R&D Theme

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

Progress until FY2022

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.

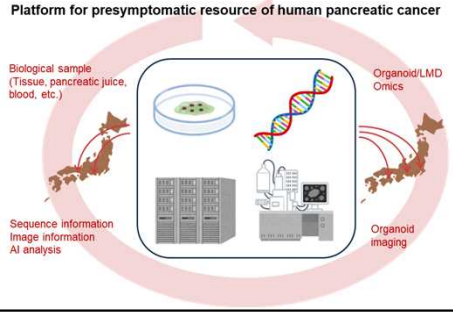
In parallel, we are establishing and accumulating organoids from the patient tissue samples. Patient organoids can be used for various experiments that are not possible with patient samples only. They are an innovative technology that opens up great possibilities for understanding developmental processes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

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 established organoids and their omics are underway.

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 new phenomena and molecular mechanisms that occur with the progression of pancreatic cancer.



Furthermore, we have developed new organoid culture techniques such as co-culture with fibroblasts.

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, the acquisition of comprehensive lipid metabolite profiles and lipid mediator profiles and the standardization of protocols for metabolic analysis are progressing.

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 sharing multi-level integrated analysis.

R&D Theme

Technology development for integrated analysis and verification of patient biometric data

Progress until FY2022

1.Outline of the project

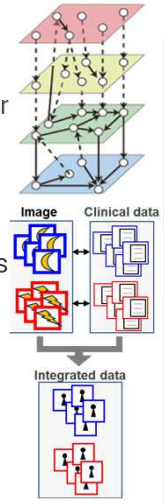
By utilizing the patient biospecimen bank, in addition to parent-derived genomic data, various data such as gene mutation and gene expression at the lesion site can be obtained. However, the utilization technology is currently very underdeveloped. In this theme, we will develop an integrated analysis 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.

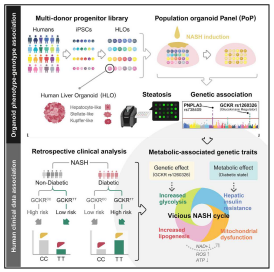
In addition to acquiring sequential data over time, imaging technology has the potential to lead to non-invasive diagnosis in the future. In this theme, we will proceed with the development of imaging technology (sensors and probes).

2. Outcome so far

Construction of an integrated analysis platform for "multi-layered data":
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 using machine learning.

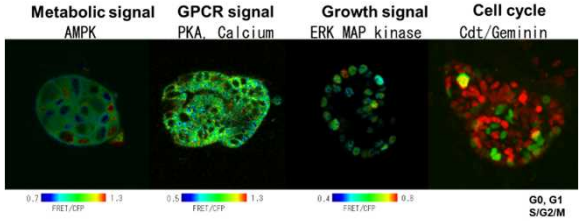


Development of next-generation cancer development model system:
We proceeded with the establishing of new mice with pancreatic cancer. In addition, we are developing a next-generation organoid culture method using iPS cells, and have clarified that in precancerous conditions with metabolic abnormalities,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



Kimura et al., Cell 2022

Building an imaging analysis platform:
We have built an imaging analysis platform that researchers can use jointly. We have also developed a drug effect detection system that expresses biosensors in pancreatic cancer patient organoids.



In parallel, we proceeded with the development of the imaging probe. Prior to clinical specimen screening, we have synthesized our own fluorescent probe group to promote multicolor, and have completed the synthesis of a red probe library consisting of 400 types.

3.Future plans

Utilizing the already established organoid and mouse models of advanced cancer, 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.

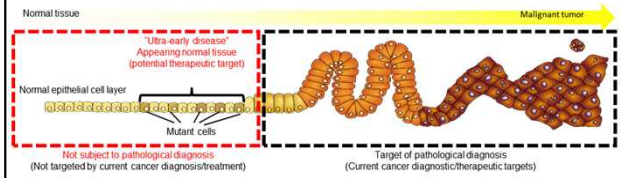
R&D Theme

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

Progress until FY2022

1.Outline of the project

In this theme, cell biology will explore the role of candidate sof 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.

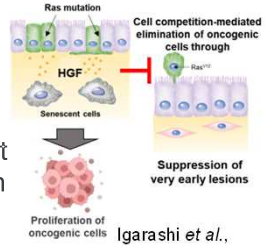
In addition to model mice and cancer cell lines, we use clinical specimens containing early-stage lesions, and patient organoids as experimental systems. We are working to understand the process and create new diagnostic and treatment concepts.

2. Outcome so far

We created a model mouse that can induce cell competition in the pancreas, and identified molecules whose expression increases during cell competition. This molecule was expressed in premalignant lesions (ADM) of pancreatic carcinoma model mice and also expressed in ADM from human pancreatic cancer clinical samples.

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

We found that elimination of cancer mutant cells by cell competition is suppressed by senescent cells. We found that senolytic drugs are effective in eliminating cancer mutant cells through cell competition.



Igarashi *et al.*, Nat Commun 2022

We created a model mouse in which cancer development increases due to the accumulation of senescent cells over time, and using this model, we identified intestinal bacteria that promote the accumulation of senescent cells and the development of cancer. In addition, we constructed an analysis system using human biological samples.

We analyzed the mechanism that various cellular stresses in the tumor microenvironment induce the expression of cancer-specific antigens through changes in RNA metabolism.

We have established a system to detect metabolic changes of amino acids and keto acids in vivo in real time. Using this, we identified the metabolic pathway of branched-chain amino acids (BCAA) in cancer cells.

Using a mouse transplantation model, we narrowed down candidate genes that are suspected to be involved in ferroptosis resistance, which is involved in the maintenance of cancer stem cells.

We have successfully identified new molecules and networks that control the asymmetric division of cancer stem cells in refractory breast cancer.

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

3.Future plans

Molecules with increased expression in pancreatic cancer precancerous lesions (ADMs) are candidate markers for early diagnosis of pancreatic cancer and valuable research tools for understanding pancreatic precancerous lesions. It can be expected that In the future, we will proceed to verify the clinical usefulness of this molecule at early-stage pancreatic cancer lesions. We will also use clinical samples, including organoids, to study the relationship between cellular senescence and intestinal bacteria, metabolic shifts in cancer, changes in stem cell characteristics, changes in cell adhesion and morphological changes.