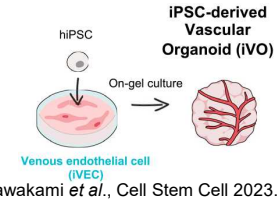
We have confirmed that patient-derived organoids can be established using a standardized method, and have accumulated the number of specimens. Through comprehensive analysis, we discovered evolutionary histories of breast cancer and novel molecular mechanisms by which progress pancreatic cancer.



Nishimura *et al.*, Nature 2023.

Masuda *et al.*, J Clin Invest 2023.

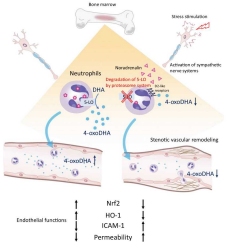
Furthermore, we have developed new organoid culture techniques including vascular organoid s and co-culture with fibroblasts.



Kawakami *et al.*, Cell Stem Cell 2023.

Construction of a multi-level integrated analysis shared database:

We have advanced the development of a whole-genome data analysis infrastructure for clinical specimens and organoids. RNA analysis has also progressed. Furthermore, we have been acquiring comprehensive lipid metabolite profiles, lipid mediator profiles and exosome profiles. The standardization of protocols for metabolic analysis are progressing.



Nishimori *et al.*, Sci Rep 2024.

3. Future plans

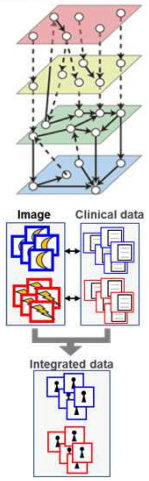
Samples of precancerous lesions, very early cancers, and advanced cancers have been collected, and patient organoids have been established. Along with the progress, we will proceed with the analysis using the platform of multi-level integrated analysis.

R&D item

2. Technology development for integrated analysis and verification of patient biometric data

Progress until FY2023

1.Outline of the project



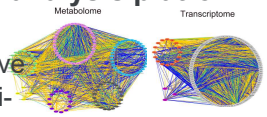
By utilizing the patient biospecimen bank, in addition to parent-derived genomic data, various data such as gene mutation and gene expression at the lesion site can be obtained. However, the utilization technology is currently very underdeveloped. In this theme, we will develop an integrated analysis method to reveal the key molecules and networks (molecules and cell/tissue/organ networks) in the onset process from "multi-layered data" derived from patients.

Since the amount of patient samples is very small, there is a big limitation as an experimental material. In order to overcome this, we will further evolve animal models and patient organoid models. By using patient organoids, it is possible for the first time to analyze biological responses to drugs and gene mutations. It also has great potential as an optimal drug selection system for individuals.

In addition to acquiring sequential data over time, imaging technology has the potential to lead to non-invasive diagnosis in the future. In this theme, we will proceed with the development of imaging technology (sensors and probes).

2. Outcome so far

Construction of an integrated analysis platform for "multi-layered data":



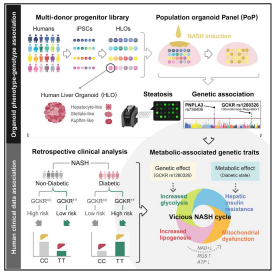
Ito et al., Sci Rep 2023.

Using mouse model data, we have advanced the development of multi-layer network estimation technology using multi-layer ohmic data. In addition, we investigated a method for pseudo-time series analysis in which organoids obtained from patients at various stages are arranged according to the onset process. Using machine learning, we developed exploratory image analysis technology and integrated analysis technology of multi-layered data. Furthermore, we have established a method to analyze cancer genome abnormalities in Japanese people across cancer types.

Experimental Medicine Jan, 2024 (Yodosya)

Horie et al., Cancer Discov 2024.

Development of next-generation cancer development model system:



Kimura et al., Cell 2022.

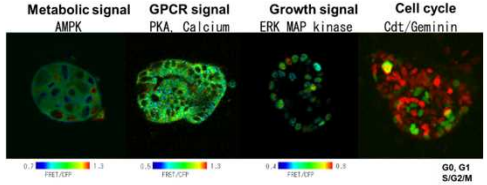
We proceeded with the establishing of new mice with pancreatic cancer. In addition, we are developing a next-generation organoid culture method using iPS cells and have clarified that in precancerous conditions with metabolic abnormalities, the risk of subsequent progression can be predicted when the single nucleotide polymorphism of the glucose metabolism gene is known.

Building an imaging analysis platform:

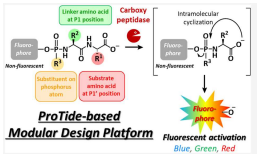
We have built an imaging analysis platform that researchers can use jointly.

健都 イメージングサポート拠点

We have also developed a drug effect detection system that expresses biosensors in pancreatic cancer patient organoids.



We have advanced the development of imaging probes and developed fluorescent probes for proteolytic enzymes based on modular molecular design methods, making it possible to detect enzyme activity in cancer tissues using fluorescence. It is expected that it will be applied to new diagnostic agents that can detect cancer sites during surgery.



Kuriki et al., J Am Chem Soc 2023.

3. Future plans

Utilizing the established organoids from very early and advanced cancer and mouse models, we will proceed with the development of integrated analysis technology for "multi-layered data." We will promote the development of next-generation organoid technology specialized for cancer research. We will continue our efforts to advance imaging technology. We will also start probe screening using clinical samples.

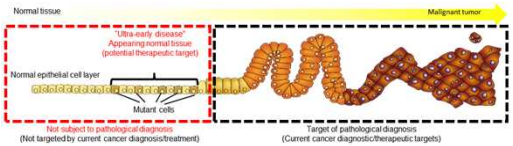
R&D item

3. Technology development for the creation of innovative diagnostic and treatment concepts based on understanding of the onset process of cancer

Progress until FY2023

1.Outline of the project

In this theme, cell biology will explore the role of candidates of early diagnosis markers and therapeutic targets revealed from the multi-hierarchical data of intractable cancer patients . We are developing the experimental system and technology necessary to evaluate its validity.

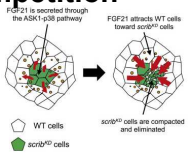


Based on mouse models, normal tissues have multiple mechanisms to eliminate abnormal cells caused by various cellular stresses (cell senescence, bacterial infection, genetic mutation, etc.) to prevent the occurrence of cancer. In addition, changes in metabolism, stem cells, cell adhesion and morphology are central characteristics of cancer cells. It is necessary to know when these cancer development process occur.

In addition to model mice and cancer cell lines, we use clinical specimens containing early-stage lesions, and patient organoids as experimental systems. We are working to understand the process and create new diagnostic and treatment concepts.

2. Outcome so far

Network analysis focusing on cell competition and cell senescence

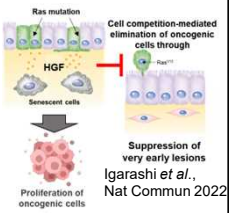


We identified a molecule whose expression increases in the pancreas of a cell competition model mouse. This molecule was expressed in premalignant lesions (ADM) of pancreatic carcinoma in model mice and human clinical samples.

Ogawa *et al.*,Curr Biol 2021

A genetic screen in *Drosophila* identified a group of genes involved in the elimination of cancer mutant or normal cells.

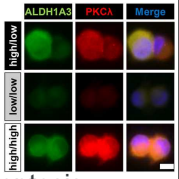
Mutant cells were found to be eliminated from normal cell populations through cell competition by issuing a “kick-me-out” signal to let them out.



We found that elimination of cancer mutant cells by cell competition is suppressed by senescent cells and senolytic drugs are effective in eliminating cancer mutant cells through cell competition. Furthermore, chromatin conformational changes in senescence cells contribute to inflammatory gene expression.

Igarashi *et al.*, Nat Commun 2022

Network analysis focusing on stem cells, cell polarity, and epithelial-to-mesenchymal transition



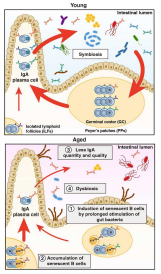
We have found that a cell polarity-related factor is associated with prognosis of pancreatic cancer patients and regulates asymmetric asymmetric division of cancer stem cells.

Kasai *et al.*, BBRC 2023

Using a mouse transplantation model, we identified candidate genes that is involved in ferroptosis resistance, which is involved in the maintenance of cancer stem cells.

We found the mechanism of filamentous process and vascular mimic formation, which are correlated with the prognosis of patients with pancreatic cancer and lung adenocarcinoma.

Network analysis focusing on intestinal flora, cancer immunity, and metabolism



We created a model mouse in which cancer development increases due to the accumulation of senescent cells and identified intestinal bacteria that promote the accumulation of senescent cells and the development of cancer. Furthermore, we discovered that age-related aging of B cells causes disturbances in the intestinal flora.

Kawamoto *et al.*,Nat Cell Biol 2023

We analyzed stresses in the tumor microenvironment that induce the expression of cancer-specific antigens through RNA metabolism and developed simultaneous measurement system for newly synthesized RNA and translation.

We have established a system to detect metabolic changes of amino acids and keto acids in vivo in real time and identified the metabolic pathway of branched-chain amino acids in cancer cells. We found that an inhibitor against chromatin-related factors is effective for leukemia .

3. Future plans

Using the organoids from early lesions of pancreatic cancer, we will clinically verify the usefulness of a molecule whose expression increases in pancreatic precancerous lesions as an early diagnostic marker and investigate the process of cancer onset to reveal the relationship between cellular senescence and intestinal bacteria, metabolic shifts, changes in stem cell characteristics, cell adhesion and morphology