EPOC will create novel ways to Conquer and Cure Cancer

EPOC Researchers Catalog

Fiscal Year 2022

Inquiry on collaborative research

if you have any requests or questions,
please feel free to contact us at the following address.

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National Cancer Center Japan

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National Cancer Center Japan

Exploratory Oncology Research & Clinical Trial Center (NCC-EPOC)

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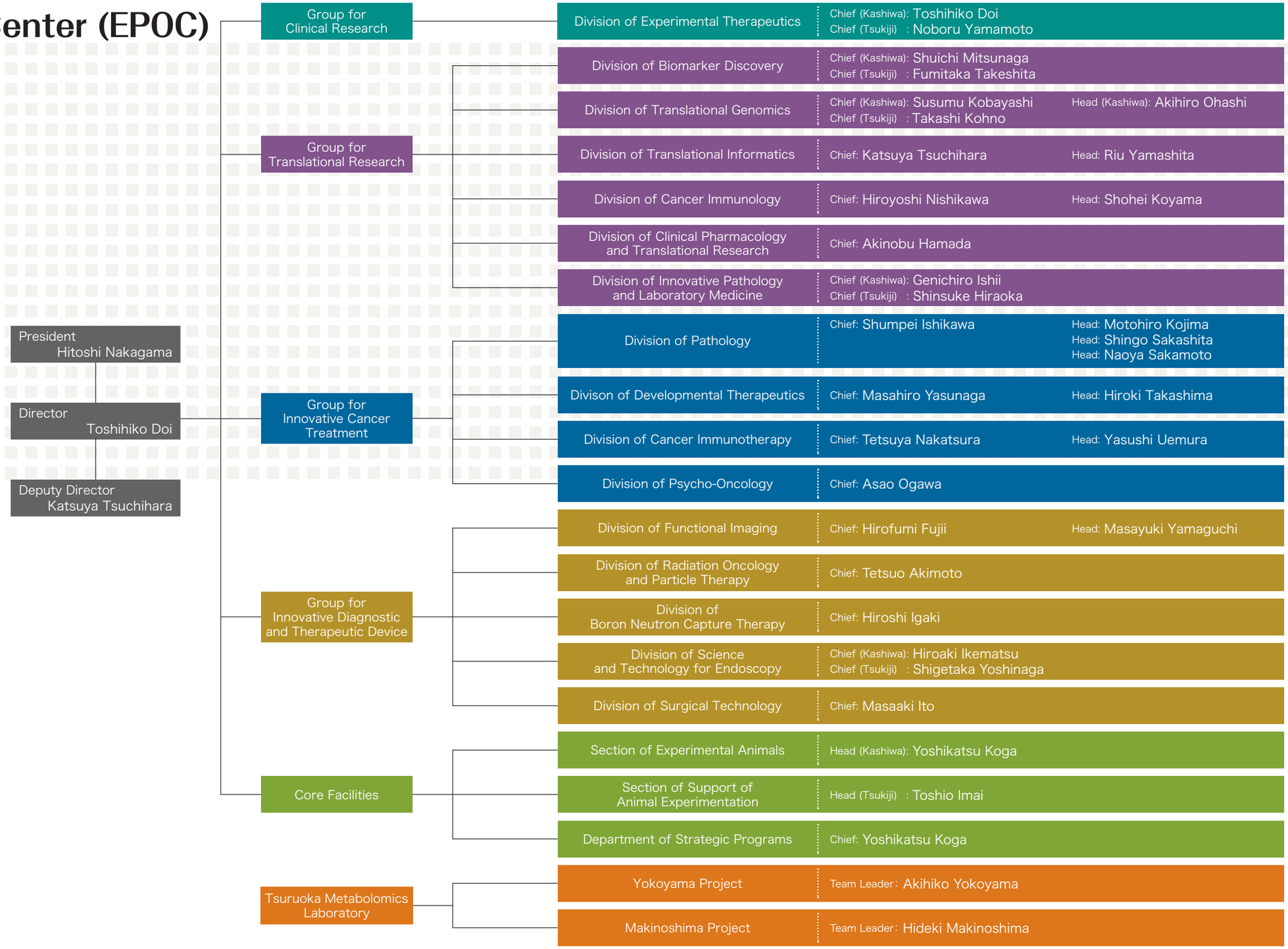
Introduction

The Exploratory Oncology Research & Clinical Trial Center (EPOC) was originally called the National Cancer Center EPOC (NCC-EPOC), which has been organized since 2012.
The NCC-EPOC was a cross-campus organization between the Kashiwa and Tsukiji campuses in NCC, aiming to eliminate a drug lag in Japan and to lead Japan-driven discovery and development of innovative drugs and medical devices. The NCC-EPOC has been working to establish a structure for conducting first-in-human (FIH) trials, investigator-initiated trials (using products from either companies or academia), and translational research (TR). In the meantime, both NCC Hospital and East Hospitals were designated as "core hospitals for clinical research" under the Medical Care Act in 2015, and the clinical trial structure was transferred and managed by both hospitals. Simultaneously, the NCC-EPOC organization was refined, and then EPOC was newly established to strengthen the development function in the NCC.
The EPOC has promoted non-clinical studies and exploratory clinical translational research (TR) that can support the clinical proof of concept (POC) declaration in early development. One of the ideal paths of how EPOC can promote TR, for example, is similar to our biomarker discovery TR field. A pathology and clinical laboratory TR field would be in charge of biomarker search, diagnostic, and laboratory test development leading to a proposal of treatment methods. It could be clinically proven and validated by our two core hospitals through FIH and/or early phase trials. Efforts should be dedicated to the development of medical devices. In fact, the BNCT medical development field has succeeded in putting next-generation radiation therapy into practical application in clinical practice, in addition to conventional particle therapy. The fields of endoscopic and surgical device development have received continuous support from EPOC, resulting in the acceleration of clinical development for new endoscopic devices, robotic surgical devices, and applications of imaging and AI.
Furthermore, the EPOC has expanded collaboration research with broad partners, like the University of Tokyo Graduate School of Frontier Sciences, Kavli Institute for the Physics and Mathematics of the Universe, Tokyo University of Science, Beth Israel Deaconess Medical Center, and Frederick National Cancer Institute, to integrate different disciplines with other innovations. Our next challenge is to integrate medical records from the hospital, and diverse data from residential communities and living environments, to create an unprecedented unique data field that might have an impact on future living environment improvement.
The refined EPOC will also collaborate with the NCC Venture Incubation Program (NCC-VIP) to encourage its translational research functions, strengthen R&D support for growing venture seed development, and improve our R&D capabilities by involving venture capital and corporate fund acquisition. We believe that every effort would make the EPOC achieve the primary goal of contributing to cutting-edge research. The mindset of “RX-EPOC,” meaning a renewed EPOC with research transformation, might be a key to maximizing our functional presence. We look forward to your continued support, cooperation, and guidance.

Toshihiko Doi, M.D., Ph.D.
Director,
Exploratory Oncology Research &
Clinical Trial Center

National Cancer Center Japan
Exploratory Oncology Research & Clinical Trial Center (EPOC)



As of October, 2022

Development of treatment for pancreatic ductal adenocarcinoma (PDAC) and cachexia

One stop service for the implementation of 'proof of concept (POC)' in PDAC patients with cachexia

Shuichi Mitsunaga, MD, PhD
Division of Biomarker Discovery (Kashiwa) Chief

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- ▶ Development of biological and clinical strategy on the crosstalk between tumor-induced inflammation and host reaction
- ▶ Testing POC in pre-clinical model
- ▶ Evaluation of POC in clinical trial and translational research

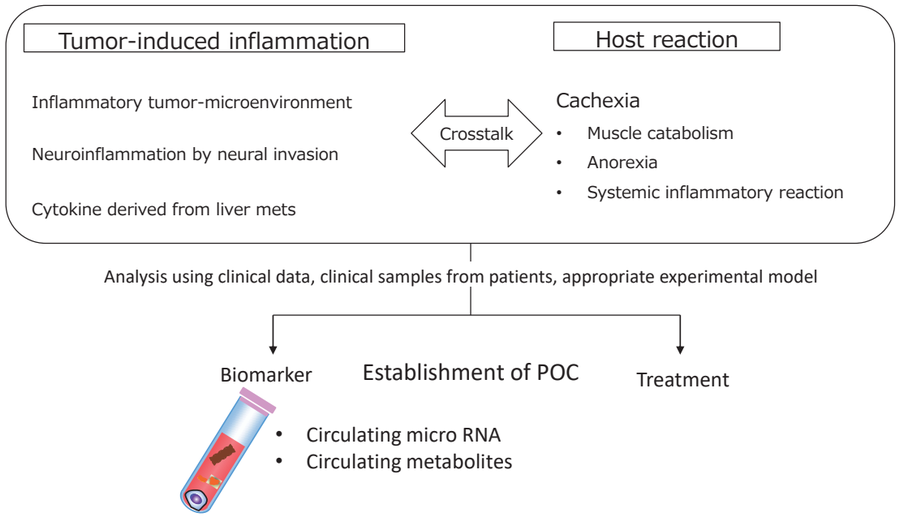
Research background & characteristics

The patients with aggressive PDAC show a very high inflammatory burden and short life expectancy, which are features of cancer cachexia, a multi-factorial metabolic syndrome characterized by ongoing loss of skeletal muscle mass. It is increasingly clear that cancer cachexia impacts physical wellbeing, anorexia, quality of life, and chemo-refractory. The crosstalk between tumor-induced inflammation and host reaction is a cause of cachexia, which has been elucidated in our research works of neuro-inflammation by neural invasion of PDAC and tumor-derived interleukin-6 from liver metastasis. Our achievements have been built on patient-derived samples, interpretation of tumor-microenvironment and clinical data, and appropriate models to test experimental treatments. Investigator-initiated clinical trial and its translational research, which were conducted in National Cancer Center Hospital East (NCCHE) and Exploratory Oncology Research & Clinical Trial Center (EPOC) on National Cancer Center Japan (NCC), revealed that the treatment of anti-inflammatory cytokine led the improvement of chemo-refractory, immune-microenvironment, and patients' symptoms in PDAC patients. Our research is focused on the development of therapy not only for tumor reduction but also for improvement of cancer cachexia.

Potential research technical cooperation & future research prospects

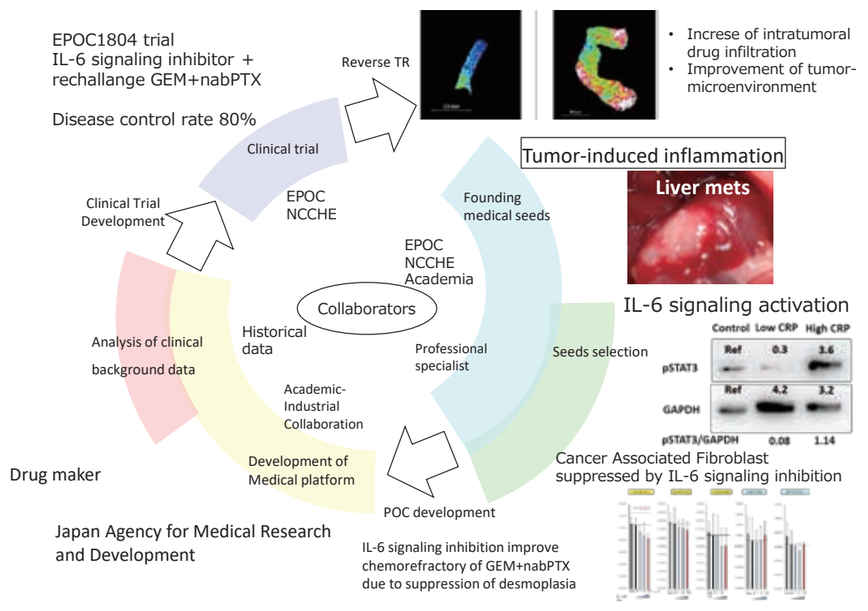
In our research work, novel therapies and biomarkers have been developed on interpretation of combining clinical samples and information, gene analyses, and various Omics information through collaborations with many external research institutes and drug discovery companies, which are built on the elucidation of the molecular mechanism of the crosstalk between tumor-induced inflammation and host reaction.
The framework of a successful POC needs biological and clinical strategy, appropriate experimental model to test POC and clinical evaluation of POC using clinical data and samples. Our achievements indicate that we have the ability for doing or consulting the implementation of POC in PDAC. Moreover, our achievements include the biomarker research for early detection of PDAC, cachexia, or chemotherapeutic efficacy. We would like to discuss various seeds for solution or detective-biomarker of PDAC-related difficulties as early detection, inflammation, desmoplasia, chemo-refractory, anorexia and cachexia.

Concept



Aimed to develop novel POCs of biomarker and treatment on the basis of interpretation for tumor-induced inflammation, host reaction, and their crosstalk

Case: Development of interleukin-6 inhibition-containing regimen for pancreatic cancer



Assessment of the cancer cells and immune cells derived from the same patients

Establishment of the functional assessment system for the T cells and cancer cells isolated from the ascites

Fumitaka Takeshita, PhD
Division of Biomarker Discovery (Tsukiji) Chief

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- **Establishment of the gastric and pancreatic cancer cell lines whose clinical information and omics data are integrated**
- **Identification of the fusion genes that are intrinsically expressed from gastric cancer cell lines**
- **Establishment of the immunological ex vivo assessment system for the T cells and cancer cells derived from the ascites of the same patients**

Research background

Although cancer cell lines are frequently used in basic studies researches and drug discovery researches, only a few omics data analysis results (such as genes and proteins) are published in terms of the cell lines of the refractory cancers common among Asian people (gastric and pancreatic cancers) due to the small number of cell lines. Focusing on gastric and pancreatic cancers, our division established the world' s largest number of unique cell lines from the patients of the National Cancer Center and conducted omics analyses. Moreover, through the analysis of these cell lines, we identified novel fusion genes and established an immunological ex vivo assessment system for the cancer cells and CD3-positive T cells derived from the same patients, and we also built a research technology platform.

Research characteristics

We established unique cell lines derived from patients (including 121 gastric cancer cell lines and 80 pancreatic cancer cell lines). With regard to gastric cancer cell lines, clinical information and omics data are already added to them, and they were utilized to identify the patient stratification markers for gastric cancer and establish the novel cell lines which intrinsically express the X-ARHGAP6/26 fusion gene. Moreover, in AMED Research on Development of New Drugs (matching type, so-called GAPFREE Project), we established an immunological ex vivo assessment system utilizing the T cells and cancer cells derived from the ascites of the same patients and confirmed its utility in the evaluation of bispecific antibodies, including T cell engagers, as well as PD-1 antibodies.

Potential research technical cooperation

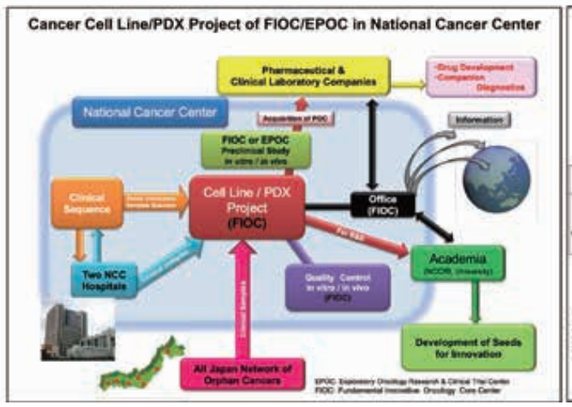
- ◆ World' s largest number of primary cell lines unique to the National Cancer Center (including gastric and pancreatic cancers)
- ◆ Immunological ex vivo assessment system by using the T cells and cancer cells in ascites obtained from the same patients
- ◆ Cell lines intrinsically having driver mutations, such as fusion genes

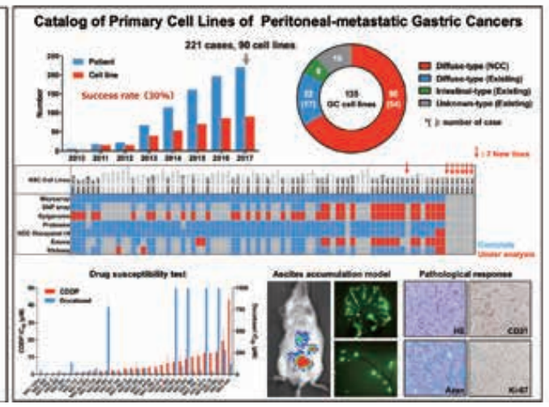
Future research prospects

Around the autumn of 2020, we will add omics data to pancreatic cancer cell lines in the same manner as gastric cancer and search patient stratification markers other than KRAS. We are also pursuing ascites-derived cell banking to prepare for the derivation of the immunological ex vivo assessment systems for bispecific antibodies and other antibody drugs and small- and middle-molecule drugs, for which drug development is increasing.

Activities of Division Biomarker Discovery in EPOC (1)

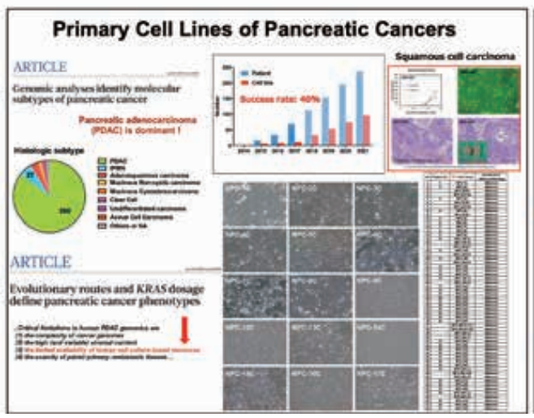
Chief : Fumitaka Takeshita
Researcher : Hiroki Sasaki **Project researcher :** Fumiko Chiwaki, Masayuki Komatsu, Moeko Inoue
Research assistant : Megumi Miyagi

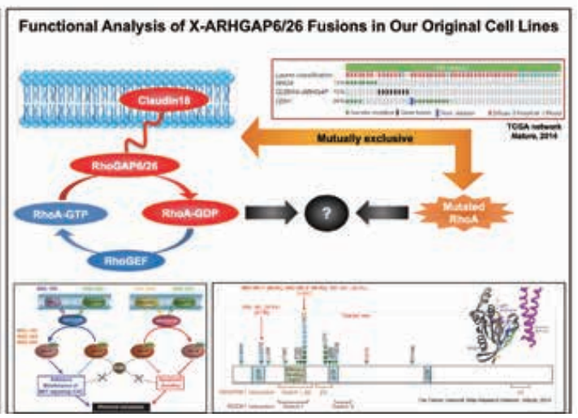




Activities of Division Biomarker Discovery in EPOC (2)

Chief : Fumitaka Takeshita
Researcher : Hiroki Sasaki **Project researcher :** Fumiko Chiwaki, Masayuki Komatsu, Moeko Inoue
Research assistant : Megumi Miyagi





Overcoming Resistance to Cancer Therapy

Understanding of mechanisms of resistance using human cancer specimens

Susumu Kobayashi, MD, PhD
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(concurrently holding a position as Associate Professor at Harvard Medical School and Beth Israel Deaconess Medical Center)
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- ▶ **Elucidation of resistant mechanisms to EGFR-TKI using human cancer specimens**
- ▶ **Development of novel cancer therapies targeting the Wnt/β-catenin pathway**
- ▶ **Optimization of cancer treatment using PDX models**

Research background

Lung cancer with EGFR mutations are reportedly predominant in east Asia. The Division of Translational Genomics (Kashiwa) focuses on translational research (TR) and promotes the integration of basic studies and clinical observations. We previously identified the T790M mutation in the EGFR gene using human lung cancer tissues that showed resistance to first and second generation EGFR inhibitors, which led to the development of third-generation EGFR inhibitors. However, resistance to third-generation EGFR inhibitors has already been reported, which may be caused by gene alterations in the EGFR gene and/or other signaling pathways.

Research characteristics

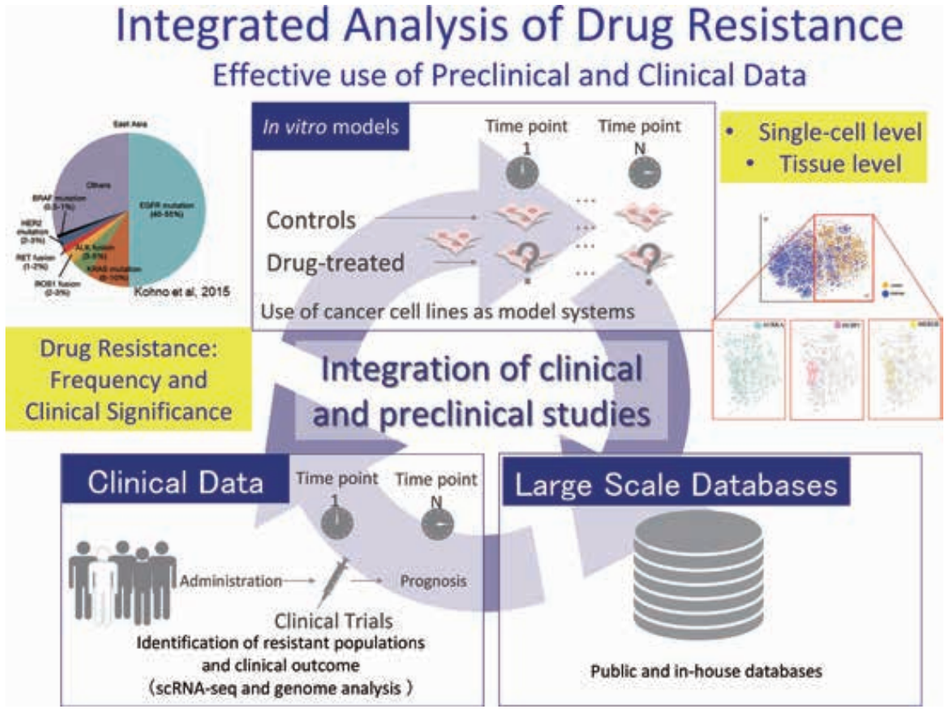
Based on our previous experiences using cancer specimens, we have developed research infrastructure and resources, such as single-cell analyses and PDX models from patients with lung cancer, to study resistance to all EGFR inhibitors. We have discovered that the Wnt/β-catenin pathway may be involved in the pathogenesis of lung cancer by analyzing human lung cancer tissues and currently try to identify novel target molecules for new cancer therapeutics. Our goal is to develop and optimize novel therapeutics using PDX models.

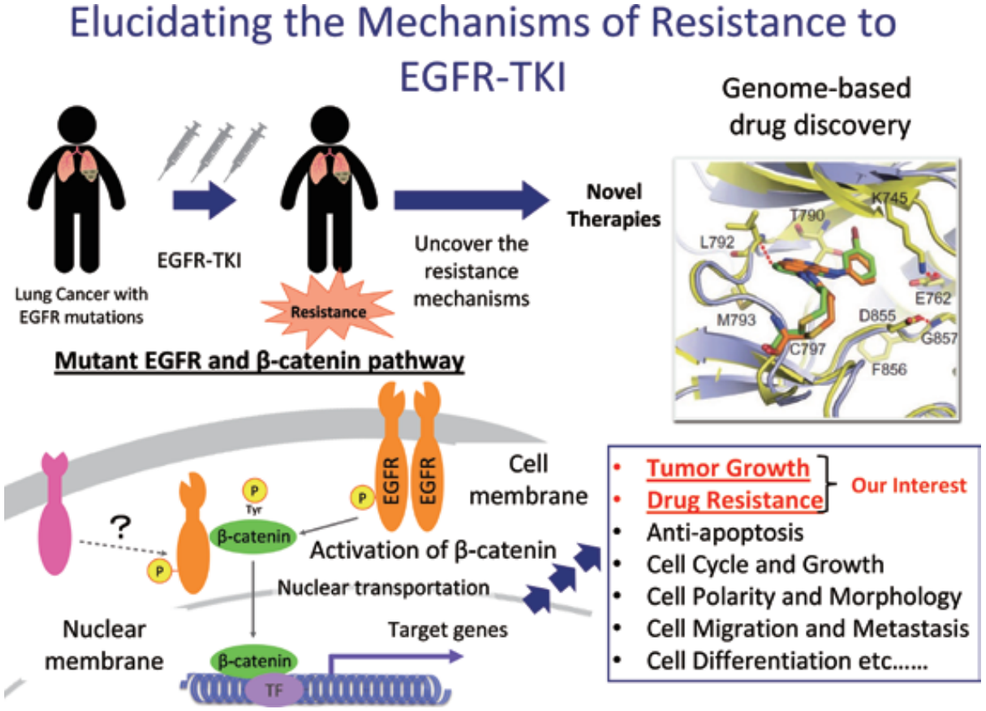
Potential research technical cooperation

- ◆ Human lung cancer cell lines resistant to one- to third-generation EGFR inhibitors
- ◆ Multi-omics data obtained from cell line models including single-cell analysis
- ◆ PDX models established from pre- and post- treatment (therapeutics and types of cancer are negotiable)

Future research prospects

We will continue to analyze multiomics data on human cancer specimens (such as genomes, epigenomes, transcriptomes, and metabolomes) to investigate genetic abnormalities, tumor-specific activation pathways, and mechanisms of resistance (i.e. EGFR inhibitors) for the development of novel cancer therapeutics.





Drug discovery targeting chromosomal instability of cancer vulnerability

Chromosomal instability-mediated cellular stress and cancer drug discovery

Akihiro Ohashi, PhD
Division of Translational Genomics (Kashiwa)　Head

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- ▶ **Target discovery in newly-established cancer models of chromosomal instability**
- ▶ **Drug discovery targeting DNA replication stress**
- ▶ **Biomarker seeking for novel molecular-targeting therapies, integrating multiple-layer data package of multi-omics analyses**

Research background

A key to success for molecular targeting cancer therapies is how accurately we could shoot the right targets, which are tightly connected to cancer hallmarks and vulnerabilities. Focusing on a pillar of cancer hallmarks “chromosomal instability” , we are currently investigating, 1) stress response pathways caused by chromosomal instability (polyploid-/aneuploid-mediated stress responses), 2) adaptive mechanisms of cancer cells against the polyploid-/aneuploid-mediated stress, and 3) correlation between the adaptive mechanisms against chromosomal instability and drug sensitivity/resistance (the adaptive mechanisms and cancer venerability). We aim to develop novel cancer therapeutics and innovative therapeutic strategies on chromosomal instability-mediated cancer vulnerabilities.

Research characteristics

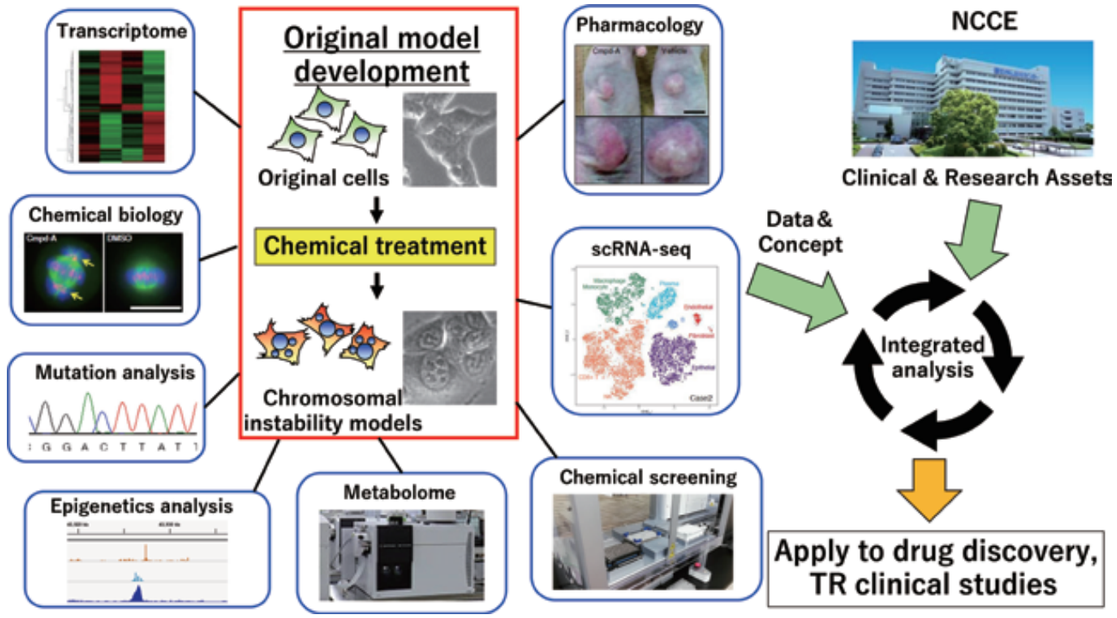
We are aiming to identify the vulnerability factors of chromosomal instability in cancer cells. Given that cancer cells manage to survive overcoming antiproliferative pressures of chromosomal instability, these vulnerability factors are expected to be “Achilles’ heel” in cancer cells, thus could be potential target molecules for the molecular-targeting therapies. We have successfully established various chromosomal instability cancer models using small molecule inhibitors as chemical tools. Utilizing these original models in the light of clinical information, we are investigating biological significance of chromosomal instability in cancer to identify the vulnerability factors. cells on basic and translational researches. In collaboration with talented researchers, we are energetically conducting a number of research programs integrating the cutting-edge technologies: multi-omics analyses of transcriptome or metabolome, chemical biology, pharmacology, cell biology, bioinformatics, and computational biology.

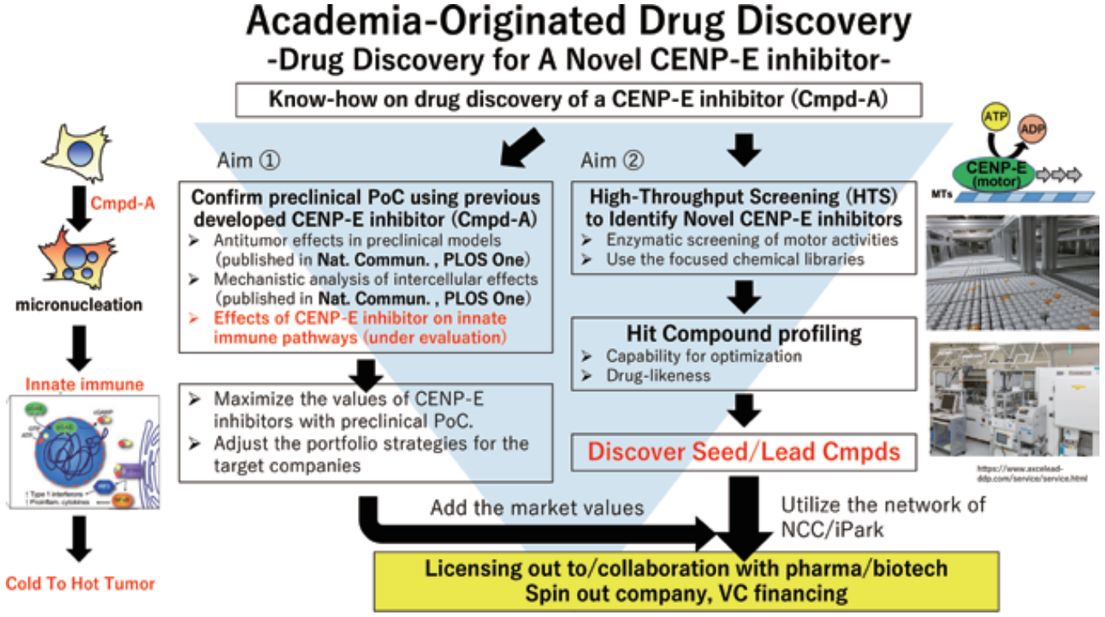
Potential research technical cooperation

◆ Chromosomal instability cancer models　◆ Multi-omics data in chromosomal instability cancer models
◆ Single-cell RNA analysis in cell lines and/or clinical specimens
◆ Screening analysis data in reference compound libraries (~3,400 cmpds)

Future research prospects

Integrating our cutting-edge technologies for basic, translational, and clinical researches, we commit to inspire the research innovation of cancer biology to be a world-leading cancer research laboratory. We also commit to contribute to development of the next generation of innovative cancer therapeutics originated in Japan.





Driving cancer genome medicine by functional genome analysis

Expansion of molecular target therapy for cancer by annotating mutations of unknown significance

Takashi Kohno, PhD
Division of Translational Genomics (Tsukiji) Chief

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- ▶ **Implementation and improvement of tumor profiling gene panel test**
- ▶ **Discovery and translation of RET fusion gene through clarification of drug resistance/response mechanisms**
- ▶ **Expansion of therapeutic drug options by annotating mutations of unknown significance**

Research background

Cancer genome medicine, in which appropriate therapeutic options are individually chosen based on information on gene alterations, is making great progress. In Japan, two tumor profiling gene panel tests have been implemented from 2019. We discovered and translated *RET* fusion gene as a new therapeutic target, while we also developed NCC Oncopanel as a tool to diagnose gene alterations. These efforts have greatly helped implementation of cancer genome medicine in Japan. Annotation of mutations with unknown significance, which are often detected in a variety of cancer-related genes by gene panel tests, is a big challenge to further progress cancer genome medicine; appropriate ways to annotate their significance for therapy are strongly needed.

Research characteristics

NCC Oncopanel test tells us about both somatic and germline mutations in cancer cells, therefore, it is useful to determine therapeutic options not only for sporadic but also for hereditary cancers. With regard to the *RET* fusion gene, clinical trials using multiple RET kinase inhibitors have been conducted, which resulted in the approval of two RET-specific inhibitory drugs, selpercatinib and pralsetinib, by the FDA in 2020. Thus, we have been achieving implementation of our own therapeutic and diagnostic seeds. By combining cancer genome analysis with supercomputer-based molecular dynamics simulation, we are now annotating a number of mutations with unknown significance in the *RET* and *EGFR* genes as for therapeutic significance. The fruits will further progress cancer genome medicine.

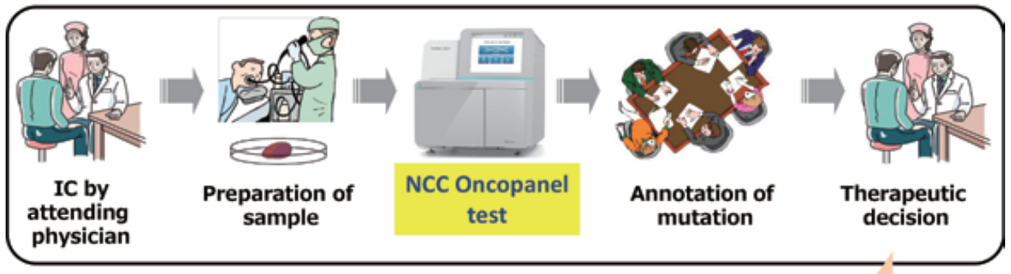
Potential research technical cooperation

- ◆ Annotation of mutations with unknown significance by molecular dynamics simulation
- ◆ Development and implementation of cancer gene tests
- ◆ Precise genome analysis of formalin-fixed paraffin-embedded tumor specimens

Future research prospects

The personalized cancer medicine based on genetic alteration has been implemented in the National health insurance system of Japan. However, only a small fraction of patients actually benefit from gene-matched therapy due to lack of actionable mutations. Aiming for the full use of genetic alteration information detected by gene panel tests, we will develop a precise and efficient mutation annotation method and more powerful genetic tests.

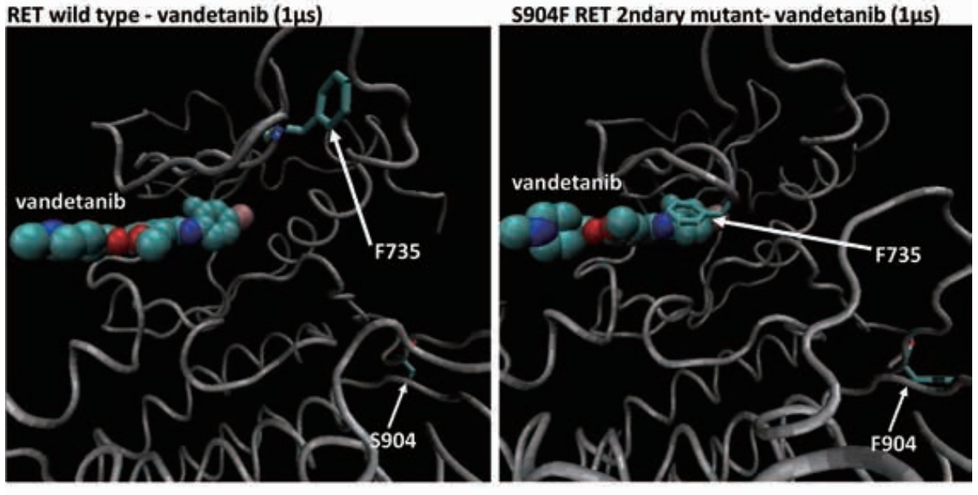
Cancer Genome Medicine Using Gene Panel Tests



114 mutation • amplification (whole exon)					12 fusion genes
ABL1	CRXL	IDH2	NF1	RAC2	ALK
ACTN4	CREBBP	IGF1R	NFE2L2/Nrf2	RAD51C	AKT2
AKT1	CTNNB1/b-catenin	IGF2	NOTCH1	RAF1/CRAF	BRAF
AKT2	CUL3	IL7R	NOTCH2	RB1	ERBB4
AKT3	DDR2	JAK1	NOTCH3	RET	FGFR2
ALK	EGFR	JAK2	NRAS	RHOA	FGFR3
APC	ENO1	JAK3	NRG1	ROS1	NRG1
ARAF	EP300	KDM6A/UTX	NTRK1	SETBP1	NTRK1
ARID1A	ERBB2/HER2	KEAP1	NTRK2	SETD2	NTRK2
ARID2	ERBB3	KIT	NTRK3	SMAD4	PDGFRA
ATM	ERBB4	KRAS	NTSC2	SMARCA4/BRG1	RET
AXIN1	ESR1/ER	MAP2K1/MEK1	PALB2	SMARCB1	ROS1
AXL	EZH2	MAP2K2/MEK2	PBRM1	SMO	
BAP1	FBXW7	MAP2K4	PDGFRA	STAT3	
BARD1	FGFR1	MAP3K1	PDGFRB	STK11/LKB1	
BCL2L11/BIM	FGFR2	MAP3K4	PIK3CA	TP53	
BRAF	FGFR3	MDM2	PIK3R1	TSC1	
BRCA1	FGFR4	MDM4	PIK3R2	VHL	
BRCA2	FLT3	MET	POLD1		
CCND1	GNA11	MLH1	POLE		
CD274/PD-L1	GNAQ	MTOR	PRKCI		
CDK4	GNAS	MSH2	PTCH1		
CDKN2A	HRAS	MYC	PTEN		
CHEK2	IDH1	MYCN	RAC1		

1. Selection of existing drugs
2. Selection of clinical trials to be enrolled
3. Selection of immune checkpoint drugs
4. Diagnosis of tumor type
5. Diagnosis of tumors of unknown primary site
7. Diagnosis of recurrence
8. Diagnosis of double cancer
9. Diagnosis of drug resistance
10. Diagnosis of hereditary cancer
11. Prognosis

Molecular Dynamics Simulation-based Mutation Annotation



Allosteric effect of S904F mutation on the stability of the RET kinase-vandetanib complex:
Appearance of a *de novo* conformer which would sterically interfere with the binding of vandetanib

(Nakaoku et al, *Nat Comm*, 2018)

Drug discovery based on translational informatics

Establishment of integrated database of non-coding RNA

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Division of Translational Informatics　Head

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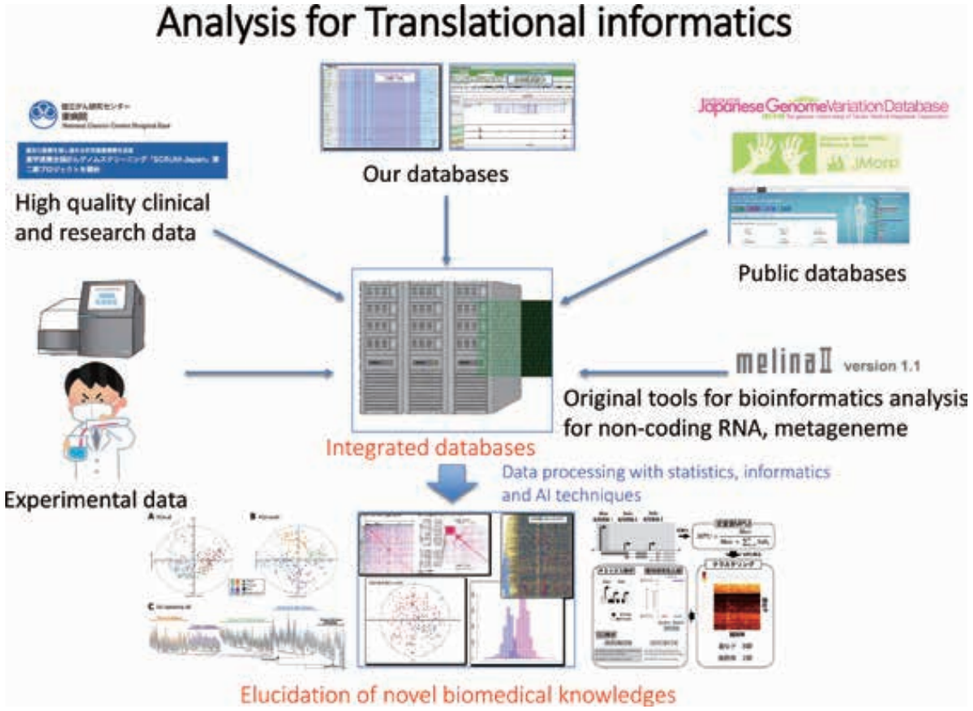
- ▶ Establishment of a database related to RNA transcription (DBTSS/DBKERO)
- ▶ Prediction of non-coding RNA sequence from the transcription start sites
- ▶ Metagenome analysis for cancer science

Research background

In cancer cells, transcriptional and translational controls should be different from normal cells and show various abnormal phenotypes. However, not so many reports have described the integrated analysis of transcriptional and translational regulation due to the lack of suitable databases. We have a unique annotation technology and databases for transcriptome data, focusing on non-coding RNA as well as coding RNA. We are also focusing on AI-aided analysis of the multi-omics data, a large amount of DNA, RNA, and meta-genome experimental data.



Research characteristics

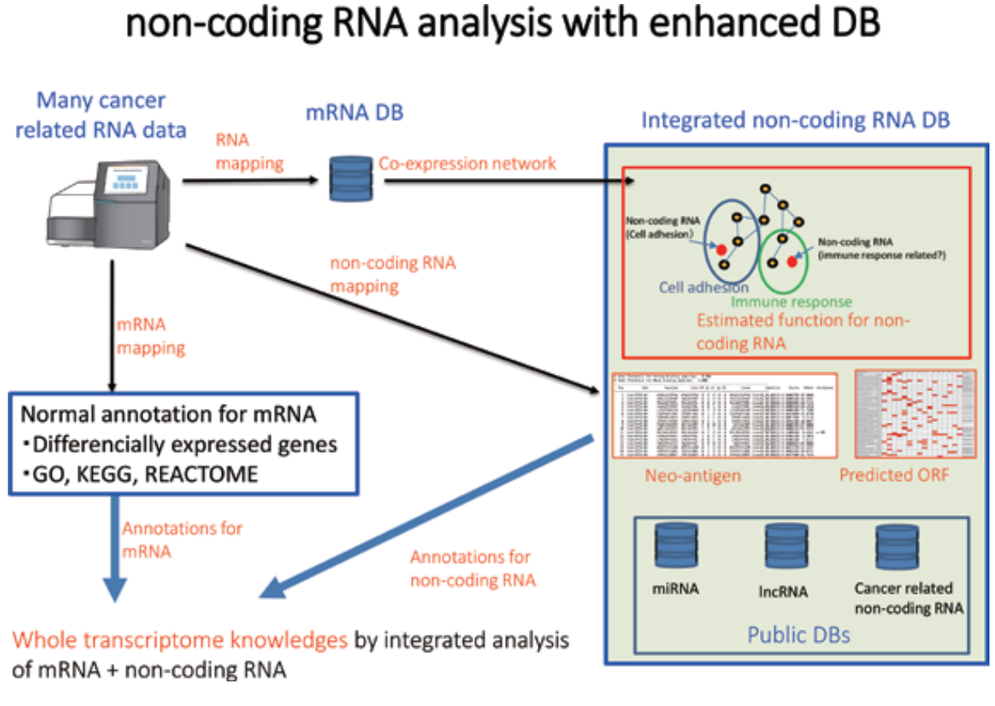
In collaboration with Prof. Yutaka Suzuki' s laboratory at the University of Tokyo, our division is involved in establishing DBTSS/DBKERO, a database describing accurate transcription start sites/RNA structures/histone modification of normal cells and cancer cells. Moreover, we are developing a database of non-coding RNAs with the potential open reading frames (ORFs) and predicted neoantigen. Using this database, we reported a short peptide, which is translated from 'non-coding' RNAs play essential biological roles in vivo. We also conducted metagenome studies of fecal from cancer patients as well as multi-omics analysis by integrated those data.

Potential research technical cooperation

- ◆ Multi-omics analysis by using DBTSS/DBKERO
- ◆ Unique annotation of non-coding RNA
- ◆ Pipelines for microbiome metagenome analysis

Future research prospects

Using the database and methods we have established, medical/biological knowledge can be elucidated from many omics big data. Moreover, through "translational informatics," such as integrating our experimental research data and public database information, we would like to link the outcomes to the development of novel pharmaceutical products.



Development of New Patient Stratification Techniques and Drugs

Establishment of analysis techniques for immune cells that reflect the tumor microenvironment

Hiroyoshi Nishikawa, MD, PhD
Division of Cancer Immunology Chief

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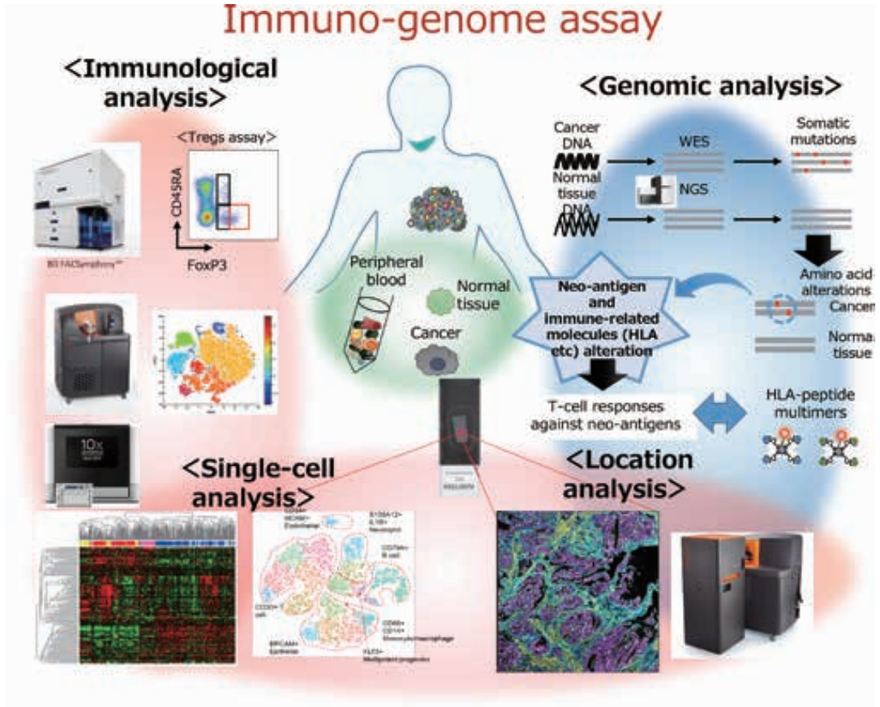
- ▶ **Techniques for examining immune cells in the tumor microenvironment**
- ▶ **Identification of patient stratification markers based on the characteristics of various types of immune cells**
- ▶ **Provision of analysis techniques for immune cells (particularly immunosuppressive cells)**

Research background

As genetic analysis becomes a common strategy, personalized medicine based on genetic analysis data on cancer cells is now being applied into the clinic. At present, therapeutic agents, molecular-targeted reagents are prescribed to patients on the basis of the genetic analysis results of cancer cells, including EGFR mutations, ALK fusion gene expression; however, data from cancer cell genetic analysis are insufficient to determine the appropriate immunotherapy for many patients. Thus, the Division of Cancer Immunology focused not only on cancer cells but also on tumor-infiltrating immune cells for the optimal application of cancer immunotherapy based on the combination of genetic and immune analyses. We apply immune cell analysis techniques to identify new patient stratification markers and will contribute to the development of personalized medicine via new drug development activities.



Research characteristics

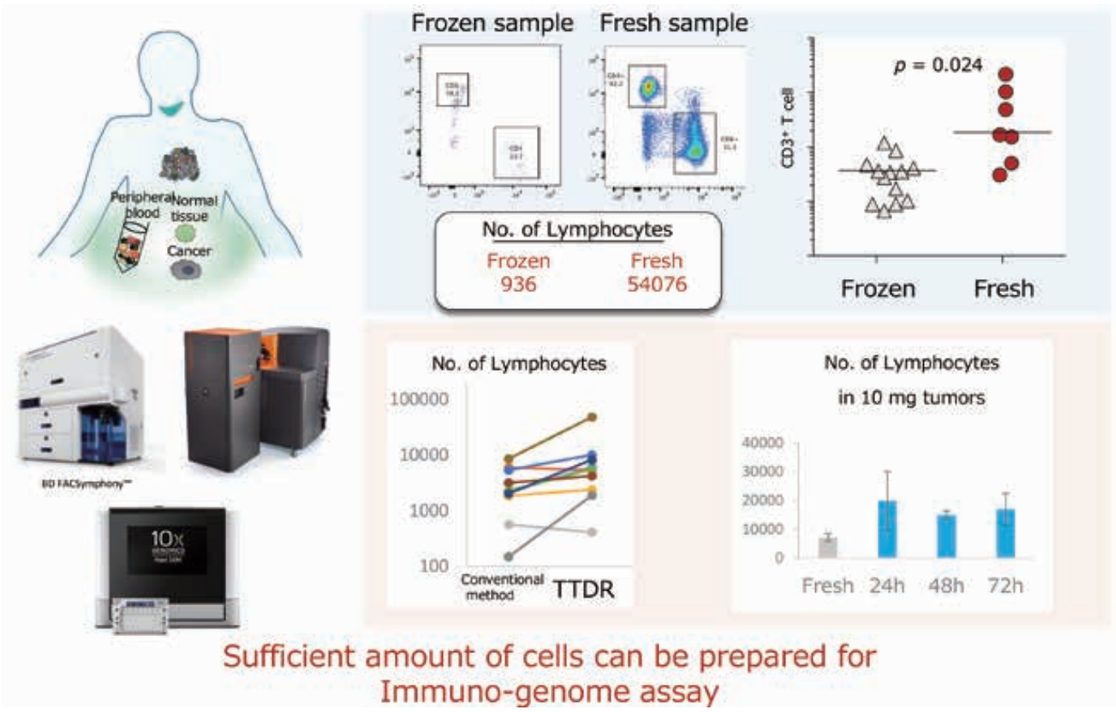
It was difficult to accurately understand the condition of immune cells in the tumor microenvironment because of the difficulty to collect sufficient amounts of samples from tumor tissues. The utilization of new techniques that we developed has enabled the extraction of immune cells while maintaining the phenotypes and functions of immune cells in the tumor microenvironment. Furthermore, using this techinique, we have identified new patient stratification markers on the basis of the expression of immune cell molecules and have prospectively evaluated their clinical benefits. We mainly focus on clarifying the immunosuppressive mechanisms of regulatory T cells (such as CD8 positive T cell anergy) and are committed to the development of new cancer immunotherapy.

Potential research technical cooperation

- ◆ Techniques for extracting the immune cells reflecting the tumor microenvironment
- ◆ Analysis of patient stratification markers based on the analysis of immune responses in the tumor microenvironment
- ◆ Provision of various immunoassay techniques by focusing on regulatory T cells for drug discovery research

Future research prospects

The current cancer immunotherapy is not effective for all cancer patients since cancer cells employ various immunoselection strategies characterized by the loss of highly immunogenic antigens and by the establishment of immune suppressive mechanisms. We will integrate the genetic analyses about cancer cells and immune cells and their positional information inside the tumor and clarify the roles of immune cells in the entire tumor microenvironment to develop effective treatment options.



Establishment of the methods to search for novel immunotherapeutic targets

Identification of novel immunotherapeutic targets by separating cells bound to antibodies

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- ▶ Various kinds of analyses specifying/concentrating only cells bound to antibody drugs
- ▶ Longitudinal monitoring of the immune cells affected by antibodies
- ▶ Immune cell profiling by using laboratory animals and human clinical specimens

Research background

In the development of pharmaceutical products, the products exhibit their effects through the complex combination of the binding rate of the products to the target molecules (occupation rate), the effects of the inhibition or activation of target molecules on cells, the improvement effects by which cells contribute to diseases, and other factors. Through the application of the antibodies recognizing IgG4 and other antibodies, separation of the cells bound to therapeutic antibodies from those not bound to them, and analysis of those cells, our division realized the assessment of the differences between cells, depending on the duration and existence of binding to antibodies. Moreover, we conduct immune cell profiling by using naturally occurring cancer model mice and clinical specimens.

Research characteristics

Peripheral blood immune cells were mixed with nivolumab (anti-PD-1 antibody), the CD8-positive T cells bound to nivolumab were separated from those not bound to nivolumab with FACS using anti-IgG4 antibodies, the gene expression patterns of the bound-type and unbound-type cells were analyzed, and the genes characterizing each type were identified. In addition, the application of the same techniques in the longitudinal monitoring of the immunocytes affected by the investigational therapeutic antibody enabled the acquisition of the data that are important for estimating the treatment duration of the investigational drug. Moreover, we analyze the immune cell profile using mice with Kras mutation or other gene modification and clinical specimens and contribute to the production of novel treatments and stratification markers.

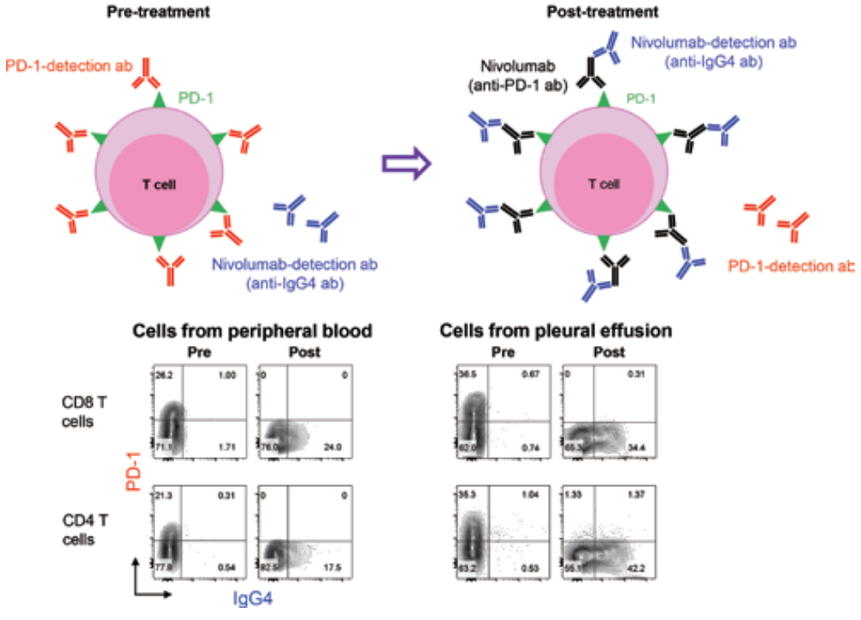
Potential research technical cooperation

- ◆ Longitudinal monitoring analysis on the immune cells affected by therapeutic antibodies
- ◆ Immune cell profiling by using human tumor tissues and peripheral blood
- ◆ Assessment of the therapeutic drugs to be given to the immune cells of naturally occurring cancer model mice

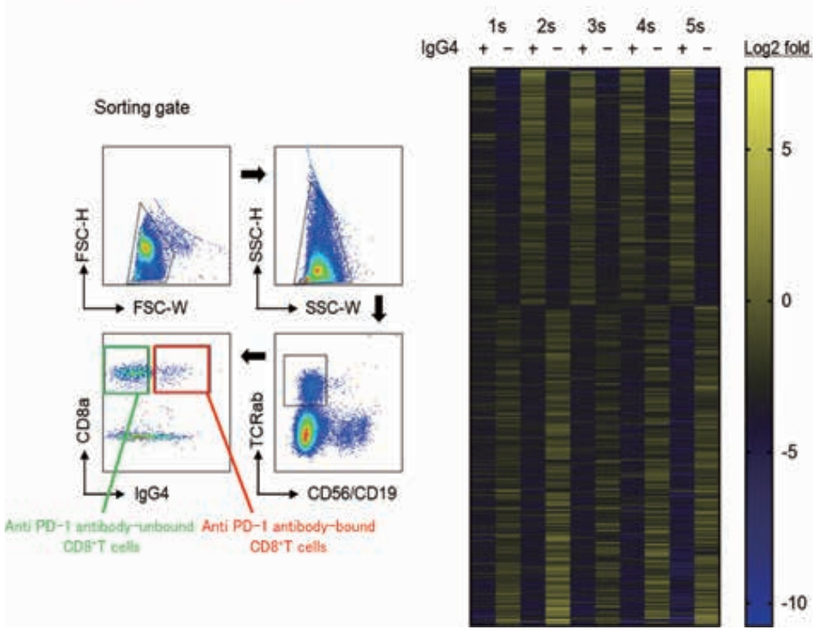
Future research prospects

By applying the monitoring techniques used for peripheral blood immune cells to cancer tissues and elucidating the differences between the cells bound and unbound to antibodies in tumor tissues, we would like to separate only the cells contributing to drug effects and examine the expressed genes and TCR, which contribute to next-generation drug discovery researches and patient stratification marker search.

Evaluating T cells bound to therapeutic anti PD-1 antibodies



Sorting T cells bound to therapeutic anti PD-1 antibodies to compare the transcriptome profile with unbound T cells



Application of PDX derived from Japanese cancer patients to drug discovery

Support for the industrial use of the PDX library linked to clinical information

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- **Establishment of the library of PDXs derived from Japanese cancer patients via government-private sector joint promotion**
- **Drug discovery researches through the utilization of PDX in which PDX analysis information and clinical information are linked to each other**
- **Clinical pharmacology researches based on pharmacokinetic/pharmacodynamic/pharmacogenetic analyses**

Research background

The development of a new animal model which reflects the heterogeneity of the human cancer tissue structures related to drug delivery or treatment resistance is anticipated. It is because the animal models used to evaluate drug effects in the field of cancer research are created by transplanting the cell lines, which exhibited effects in in vitro studies to immunocompromised mice. Focusing on the patient-derived xenograft (PDX) model, which can retain cancer tissues' characteristics, our division developed a PDX library through the joint effort of the government and private sectors. Moreover, the industrial use of the PDX library was realized. We also conducted pharmacokinetic analyses, mass analyses, and other analyses required in drug discovery.

Research characteristics

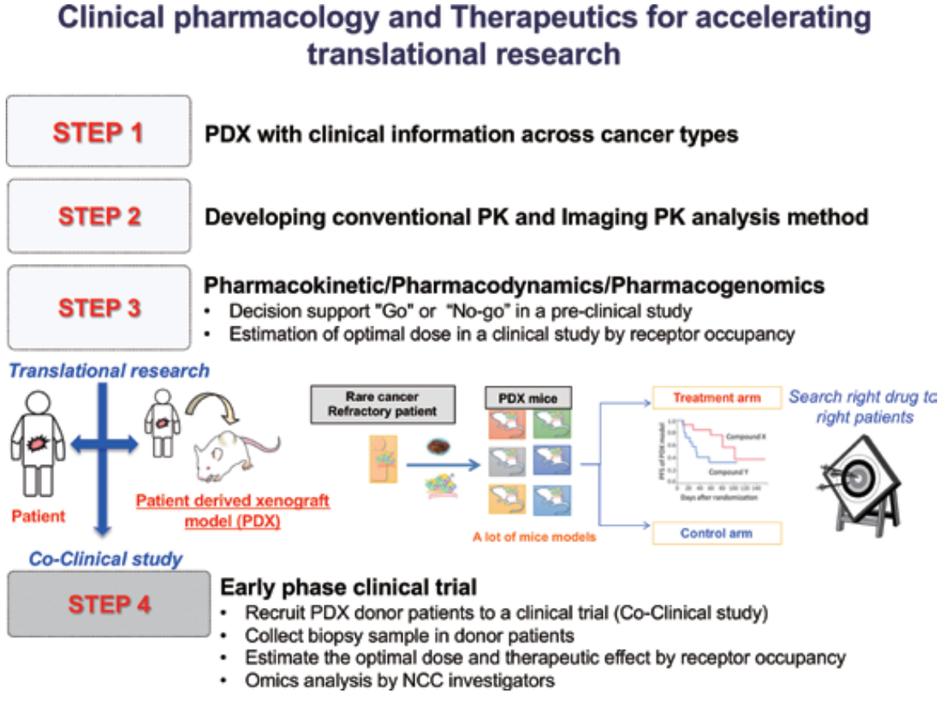
With regard to PDX libraries, the national-level improvement of a framework for realizing their industrial use in Japan is desired. The establishment of PDX libraries is expensive in terms of PDX establishment, quality assurance, maintenance, etc. Research of our division is accepted as a CiCLE Project of Japan Agency for Medical Research and Development and utilized to improve a PDX library in cooperation with the National Institutes of Biomedical Innovation, Health and Nutrition, and LSI Medience Corporation. In addition to analyzing the established PDXs and obtaining histopathological findings, cancer genomes, gene expressions, and other information, we unitarily manage them in combination with clinical information and provide them to companies and academic institutions. Moreover, we conduct clinical pharmacology researches based on pharmacokinetic/pharmacodynamic/pharmacogenetic analyses.

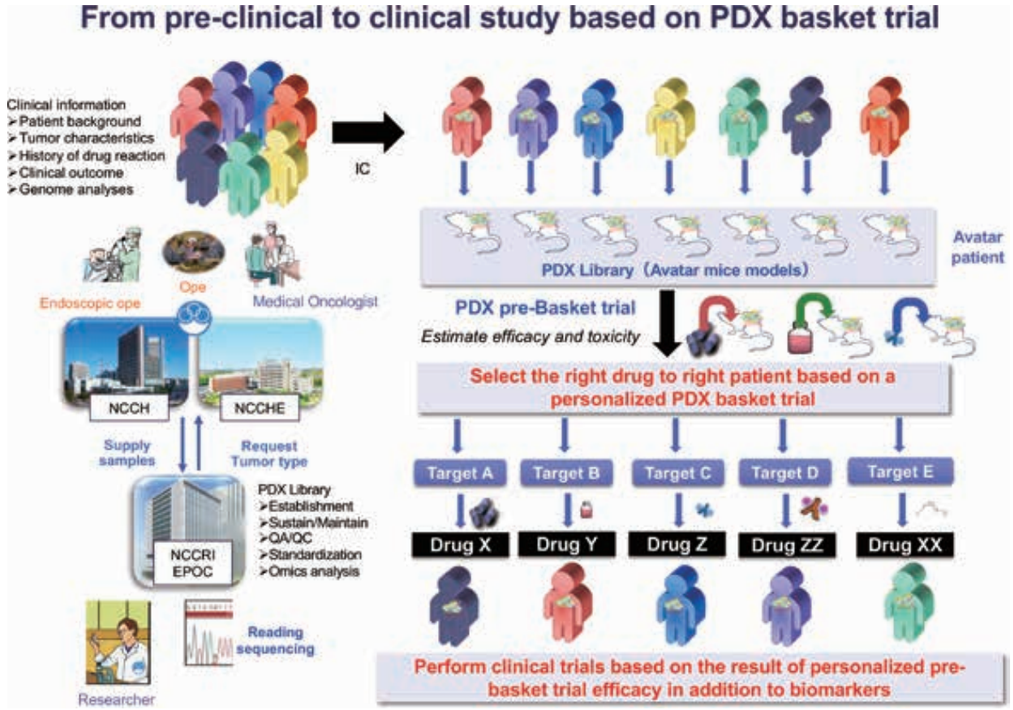
Potential research technical cooperation

- ◆ Characteristic mice included in the library of PDXs derived from Japanese cancer patients
- ◆ Drug discovery support by utilizing the PDX library
- ◆ Pharmacokinetic/pharmacodynamic/pharmacogenetic analyses

Future research prospects

By unitarily managing PDX analysis information (including histopathological findings, cancer genomes, and gene expressions) and clinical information and mutually comparing the effects and action mechanisms of pharmaceutical products between mice and humans, we achieve our goal of contributing to genomic medicine development and drug discovery researches.





Application of Fibroblasts to Drug Development

Clarification of drug resistance caused by cancer-associated fibroblasts

Genichiro Ishii, MD, PhD
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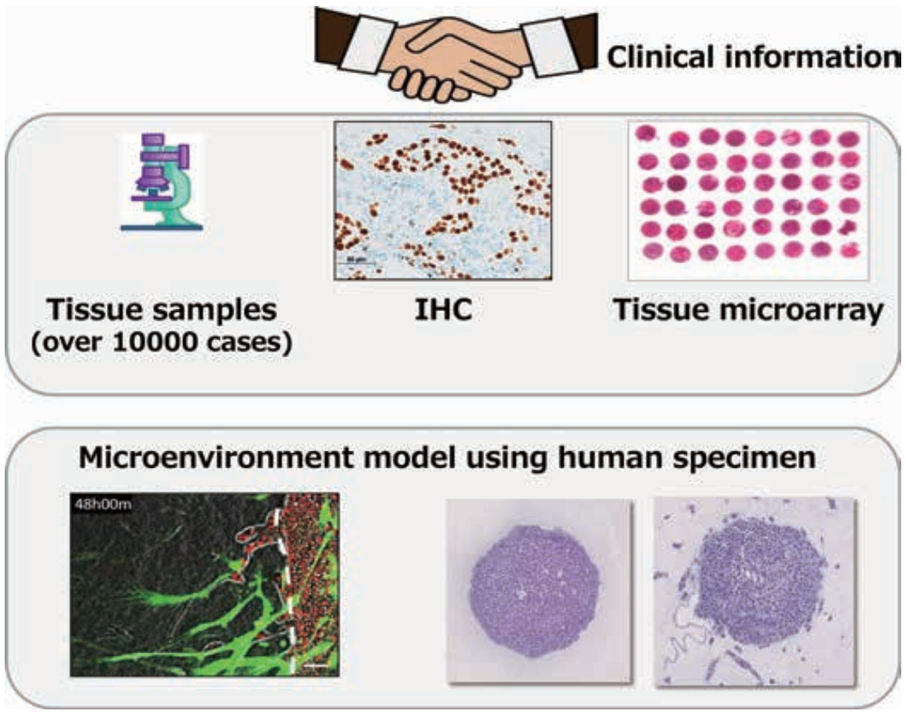
- **Establishment of primary cultured fibroblasts derived from the cancerous and noncancerous tissue samples of the same patients**
- **Establishment of primary cultured fibroblasts before and after drug treatment**
- **Creation of cancer organoids containing fibroblasts and cancer cell lines**

Research background

The solid tumor microenvironment has a complicated structure composed of various cells, including cancer cells, fibroblasts, and immune cells. Recent studies show that intratumoral fibroblasts are functionally and phenotypically heterogenous and affect the drug sensitivity of cancer cells via the interaction with these cells. Division of Innovative Pathology and Laboratory Medicine (Kashiwa), in cooperation with the Department of Pathology and Clinical Laboratories at the Hospital East, has established fibroblasts derived from human cancer tissues to clarify new mechanisms of cancer progression and develop new therapeutic agents.



Research characteristics

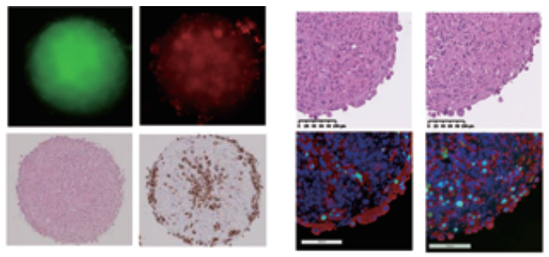
Division of Innovative Pathology and Laboratory Medicine (Kashiwa) has built a technology for establishing the primary cultured cells of cancer-associated fibroblasts (CAFs) from tumors, such as human lung and gastric cancers. We have also established normal fibroblasts (Non-CAFs [N-CAFs]) simultaneously from noncancerous tissue samples from the same patients and identified the biological characteristics of CAFs by comparing CAFs and N-CAFs with clinical information in mind. We also started drug sensitivity evaluation after establishing a system for cancer organoids mixed with CAFs and cancer cell lines. We have established CAFs from human cancer tissues that are not treated with drugs, and we recently succeeded in establishing the CAFs from those treated with drugs. We will attempt to clarify the causes of CAF-induced drug resistance.

Potential research technical cooperation

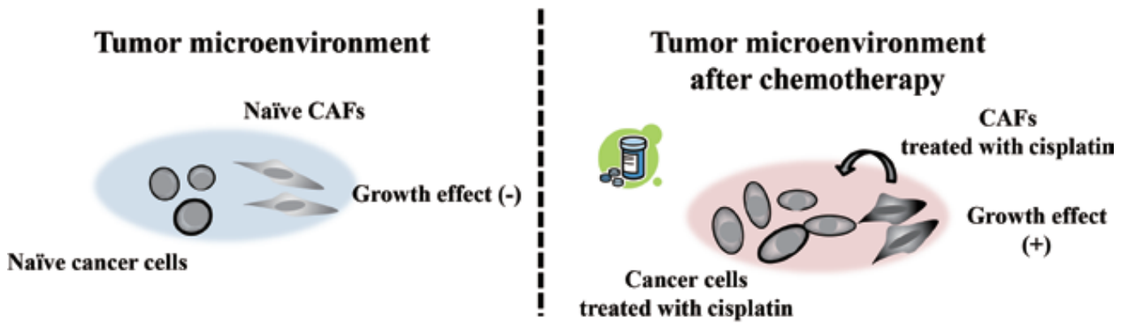
- ◆ CAFs and N-CAFs from the same patients
- ◆ System for cancer organoids mixed with CAFs and cancer cell lines
- ◆ Establishment of CAFs before and after drug treatment

Future research prospects

We will try to clarify the roles of CAFs in the tumor microenvironment before and after drug treatment. Focusing on the interaction between drug-exposed CAFs and drug-exposed cancer cells, we will develop a novel therapeutic strategy.



Organoids using tissue-derived CAFs and cancer cells
(Lung Cancer, 2019;100-107)



Cancer-associated fibroblasts and their microenvironment in post-chemotherapy recurrence
(Human Cell, 2019; 453-464, and in press)

Structuring Histopathological Images for Integrated Diagnosis

Quantification the histopathological images and integration with other medical data

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- ▶ Quantifying high-dimensional spatial information of histopathological images.
- ▶ Deep learning technology resistant to noise specific to clinical specimens.
- ▶ Quantitative integration with clinical information such as genomic information

Research background

Highly accurate and integrated diagnosis requires interpretation of highly dimensional information from a combination of multimodal data. Unlike numerical data such as clinical laboratory data and genomic data, histopathological images used for pathological diagnosis are not structured information, making quantitative integration with other data difficult. In this field, we are developing image data acquisition and artificial intelligence technologies to quantify the high-dimensional spatial information of histopathological images while eliminating the problem of noise caused by quality variations of clinical specimens. This technology will enable quantitative integration of histopathological information with other clinical information, such as genomic information, to make high-level clinical decisions.

Research characteristics

Histopathological images contain complex and highly dimensional information composed of the spatial arrangement of various types of cells. From this information, we construct a deep neural network that can incorporate clinically important biological meaning and quantify it as high-dimensional features. In the process of obtaining histopathology images, there is a bias in artificial intelligence analysis due to the existence of noise caused by variations in specimen processing and image acquisition, etc. We are also developing data acquisition and analysis techniques that are less susceptible to such biases.

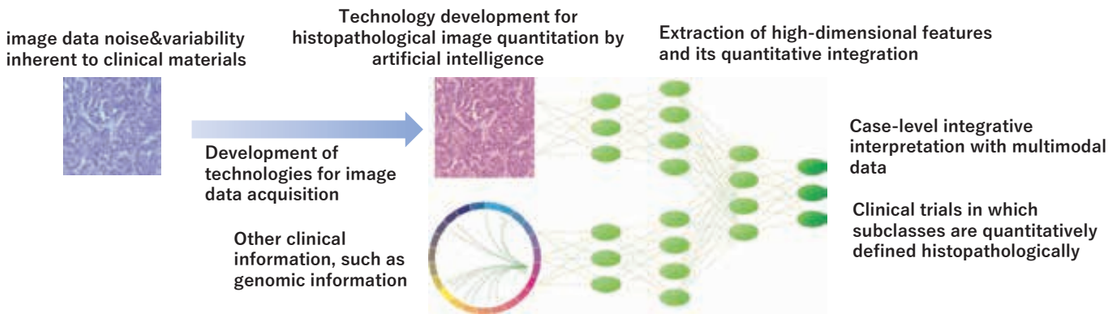
Potential research technical cooperation

- ◆ Quantification of histopathological images using artificial intelligence
- ◆ Image data library of clinical pathological tissues
- ◆ Data library combined with clinical data

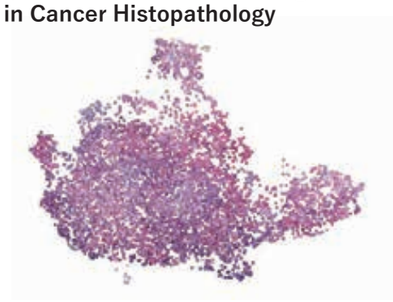
Future research prospects

By making it easier to handle complex information that has been interpreted by pathologists as numerical values, quantitative integration with other clinical information will advance and multimodal diagnosis will become possible. Clinical trials and clinical studies focusing on subclasses quantitatively defined with histological images, which have been difficult to do in the past, will also become possible.

Structuring Histopathological Images for Integrated Diagnosis



Quantification of Morphological Diversity in Cancer Histopathology



Cell Reports 38(9):110424. 2022

Two-dimensional mapping of histopathological images of approximately 7,200 cases of 32 cancer types quantified by artificial intelligence. Histopathologically similar images are placed nearby, and dis-similar ones are placed far away, so that the overall picture of cancer diversity can be quantitatively grasped.

Actions for the establishment of pathological assessment method for tumor regression

Residual tumor areas as an objective pathological assessment method of tumor regression

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- ▶ Proposal of a novel pathological assessment methods based on the size of residual tumor areas
- ▶ Pathological evaluation to elucidate the pathogenesis of physical abnormalities in human cancer tissue
- ▶ Gene expression analysis to elucidate the pathogenesis of physical abnormalities in human cancer tissue

Research background

Tumor regression after chemo-radiation therapy is evaluated by the regression in tumor size after the product administration. Next, abnormal tumor physiology in tumor is highly variable and is reported to correlate with tumor stage, prognosis, and therapeutic effect. On the other hand, the techniques for measuring the tumor physiology is limited, and the biological implication of the physiology in human tumors are not explained well. Our division found that the area of residual tumor (ART) in surgically resected pancreatic cancer specimens determined the prognosis. Moreover, we developed a device to quantitatively measure the hardness of tumors and conducted an analysis on the changes in gene expression depending on the physiology of tumors.

Research characteristics

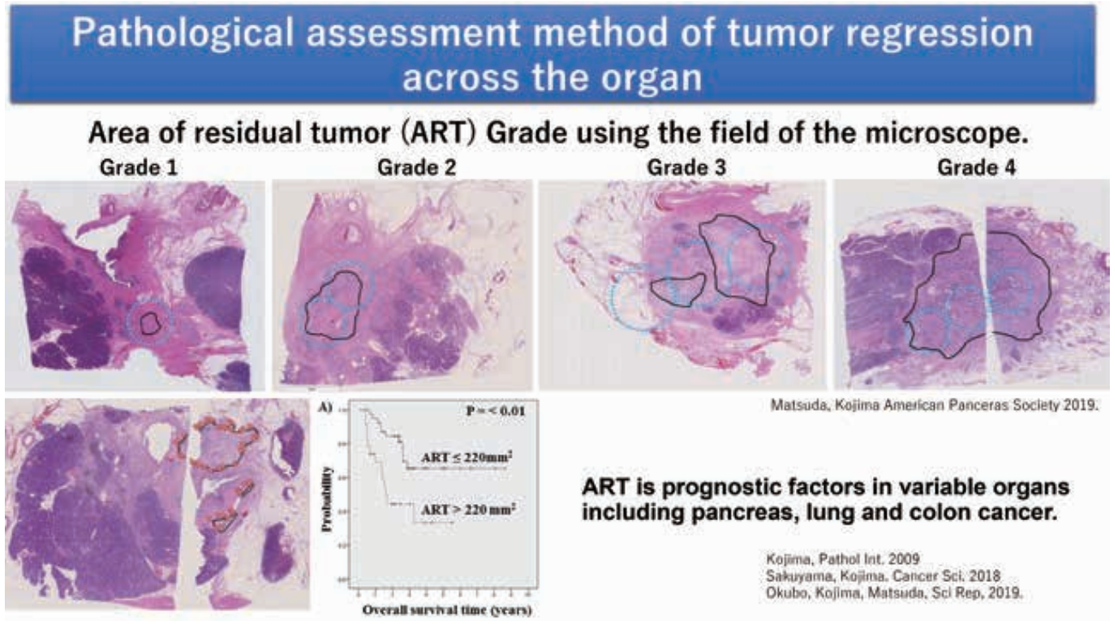
As a result of the measurement of the ART in the surgical specimens of pancreatic cancer following neoadjuvant treatment, we elucidated that the small ART group had a better prognosis than the large ART group. On the other hand, other reported assessment methods of CAP, Evans, and JPS grade did not associated with the prognosis. Furthermore, compared with other methods, ART showed less inter-observer difference among the pthologists. In addition, ART is also available as a prognostic factor in lung, colon, and gastric cancer. Therefore, ART can be used in the clinical trials as a biomarker. ART enables the comparison of therapeutic effects with standard therapy in a short time. We obtain the data which exhibit the utility of the stiffness of tumor tissues for the diagnosis and/or malignancy prediction and can be link them to the development of diagnostic medical devices. The stiffness of tumor tissues strongly correlates with the amount of collagenous fiber and the actin expression of fibroblasts. An exhaustive analysis revealed that gene expression largely differed between hard and soft tumors. Our experience, measuring method, and analytic strategy may also contribute to the establishment of new therapeutic strategy target on the tumor stroma and physiology.

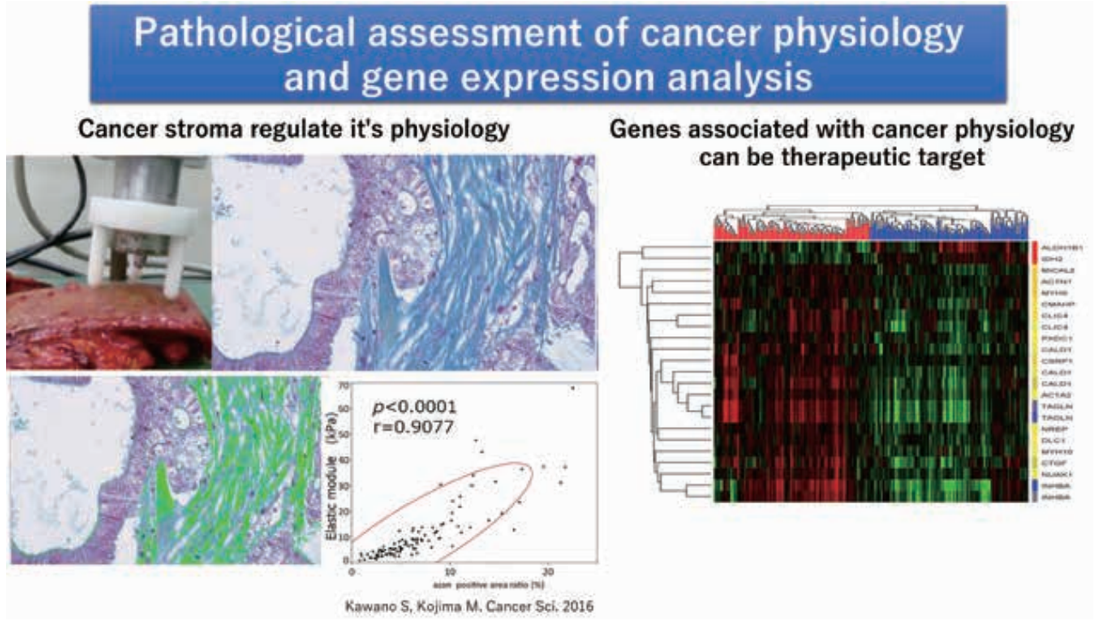
Potential research technical cooperation

◆ Response evaluation method based on ART　◆ Methods of measuring the stiffness of tumors
◆ Comprehensive analysis associated with the physiology of tumors, and pathological interpretation.

Future research prospects

We will adopt ART in variable cancers in aim for the development of the pathological assessment methods which can shorten the study period and reduce costs in clinical trial of variable organ. In addition to the development of clinical sensor, we will aim for constructing new therapeutic strategy target on tumor physiology.





Creating a Foundation for the Dissemination of AI in Pathological Diagnosis

Standardization of pathology images

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- ▶ Development of fully automated specimen preparation machine
- ▶ Creation of SOPs for standardized images
- ▶ Creation of database with standardized images

Research background

The pathological diagnosis of cancer is made by microscopic examination of pathological tissue by a pathologist, which enables not only diagnosis but also acquisition of basic clinical data such as prognostic factors and stage of disease. However, due to the shortage of pathologists, regional disparities in pathological diagnosis have emerged.
AI-assisted pathology diagnosis technology has the potential to improve diagnostic accuracy and reduce regional disparities through diagnostic assistance. However, in order for AI-assisted pathology diagnosis technology to work properly everywhere, pathology images including specimens must be standardized. In this field, we are organizing the foundation for correcting disparities in pathology diagnosis using AI through standardization of pathology images.

Research characteristics

In order to build pathological diagnosis support technology using AI, it is considered essential to first standardize images (standardization of all processes in the image creation process). Therefore, we are developing equipment to fully automate pathology specimen preparation and image acquisition. Currently, in collaboration with equipment manufacturers, we are studying the items necessary for standardization (specimen preparation and imaging conditions, etc.) and are aiming to create SOPs for standardized images. Using these standardized images, we hope to select the necessary data sets for machine learning and build a platform for AI-assisted pathological diagnosis technology.

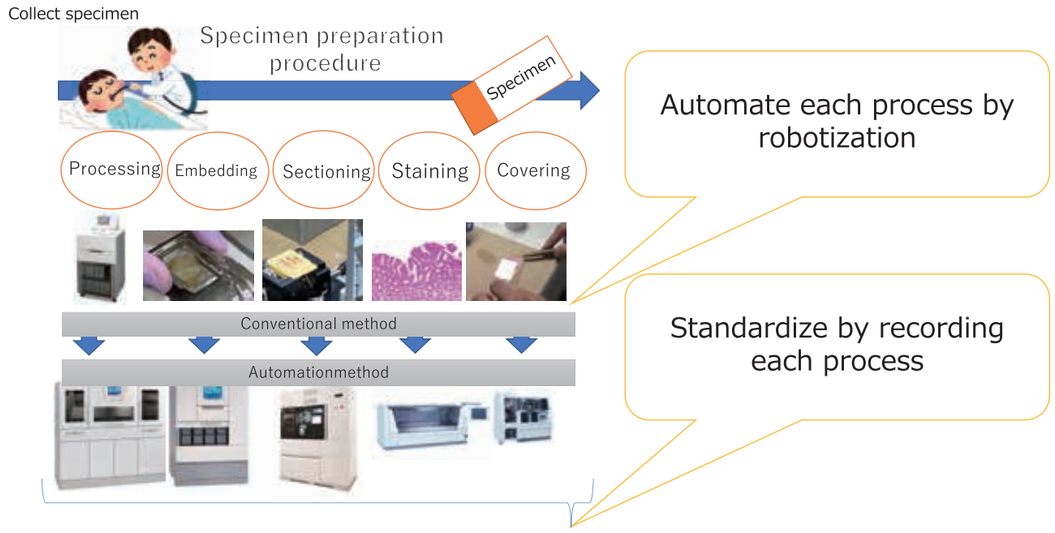
Potential research technical cooperation

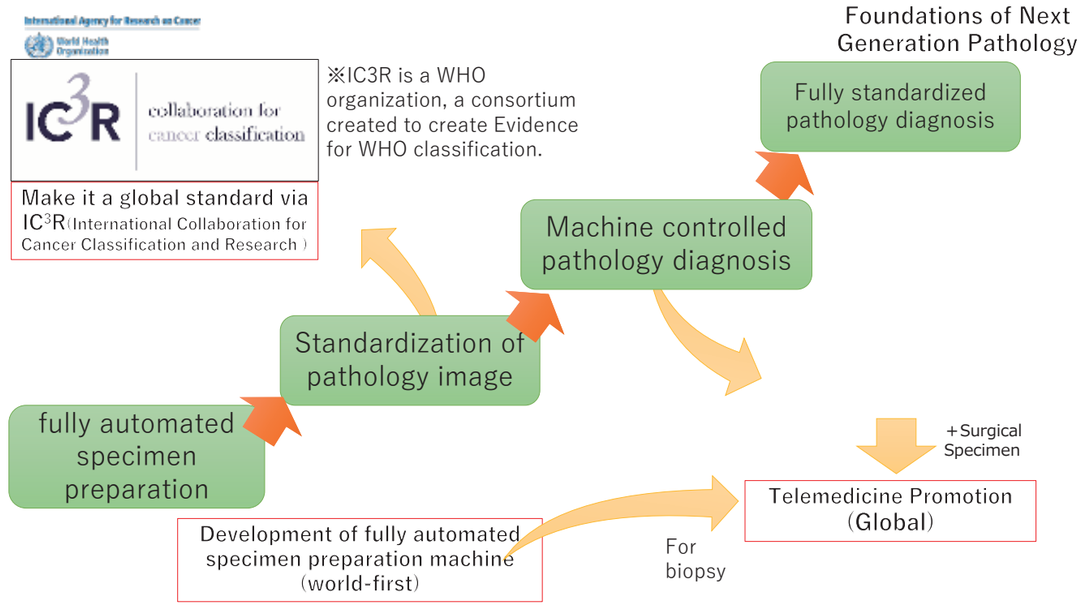
- ◆ Creation of a standardized pathology image database
- ◆ Educational programs to develop human resources for AI technology

Future research prospects

Based on the SOPs created, we plan to verify whether standard images can be created not only at our own institution but also at other institutions. We also aim to disseminate the significance of the established standardization and standardization items to the world through IC3R (The International Collaboration for Cancer Classification and Research). We believe that AI-assisted pathology diagnosis technology worldwide will compensate for the shortage of pathology resources and reduce medical disparities, especially in regions with few pathologies.

Project of fully automatic specimen preparation





Cancer Stem cell research using organoid

Elucidation of the molecular mechanisms by which cancer stem cells acquire resistance to therapy

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- ▶ **Establishment of resistant organoids against anticancer drugs**
- ▶ **Omics analysis using the organoids**
- ▶ **Generation of therapeutic agents targeting cancer stem cells and diagnostic markers of drug resistance**

Research background

Cancer stem cells are thought to survive anticancer therapy and play an important role in the acquisition of therapeutic resistance, but the detailed mechanisms are unknown. Organoids are a three-dimensional culture method for stem cells and other cell populations. This culture method has the advantage that it is easy to obtain results similar to those of cancer cells in drug screening, etc., because it is possible to culture cells while maintaining characteristics similar to the cancer cells in the patients in in-vivo . We aim to establish gastrointestinal cancer organoids that are resistant to anti-cancer drugs and to elucidate the molecular mechanisms by which cancer stem cells acquire resistance to anti-cancer drugs.

Research characteristics

Organoids were established from tumor tissues collected from patients with gastrointestinal cancers (mainly gastric and colorectal cancers). By continuously exposing these organoids to anticancer agents such as 5-FU and platinum, we have established gastrointestinal cancer organoids that are resistant to anticancer agents. These organoid cultures allow us to increase the number of stem cells, which are conventionally scarce, and thus enable omics analysis focused on stem cells. We are currently analyzing gene expression profiles in anti-cancer drug-resistant organoids to identify candidate molecules involved in the acquisition of anti-cancer drug resistance in cancer stem cells.

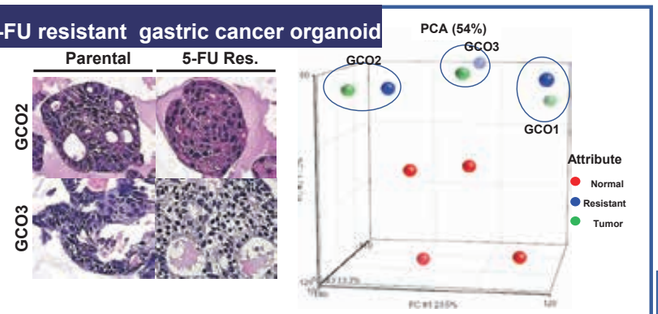
Potential research technical cooperation

- ◆ Technics concerning organoid culture
- ◆ Provision of organoid library with clinical information of patients

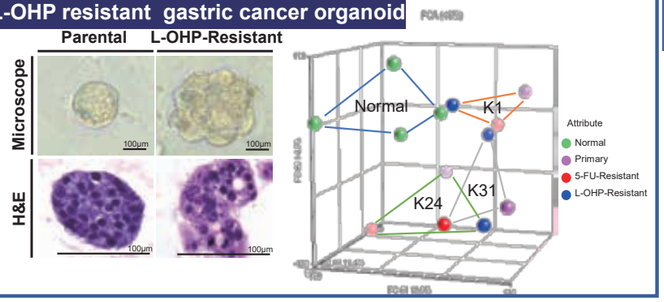
Future research prospects

We believe it is important to define the biological features that distinguish cancer stem cells from normal stem cells. In addition, we would like to explore the molecular mechanisms by which not only cancer stem cells but also their surrounding cancer cells may acquire therapeutic resistance upon stimulation from cancer stem cells. Through this research, we aim to create therapeutic agents targeting cancer stem cells and diagnostic markers of therapeutic resistance.

5-FU resistant gastric cancer organoid



L-OHP resistant gastric cancer organoid



Novel Therapy Targeting Cancer Stem Cells in Gastric Cancer

Novel diagnostic marker for anticancer drug resistance in gastric cancer

Establishment of an assessment system by using TIL-derived T cells

Assessment of the cancer cells and TIL-derived T cells derived from the same tumor

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- ▶ **Improvement of the novel pharmacological assessment system by using the cancer cells and TIL-derived T cells derived from the same tumor**
- ▶ **Discussion on the development of novel technologies to induce PBMC to TIL**
- ▶ **Advanced mass spectrometry method which can identify unidentified molecules**

Research background

Since tumor-infiltrating lymphocytes (TILs) have already received antigen presentation, they are considered to exhibit higher abilities of infiltration to tumors and tumor-specific attack than PBMC-derived lymphocytes. However, PBMC-derived lymphocytes are commonly used in researches and clinical practices, as the application of TIL to researches is limited. Our division is progressing researches, with the aim of developing the pharmacological assessment system using patient-derived cancer cells and TILs and establishing technologies to induce PBMC-derived lymphocyte to TILs. In addition to the combination therapy with bispecific antibody (BsAb), we continuously conduct researches on ADC, radioimmunotherapy, photoimmunotherapy, and novel mass spectrometry.

Research characteristics

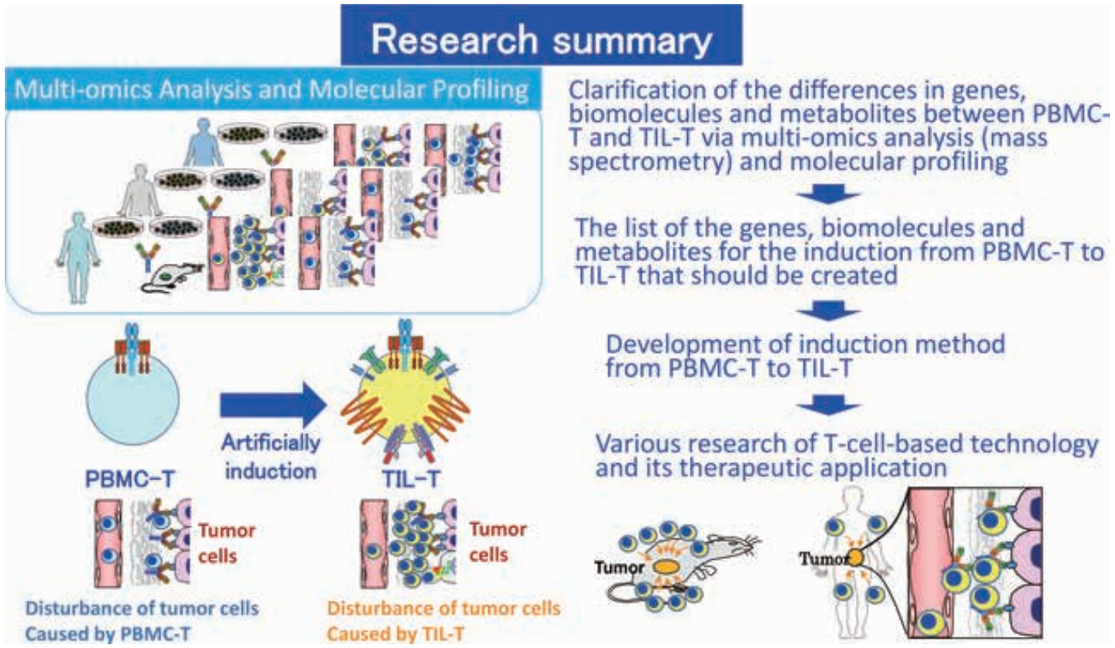
The utilization of the lymphocytes, in addition to cancer cells, is important for the researches on immunotherapy. Our division is improving the experiment system in which cancer cells and TILs can be separated from tumors and cultured and which enables the functional assessment of lymphocytes. Moreover, after the artificial induction of PBMCs to TILs, the T cells that exhibit high abilities of local infiltration and attack can be used as resources for various researches and developed into innovative therapeutics. Moreover, in collaboration with academic institutions, we are establishing a novel mass spectrometry method that can identify previously unidentified molecules.

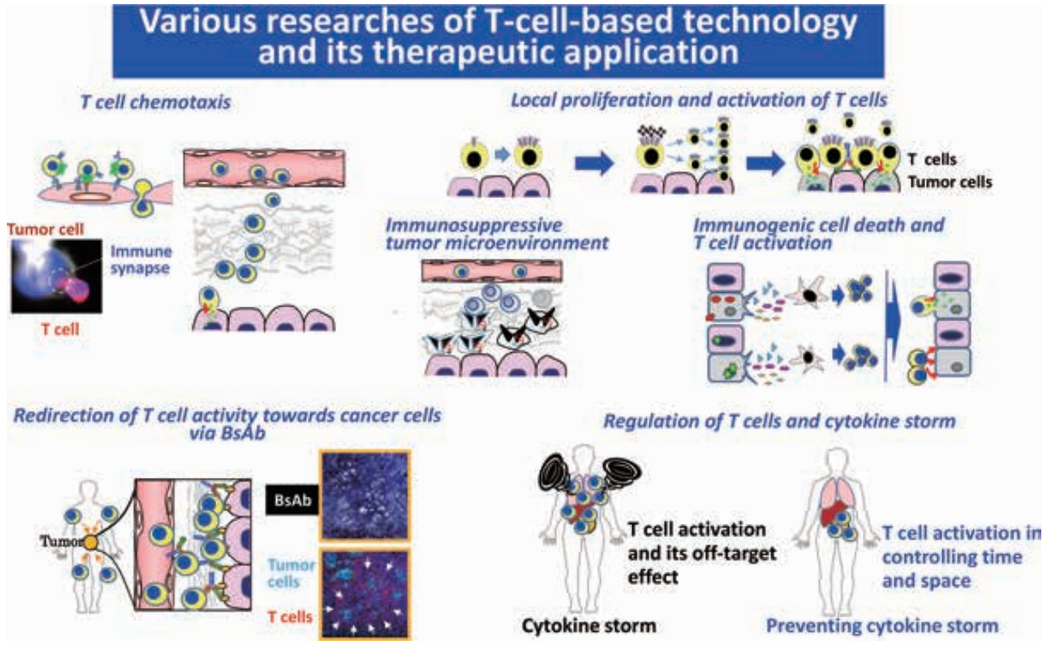
Potential research technical cooperation

- ◆ Pharmacological assessment system for the cancer cells and TILs isolated from tumors
- ◆ Newly established mass spectrometry method
- ◆ Platform technologies for BsAb, ADC, radioimmunotherapy, and photoimmunotherapy

Future research prospects

We have established a lot of platforms for the discovery/improvement/assessment of drug discovery seeds. In the future, we would like to improve/assess drug discovery seeds originating from companies and academic institutions as well as the seeds that we found and then deliver them as pharmaceutical products to patients as fast as we can.





Development of armed antibodies

Development of antibodies labeled with alpha-emitting radionuclides

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- ▶ **Preclinical study of armed antibody such as antibody-drug conjugate and monoclonal antibody labeled with alpha-emitting radionuclides**
- ▶ **Pharmacokinetic evaluation of antibody-based drugs**
- ▶ **Application of novel antibody modification and engineering technologies to armed antibody development**

Research background

Armed antibodies such as antibody-drug conjugate and monoclonal antibody labeled with therapeutic radionuclides accumulate in tumor via antigen-antibody reaction and the enhanced permeability and retention (EPR) effect, and exert a potent antitumor effect.
Alpha radiation is characterized by a high linear energy transfer (LET) that results in efficient cell death via deoxyribonucleic acid (DNA) double-strand breaks and a short range in tissue compared to other types of radiation. Thus, increasing attentions have been paid to cancer treatment with alpha-emitting radionuclides. In order to achieve potent antitumor activities without harmful effects on normal organs, selective accumulation of alpha emitters in tumor is important. We are developing novel antibody-based delivery systems for alpha radiation therapy.

Research characteristics

Antibody modification, linker technology and radionuclide production are essential for development of radioimmunotherapy (RIT), a cancer treatment that utilizes radioactive antibodies. We are developing monoclonal antibodies labeled with alpha-emitting radionuclides through collaboration with organic chemists and nuclear scientists. Using astitatine-211 (211At), an alpha emitter, we demonstrated that 211At-induced radiochemical reaction denatures radioactive antibodies, resulting in disruption of cellular binding and in vivo antitumor activity, whereas sodium ascorbate, a free radical scavenger, successfully prevents antibody denaturation, contributing to the maintenance of binding and antitumor activity. Protection against 211At-induced radiolysis is required in order to achieve successful antitumor activity with 211At-RIT.

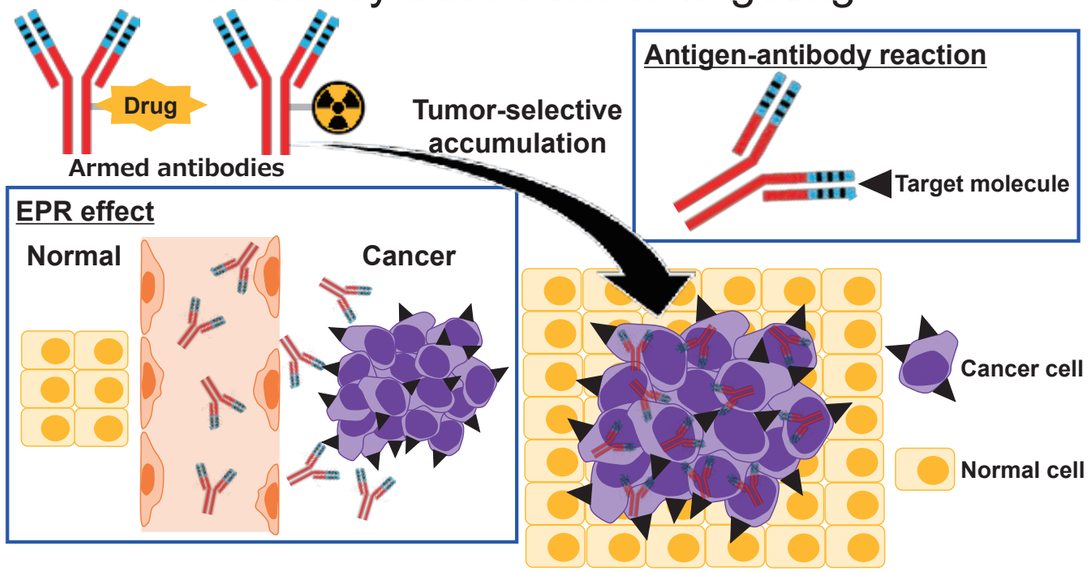
Potential research technical cooperation

- ◆ Antibody modification and labeling
- ◆ Pharmacokinetic evaluation of radioactive antibody

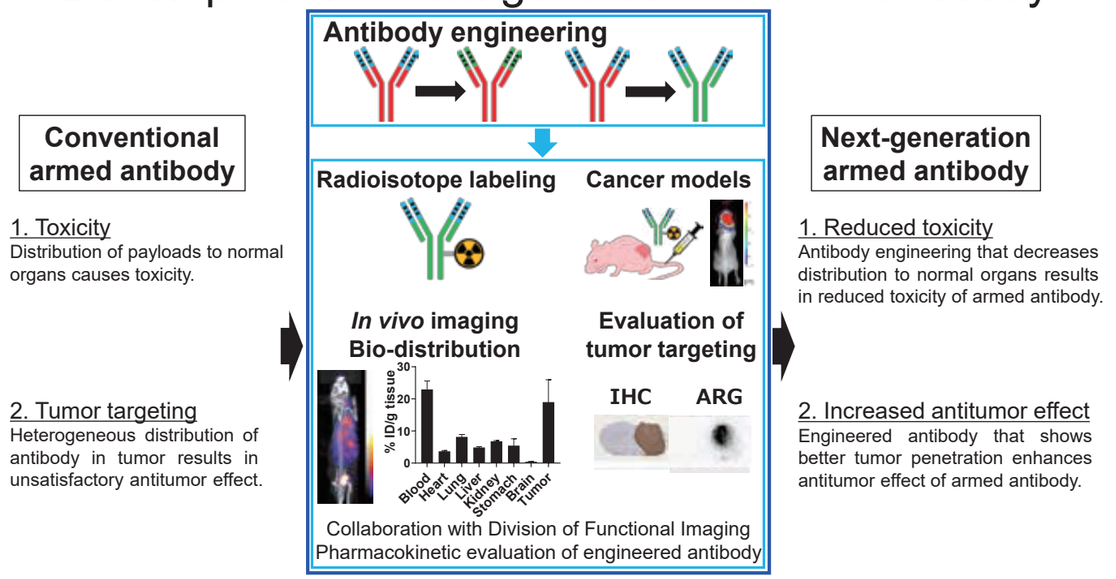
Future research prospects

In addition to 211At, we are interested in development of RIT that utilizes other alpha emitters.
Using antibody engineering and modification technologies, we will prepare radioactive antibodies that exert greater antitumor affects and less toxicity than our prototype.

Antibody-based tumor targeting



Development of next-generation armed antibody



T Cell Therapy Targeting Unique Cancer Antigens

GPC3-, HSP105-, and neoantigen-targeted T cell therapy

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- ▶ GPC3-targeted TCR-T/CAR-T cell therapy and HSP105-targeted TCR-T cell therapy
- ▶ Personalized T cell therapy by restored tumor-reactive, tumor-infiltrating lymphocytes
- ▶ Use of blood for the risk diagnosis of cancer development and cancer prophylaxis by vaccination

Research background

Many genetic mutations are accumulated in cancer cells, thus leading to the emergence of cancer antigens indicative of cancer cells. Cancer antigens are usually not present in the body and are recognized as foreign by lymphocytes (particularly CD8+ T cells). Once the cancer antigens are recognized as foreign, they are attacked by CD8+ T cells and are eliminated from the body. We identified GPC3 and HSP105, which are known as cancer antigens, and are conducting research for a wide range of clinical applications, including cancer prevention and treatment. A clinical study of GPC3 peptide vaccines has produced outstanding results (i.e., postoperative recurrence was not observed and reoperation was not needed in children suffered from multiple times relapses of intractable cancers).

Research characteristics

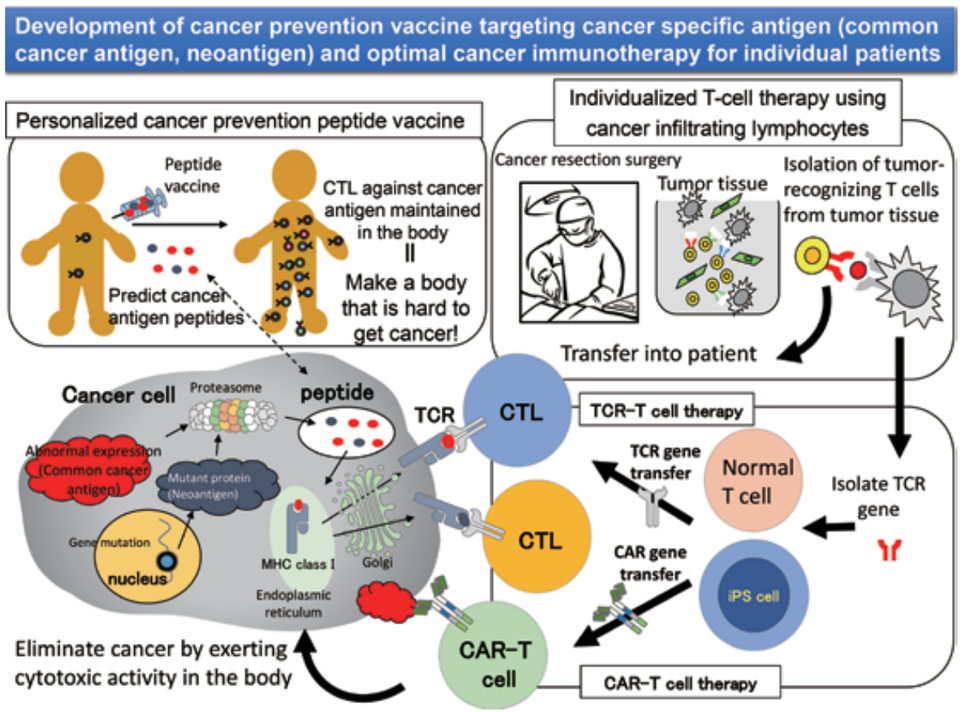
The Division of Cancer Immunotherapy explores the application of unique cancer antigens for prevention and treatment. When GPC3 peptide vaccines were administered to five children with refractory hepatoblastoma who had multiple episodes of relapse and surgery, the cancer did not recur within 6 years, and no treatment was needed. A deficiency (impaired function) of tumor-infiltrating lymphocytes (TILs) has been reported to reduce the efficacy of anti-PD-1 antibodies and cell-based therapy. We are undertaking a “TIL rejuvenation study” to cure the deficiency of tumor-reactive, tumor-infiltrating lymphocytes by aiming at the realization of TIL therapy in which the restored TILs are returned to the body. Furthermore, we are also studying the practical applications of genetically modified T cell therapy, such as GPC3-targeted CAR-T and HSP105-targeted TCR-T, for patients who fail to respond to the TIL therapy.

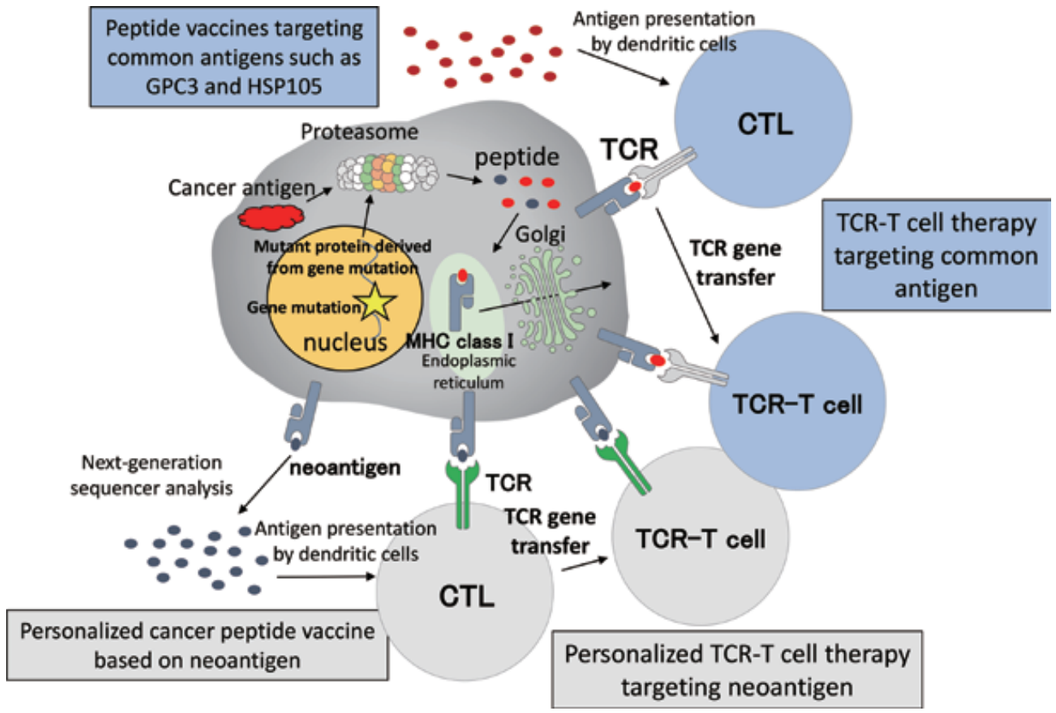
Potential research technical cooperation

- ◆ GPC3 and HSP105 peptide vaccines and TCR-T/CAR-T cell therapy
- ◆ Personalized T cell therapy for clinical application
- ◆ Use of blood for the risk diagnosis of cancer development and cancer prevention by vaccination

Future research prospects

We aim to achieve the practical use of TCR-T/CAR-T cell therapy by targeting unique cancer antigens, such as GPC3 and HSP105, and by using personalized tumor-reactive TIL/TCR-T cell therapy. We are also committed to the development of blood-based diagnostic methods for cancer development risk and vaccines for cancer prevention.





Development of immune cell medication for cancer treatment

Establishment of an off-the-shelf-type immune cell platform

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- ▶ Development of universal-type effector cell therapy
- ▶ Establishment of an antigen-presenting cell platform for cancer vaccines
- ▶ Development of cellular medication controlling cancer immune environment

Research background

Recently, immune cell therapy, which eliminates cancer through the administration of genetically engineered immune cells, exhibits excellent therapeutic effects. However, since the current cancer immune therapy uses the autologous cells obtained through blood sampling, there are problems that the therapeutic effects differ between patients, and that the cells cannot be used for treatment when their number is small. Therefore, we are working for the development of effector cells independent of blood sampling, of methods to induce effector cells and myeloid cells from induced pluripotent stem cells (iPSCs), and of technologies to ensure that there are sufficient cells for treatment and to produce uniform cells, as well as for the improvement of the therapeutic effects by using them.

Research characteristics

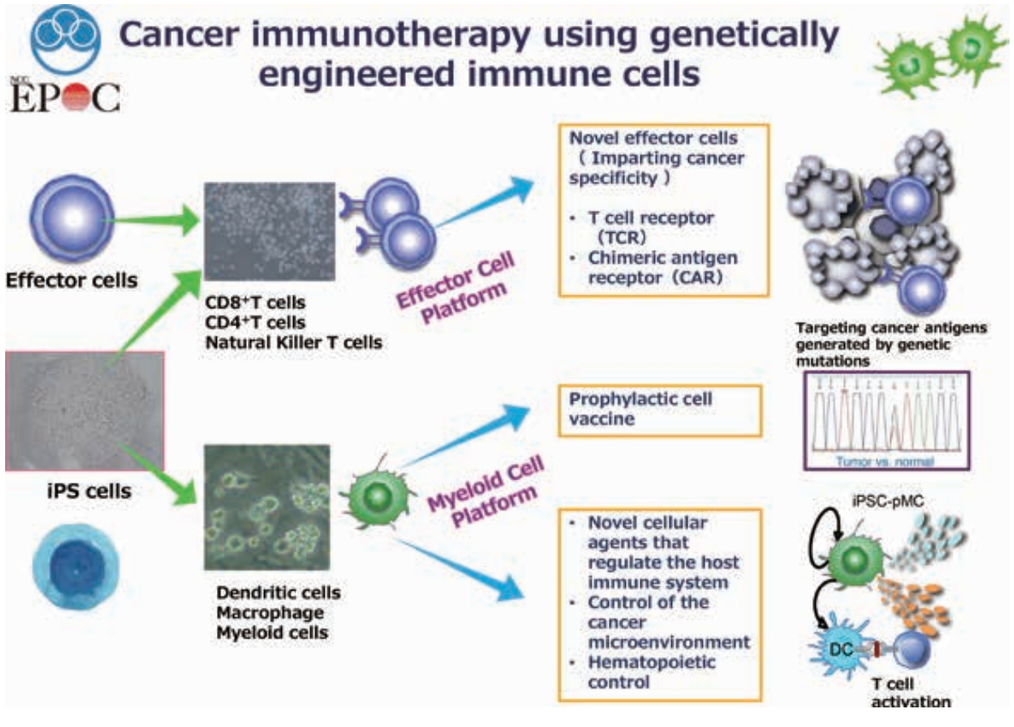
To provide off-the-shelf-type immune cell medication, we are working for the development of universal-type effector cells. Meanwhile, we also develop technologies for the efficient activation of cancer-reactive T cells by adding cancer antigen peptides to iPSC-derived antigen-presenting cells. Recently, we elucidated that inoculation of genetically engineered iPSC-derived myeloid cells to some of mouse cancer tissues could change cancer microenvironment and induce the systemic elimination of cancer by the cancer-reactive T cell response. This system is excellent with immune checkpoint inhibitors and exhibits synergistic effects with them.

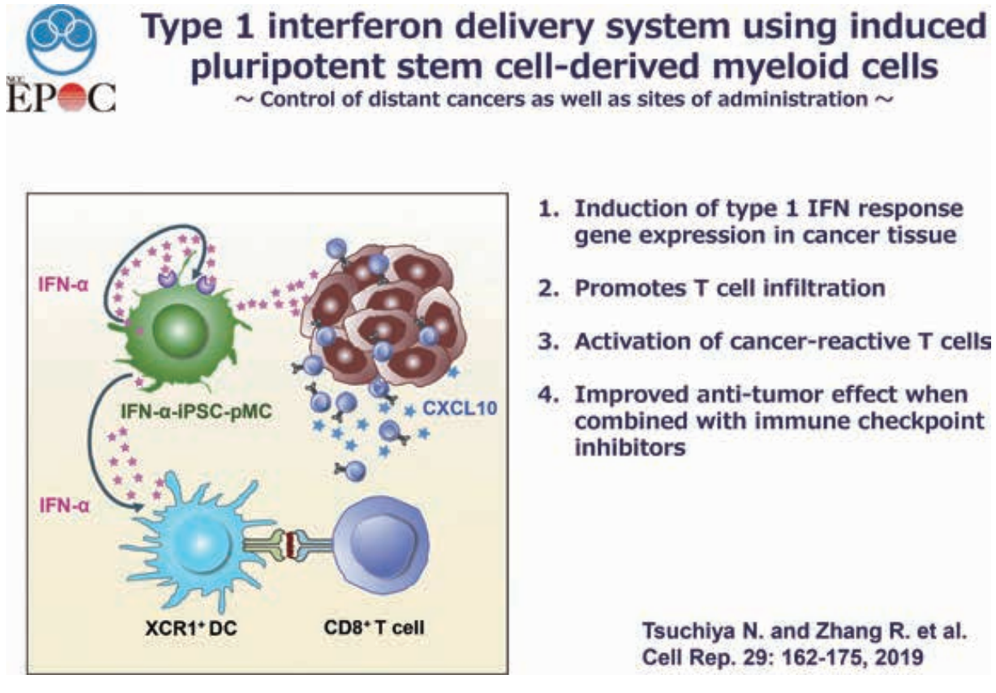
Potential research technical cooperation

- ◆ Technologies for establishing the universal-type effector cells in which cancer antigen receptors will be introduced
- ◆ Cellular vaccine technologies for cancer treatment based on iPSC-derived myeloid cells
- ◆ Provision of the iPSC-derived myeloid cells which induce T cell infiltration in cancer tissues

Future research prospects

Our research outcomes suggest the potential that the utilization of universal-type effector cells and/or iPSCs eliminates the need for blood sampling from cancer patients, realizes mass production, and leads to the production of cellular drugs exhibiting stable effects. In addition to elucidating their effects with the use of mouse models, we will establish the cellular products which can be administered to humans and aim for their practical use.





Provision of Elderly Oriented Care

Training programs for providing appropriate medical care to the elderly

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- ▶ **Training programs for educating staff on delirium and spreading the knowledge of delirium**
- ▶ **Provision of cancer treatment support programs for dementia patients**
- ▶ **Pathophysiological studies on chemobrain**

Research background

Psycho-oncology is a composite discipline that seeks to clarify the anthropological side of cancer by applying knowledge in fields such as psychiatry, oncology, psychology, sociology, and ethics. As a society ages, the number of dementia patients undergoing cancer treatment increases. The development of delirium (cognitive impairment) during cancer treatment may also increase the risk of falling and interfere with daily activities after discharge. The Division of Psycho-Oncology is attempting to develop a system that can be implemented effectively at medical institutions in Japan for ensuring that elderly patients safely receive treatment and have a high quality of life during the treatment period.

Research characteristics

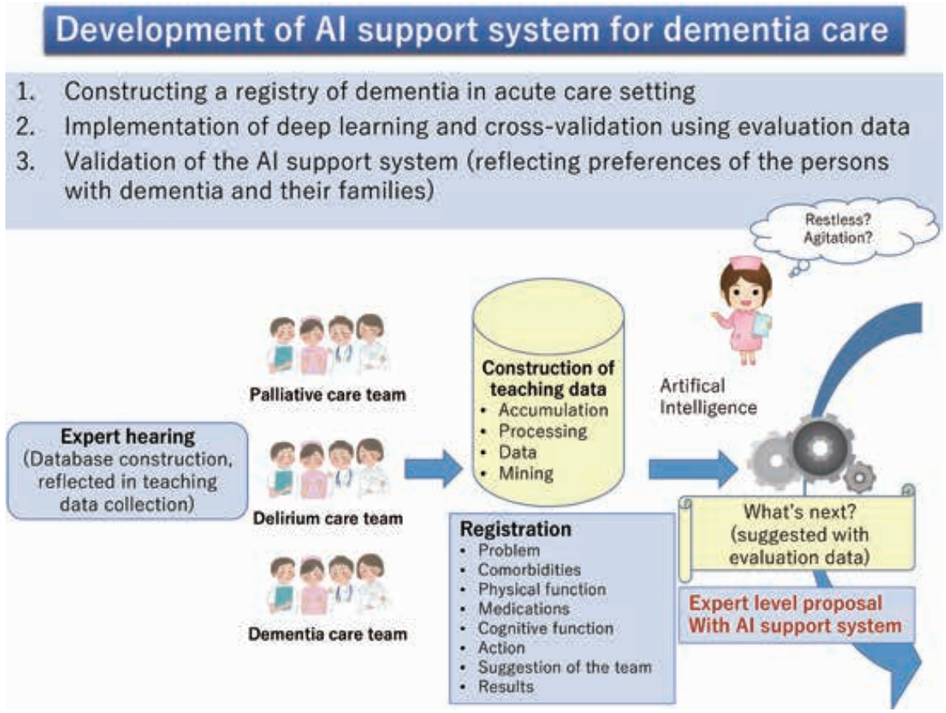
As the only research division in Japan specializing in mental support for cancer patients, the Division of Psycho- Oncology work in coordination with the Department of Psycho-Oncology at the Hospital East on initiatives for the development and provision of optimal support methods for patients, parents, bereaved family members, and medical staff. We have developed training programs to support healthcare professionals who respond to delirium. We have also created programs for supporting healthcare professionals to ensure that dementia patients can receive cancer treatment in a proper and smooth manner. We are conducting a study to reveal the pathophysiology of delirium and chemobrain (a temporary decrease in cognitive function, such as memory and concentration, during and after anticancer treatment).

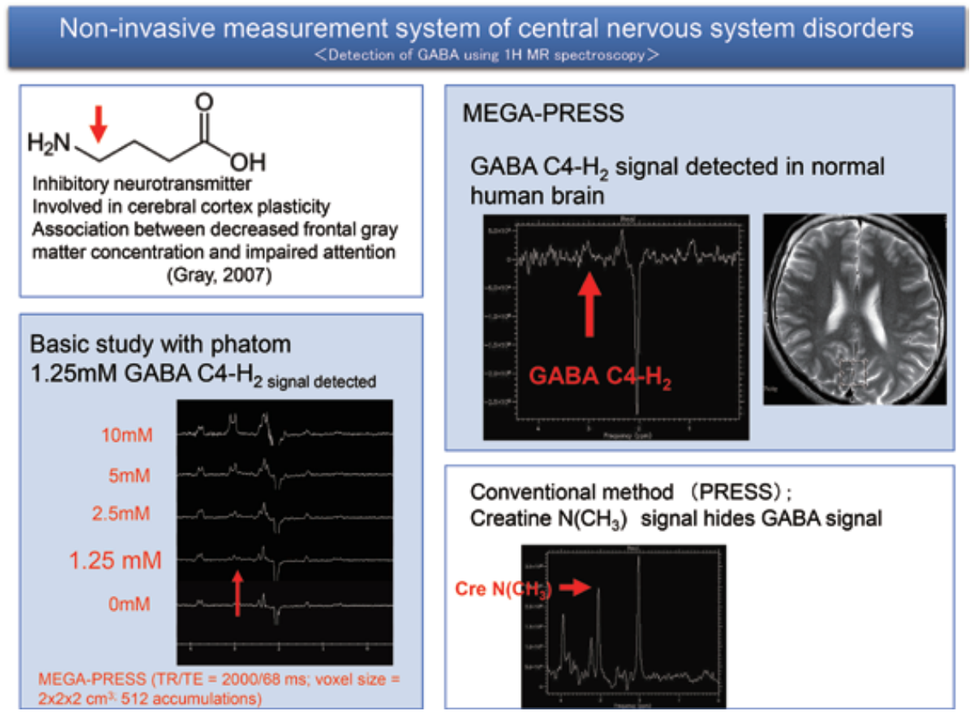
Potential research technical cooperation

- ◆ Delirium education and training programs
- ◆ Cancer treatment support programs for dementia patients
- ◆ Pathophysiological findings of chemobrain

Future research prospects

Given that studies on the pathophysiology of delirium are lacking, we want to clarify the mechanisms of delirium and develop an automatic sensor system for delirium induced by cancer treatment. Once chemobrain develops, patients will suffer from poor concentration and severe forgetfulness, which will greatly affect their social life in the workplace or at home. We will make an effort to develop therapeutic agents for chemobrain and encourage cancer patients to return to society early.





Clinical Application of Alpha Ray-Emitting Radionuclide therapy

Establishment of alpha ray-emitting radionuclides therapy system for TR studies and clinical trials

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- ▶ **Non-clinical studies utilizing advanced facilities for alpha ray-emitting radionuclides**
- ▶ **TR studies with alpha ray-emitting radionuclides including the evaluation using human cancer tissues**
- ▶ **Development of imaging techniques for theranostics**

Research background

Early cancer detection and the development of effective cancer treatment have improved the prognosis of cancer patients; however, no good treatment has been established for patients with some intractable cancers. The Division of Functional Imaging is developing various diagnostic imaging techniques (e.g., nuclear medicine tests, magnetic resonance imaging [MRI] tests, optical imaging tests) for the visualization of intractable cancer lesions and their characteristics to improve the prognosis of patients suffering from intractable cancers. Furthermore, we have applied these diagnostic techniques to novel treatment methods for intractable cancers (theranostics).

Research characteristics

The Division of Functional Imaging has established a technology for detecting microscopic pancreatic cancer in mice by using high-affinity RGD peptides combined with radionuclides. We are trying to put this technology to practical use as a diagnostic agent for pancreatic cancer to improve the prognosis of patients with pancreatic cancer. Furthermore, we have recently built research facilities where alpha ray-emitting radionuclides can be used in the Kashiwa Campus, thus enabling us to conduct TR for nuclear medicine therapy. We have newly built facilities for the GMP-compliant synthesis of investigative drugs and plan to conduct a new clinical trial including alpha ray- emitting radionuclides. We are also working on the development of unique theranostics based on the combined use of novel diagnostic imaging techniques (including 3D optical imaging using near-infrared lights with longer wavelength than 1,000 nm).

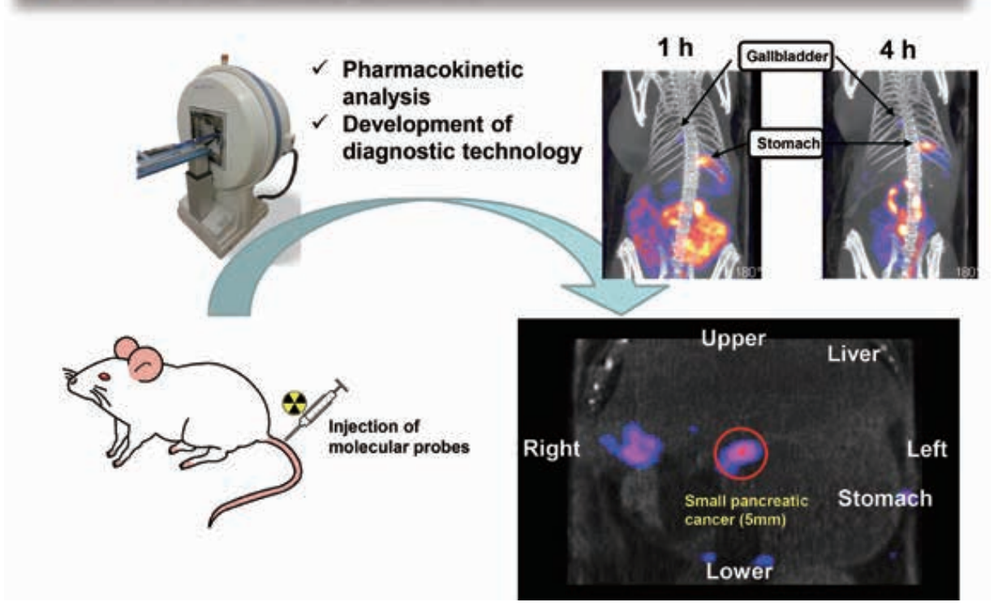
Potential research technical cooperation

- ◆ Provision of nonclinical research facilities where radionuclides can be used.
- ◆ TR utilizing radionuclides
- ◆ Development of theranostics using tomographic imaging of near-infrared lights with long wavelengths

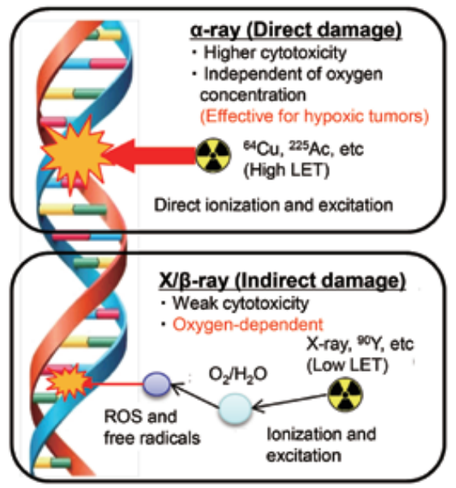
Future research prospects

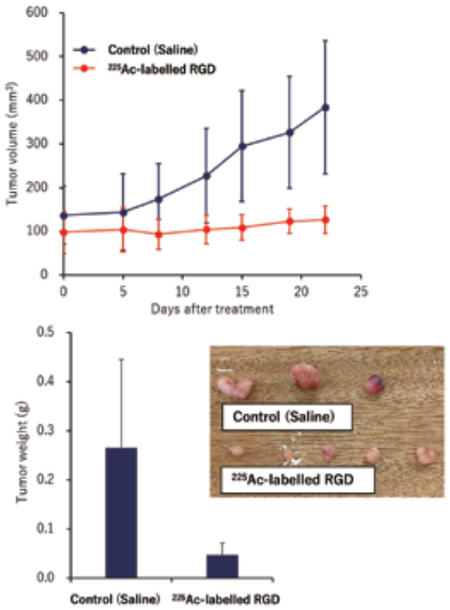
In Japan, there are small number of facilities where non-clinical studies and clinical trials using radionuclides can be seamlessly performed. The Division of Functional Imaging is well collaborating with the Hospital East to conduct TR studies using human cancer tissues and perform drug development researches. We are also actively engaged in the research and development of theranostics, which is a combination of diagnosis and treatment, for its clinical application.

Development of radio-theranostics using high-resolution SPECT/CT for small animals



TR research using high-energy alpha radionuclides





High-field MRI to strongly support drug discovery researches

Selection of development candidates via high-throughput MRI examination for multiple animals

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- **Simultaneous MR imaging for multiple mice can quickly acquire information on changes in interior as well as sizes in orthotopic tumor models before and after administration of drugs**
- **Changes in low molecular weight metabolites can also be measured non-destructively using in vivo MRS technique**
- **Newly developed SPIO-enhanced MR imaging can monitor irradiated areas during radiation therapy**

Research background

Various imaging technologies, including IVIS and MRI, are available in cancer drug discovery researches in order to longitudinally monitor the size of the lesions in cancer animal models. Simultaneous MR imaging for multiple mice can promote the application of MRI in the field of cancer drug discovery because it accelerates MR examination time per animal which typically had been 1 h using a conventional scanner. In particular, our division can measure the morphological as well as metabolic changes in small cancer lesions and organs in mice using a dedicated 9.4-tesla MRI scanner. Moreover, we established a method for detecting irradiated areas by utilizing the properties of superparamagnetic iron oxide (SPIO) contrast agent.

Research characteristics

We have improved throughput of MRI examination for tumor-bearing animals approximately fourfold utilizing the combination of a high-field MRI scanner and high-sensitivity detector dedicated for multiple animal imaging. By using a 9.4-tesla horizontal MRI scanner that has currently the second-highest magnetic field in Japan, we longitudinally evaluated the size of orthotopic brain tumors in mice before and after the administration of IDH1 inhibitor. Moreover, our MR spectroscopy (MRS) technique enabled to monitor oncometabolites, like 2-hydroxyglutarate, during IDH1 inhibitor therapy. By utilizing the delay of SPIO contrast agent excretion from the irradiated liver tissues, we established a method for assessing the extent of irradiated liver areas during radiation therapy, which may assist radiation oncologists to predict the severity of radiation-induced liver injury.

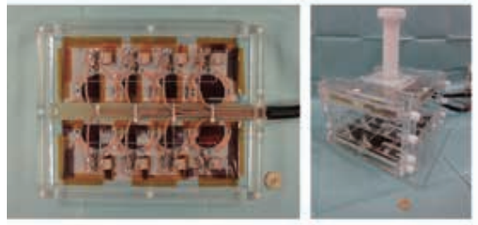
Potential research technical cooperation

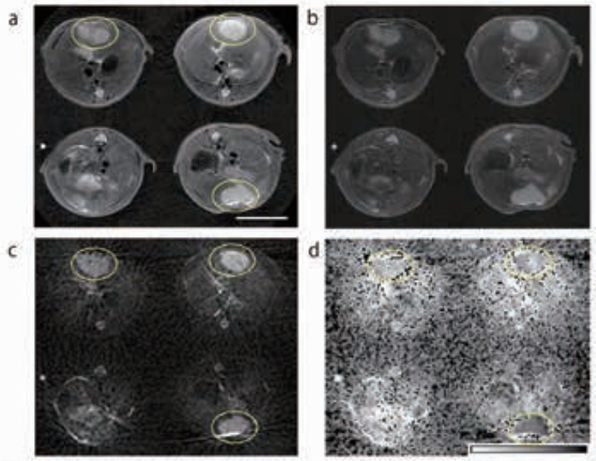
- ◆ High-throughput preclinical MR imaging for a large number of animal cohort.
- ◆ MRS for non-invasive measurements of metabolites in cancer and non-cancer tissues
- ◆ Methods to assess radiation exposure areas by using SPIO-enhanced MR imaging

Future research prospects

Unlike bioluminescence imaging, MR imaging does not require genetically modified cells to monitor tumor growth, so that it can be well suited to observe orthotopically transplanted tumors in PDX models. More importantly, our multiple animal MR imaging technique could strongly assist drug development research using such PDX models, providing efficient imaging tests that can be utilized for narrowing down of development candidates and the selection of the cancer types to be included in the indications.

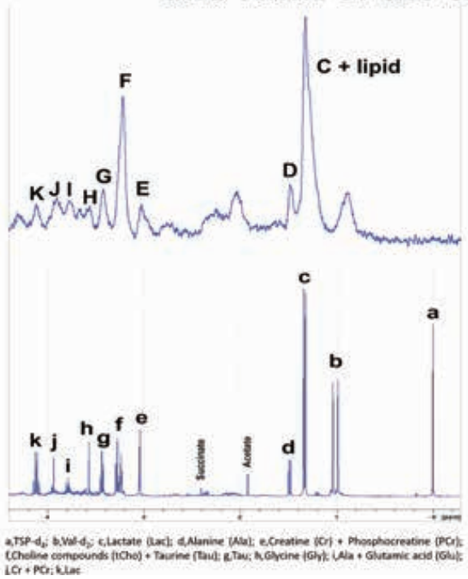
Multiple animal MRI for four orthotopic hepatoma-bearing rats



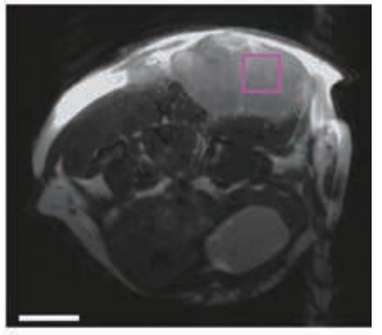


Four hepatoma-bearing rats are anesthetized and the two are placed in the upper row and the other two in the lower row. By using a special pulse sequence, signal-to-noise ratio is improved and motion artifacts are effectively reduced (a). For comparison, a representative image acquired by using a conventional pulse sequence is shown (b). The special pulse sequence allows to acquire a diffusion-weighted MR image (c) and apparent diffusion co-efficient map (d). For further information, please refer the paper written by Yamaguchi, et al. in JMRI 2013;38:225–230

In vivo MRS of the small cancer lesion in a mouse and NMR of the tumor extract



a,TSP-d_4; b,Val-d_8; c,Lactate (Lac); d,Alanine (Ala); e,Creatine (Cr) + Phosphocreatine (PCr); f,Choline compounds (tCho) + Taurine (Tau); g,Tau; h,Glycine (Gly); i,Ala + Glutamic acid (Glu); j,Cr + PCr; k,Lac



Low molecular weight metabolites which represent metabolic activity in cancer cells, including lactate, creatine phosphate, and so forth, can be quantitatively and non-destructively measured within 10 minutes. These data were presented in the 2012 Annual Meeting of Japanese Society for Magnetic Resonance in Medicine.

Maximization of the value of radiotherapy

Development of the drugs which improve the immune responses provoked by radiotherapy

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- ▶ **Experimental system to assess the cellular responses induced by radiation**
- ▶ **Development and their clinical introduction of new treatments, including intensity-modulated proton beam therapy**
- ▶ **Conduction of multicenter clinical trials of proton beam therapy**

Research background

Proton beam therapy is one of the forms of radiotherapy that enable us to deliver higher dose to tumor while keeping dose to risk organ within acceptable level. In Japan, localized prostate cancer, pediatric cancer, bone and soft tissue sarcoma, and some of head and neck cancers (non-squamous cell carcinoma except for pharynx cancer) have been covered by the National Health Insurance. Seventeen proton beam therapy facilities are now operating as of July 2020. With regard to clinical aspects, our division verifies the clinical effectiveness of proton beam therapy through multicenter clinical trials, develops novel technologies including intensity-modulated proton beam therapy (IMPT), and implements their clinical introduction. In addition, we progress the basic researches on the radiation-induced immune responses of cancer cells and translational researches (TR), including the significance of liquid biopsy, by using clinical specimens.

Research characteristics

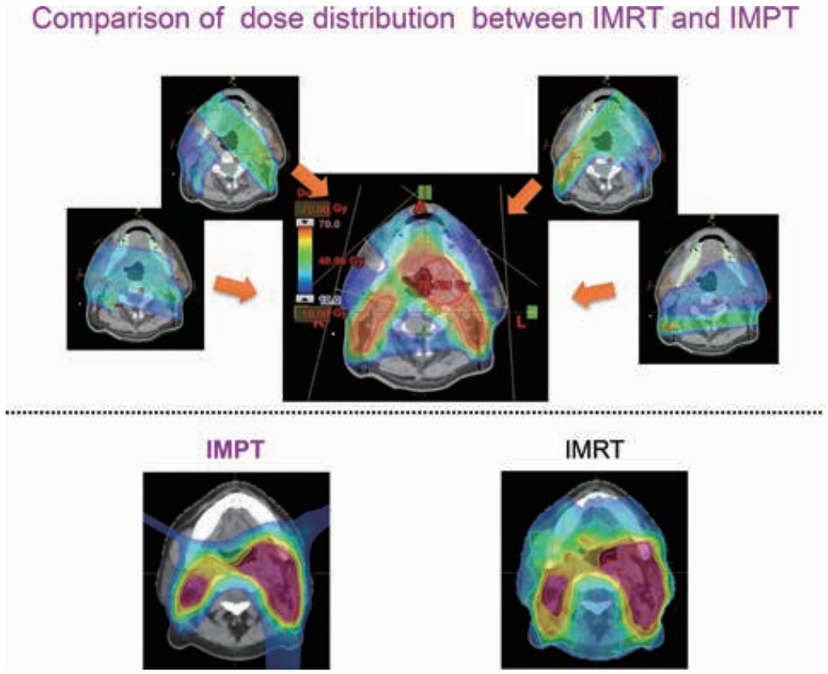
Regarding proton beam therapy machines clinically used, treatment machines with various specs are used clinically. For a safe and accurate conduction of multicenter clinical researches, our center plays a key role in the medico-physical standardization and development of the method of quality control and assurance of proton beam therapy. Based on this, we are now planning to conduct multi-center clinical trial under Advanced Medical Care System B to prove the effectiveness of IMPT, a constructive technology for the scanning method. We also started preparing the guideline on the intensity-modulated particle therapy, including IMPT. Moreover, to maximize the effects of the combined use of radiotherapy and immunotherapy, we establish a cell assessment system and conduct screening of the drugs which modify the immune responses of cancer cells to radiation.

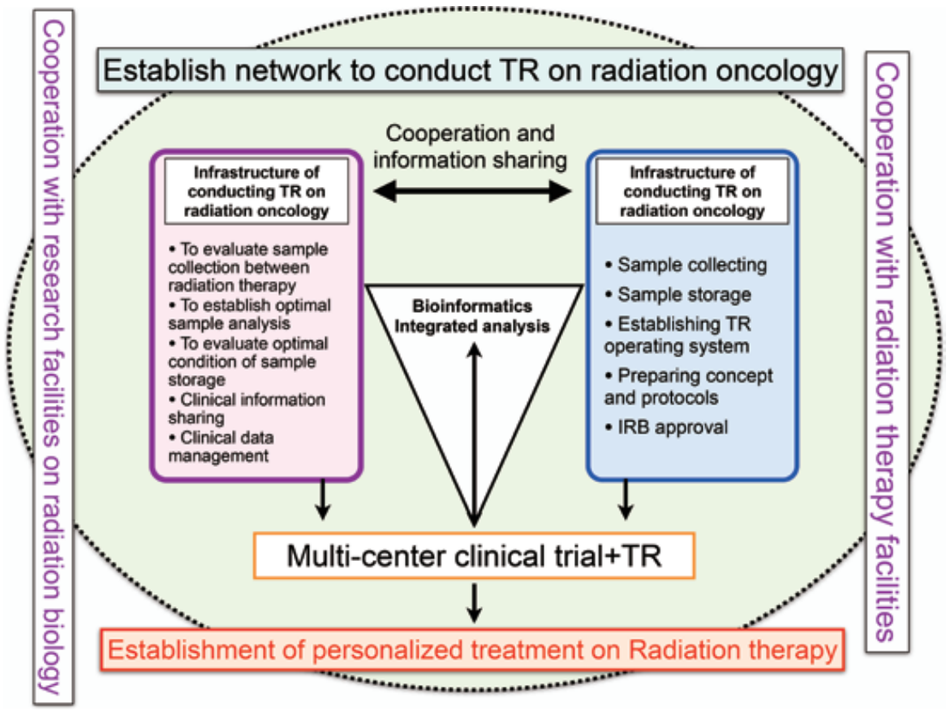
Potential research technical cooperation

◆ Clinical and medico-physical methods to assess high-precision radiotherapy technologies, including IMPT
◆ Techniques to analyze the radiation responses of cancer cells

Future research prospects

In addition to developing the biomarkers which can predict the response of radiotherapies, including particle beam radiotherapy, and maintaining the centers of excellence which promote radiotherapy-related TRs, we are developing novel therapeutic drugs utilizing the self-developed system to assess the cellular responses associated with exposure to radiation. In addition, we are introducing AI to the image-guided technologies at treatment planning and before, during, and after treatment, with the aim of developing a more accurate radiotherapy.





Toward promotion and development of BNCT

To expand indications of BNCT with a small accelerator-based system installed in the hospital

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- ▶ Development and promotion of hospital-based BNCT
- ▶ Promotion of clinical trials of BNCT
- ▶ Development of new boron agents

Research background

Boron Neutron Capture Therapy (BNCT) is a cancer treatment modality that selectively kills cancer cells using alpha particles and Li nuclei generated by the nuclear reaction of boron (10B) and thermal neutron. The boron compound is specifically incorporated into cancer cells. The α particle and Li nucleus generated within the cancer cells reaction have a range of about the diameter of a single cell, so they can efficiently cut the DNA of cancer cells and kill them with minimal adverse effect on the normal cells surrounding the tumor. In order to promote and develop BNCT, our division is engaged in basic and clinical research on BNCT in cooperation with related departments.

Research characteristics

BNCT implementation requires the uptake of boron compounds into cancer cells and an environment of external neutron irradiation, such as an accelerator or nuclear reactor. To predict the amount of boron uptake into cancer cells in advance, we have developed and improved the 18FBPA PET examination method. We have also made efforts to jointly develop a small accelerator that can be installed in hospitals, and are currently conducting a single-center clinical trial of BNCT for malignant melanoma and angiosarcoma in collaboration with the Departments of Radiation Oncology and Radiological Technology, and Radiation Safety and Quality Assurance Division at National Cancer Center Hospital. We are also working with academic societies to propose international standards for neutron irradiation equipment for BNCT and standard methods for measuring neutrons.

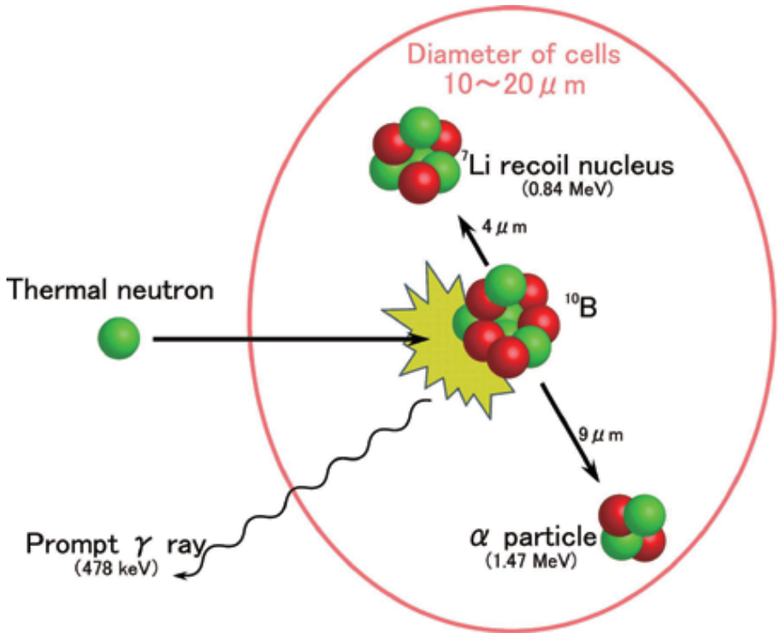
Potential research technical cooperation

- ◆ The use of neutron irradiation system of hospital-based accelerator
- ◆ 18FBPA PET examinations
- ◆ Development of new boron agents

Future research prospects

The indication for BNCT is defined by the uptake of boron agents in tumors. We intend to develop new boron agents to replace the existing BSH (borocaptate) and BPA (p-boronophenylalanine; borofalan) and expand the range of treatment indications for BNCT. We are currently conducting a single-center clinical trial, and following the regulatory approval of the neutron irradiation system for BNCT and the expansion of the indications for boron agents, we are moving forward with research and development intending to conduct multicenter clinical trials.

The principle of BNCT



Neutron irradiation system for BNCT installed at the National Cancer Center Hospital

Seeds cultivation by endoscopists

Bridging from the cultivation of academia-derived seeds to pharmaceutical approval

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- ▶ **Development of an endoscopic device using near-infrared light hyperspectral imaging**
- ▶ **Development of a photoacoustic imaging endoscopy which visualizes the deep blood vessels**
- ▶ **Pharmaceutical approval of an imaging device which visualizes oxygen saturation**

Research background

Our division creates an interdisciplinary collaboration framework with companies and technological universities. Moreover, we proactively cultivate the seeds of external origin, as well as those of the National Cancer Center internal origin, based on findings as endoscopists. We have been collaborating with the Tokyo University of Science on the Superhuman Medical Care Project since fiscal year 2018 and jointly working for the development of endoscopic diagnosis devices using near-infrared light; with regard to the National Defense Medical College, we are jointly working with them for the development of photoacoustic imaging endoscopies, with the aim of visualizing the intramural deep blood vessels. Moreover, we will carry over the seeds cultivated in our division to the Department of Endoscopy of the National Cancer Center Hospital East and jointly conduct clinical trials with them, aiming for pharmaceutical approval.

Research characteristics

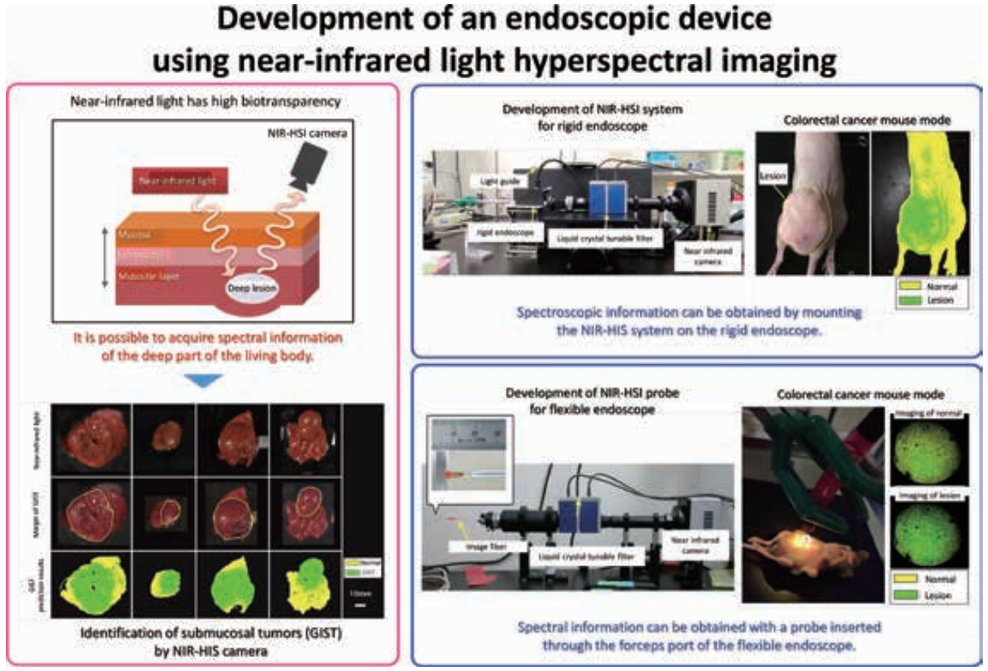
Our division conducts researches on near-infrared light hyperspectral imaging (NIR-HSI) by combining near-infrared lights, which reach the deep parts of the body (around a few centimeters), and hyperspectral imaging cameras, which exhibit a high spectroscopic capability. As a result of machine learning of the NIR-HSI-obtained images of gastrointestinal stromal tumor (GIST), the prediction of the range of GIST was realized. Moreover, we confirmed that the deep blood vessels in the specimens after gastrointestinal surgeries can be depicted by using a photoacoustic imaging device. Moreover, in 2017, we obtained pharmaceutical approval for an imaging device which visualizes oxygen saturation, focusing on the hypoxic condition of the inside of the tumors.

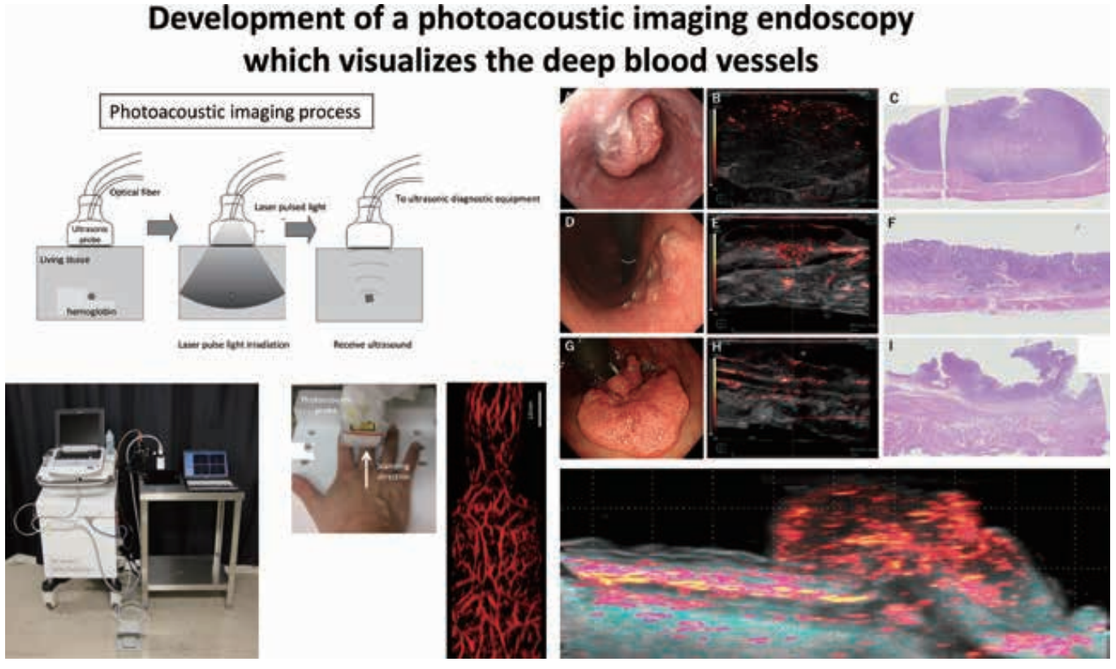
Potential research technical cooperation

- ◆ NIR-HSI technologies
- ◆ Photoacoustic imaging device
- ◆ Oxygen saturation endoscopic device

Future research prospects

The greatest advantage of gastrointestinal endoscopy is the prevention of death caused by gastrointestinal tumors through early detection, proper diagnosis, and early treatment. We will continuously aim for the reduction of the number of deaths caused by gastrointestinal cancers through the development of novel diagnostic and therapeutic devices.





Creation of new endoscopy-related technologies

Frontier toward possibilities for endoscopic diagnostic and therapeutic procedures

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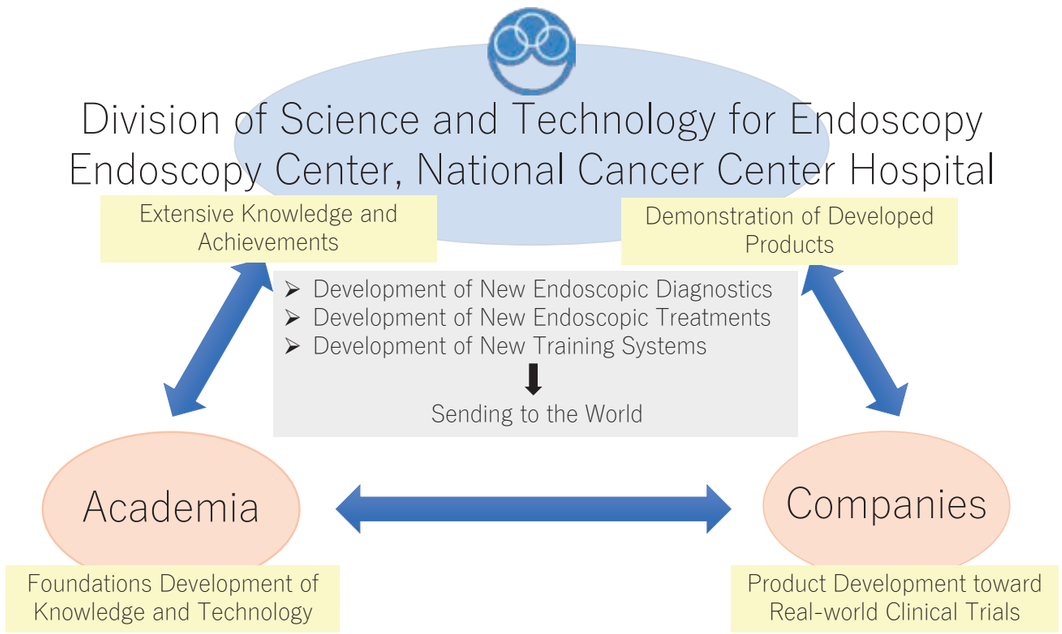
- ▶ **Development of endoscopic diagnostic and therapeutic equipment and training systems**
- ▶ **Development of diagnostic and therapeutic procedures using endoscopic ultrasound**
- ▶ **Development of next stage diagnostic and therapeutic techniques using endoscopes**

Research background

Endoscopy is used to enter human body to "detect" and "diagnose" lesions and disorders and to "treat" those. However, in diagnosis, there are limitations in the ability to detect lesions and in the accuracy of diagnosis. In treatment, there are still issues such as the existence of difficult-to-treat lesions, treatment-related complications, and the limited number of medical specialists. To conquer those issues, our department is working to develop innovative endoscopic diagnostic and therapeutic devices and training systems, as well as new diagnostic and therapeutic approaches using ultrasound echo-endoscopes from the gastrointestinal tract to the extraintestinal tract, a characteristic not found in intraluminal endoscopy in collaboration with companies and academia.



Research characteristics

In this field, we are working on research and development by identifying medical needs related to endoscopy.
One of our ongoing projects is the research and development of innovative endoscopic diagnostic and treatment devices and training systems, prioritizing needs and feasibility in collaboration with optical device manufacturers in the National Cancer Center Research Institute's Partners Laboratory.
In addition to gastrointestinal endoscopy, we are also seeking to apply the knowledge gained from the development to other fields (respiratory endoscopy, surgery, gynecology, etc.).

Potential research technical cooperation

- ◆ Development of endoscopic instruments that meet the daily medical needs of clinicians
- ◆ Development of endoscopic devices based on abundant high-quality clinical data
- ◆ Development of new treatment utilizing the delivery device using endoscopy

Future research prospects

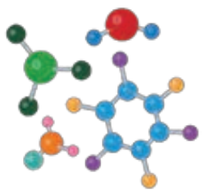
We also aim to develop endoscopy-related devices and drugs from new approaches. For example, we hope to combine new technologies such as molecular imaging and functional imaging for early detection of lesions. We also hope to develop drugs that can be injected directly into lesions that are difficult to resect by endoscopy. For this purpose, we would like to strongly collaborate with companies and academia.

Short-term Perspective

✓ Improvement of endoscopy and endoscopy-related equipment
- Improve image quality, insertability and operability
- Improvement and development of devices

✓ Development of training and support systems
- Development of training software for diagnosis and treatment
- Development of AI-based diagnostic support systems

Long-term Perspective



✓ Development of new endoscopic diagnostics leading to therapeutic strategies
- Molecular Imaging
- Diagnosis of depth, metastatic risk, and drug sensitivity

✓ Development of new endoscopic procedures
- Full-thickness resection, complete closure and suture, etc.

✓ Expanding into other fields
- Application to respiratory endoscopy
- Application to rigid specula such as surgical, urological, and gynecological fields

Equalization and efficiency improvement of surgical treatments in Japan

Reduction of the gaps between sites and operators by information-powered surgery

Masaaki Ito, MD, PhD
Division of Surgical Technology Chief

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- ▶ **Development of the surgical support system equipped with the expert's brain with the aim of streamlining surgical tasks**
- ▶ **Establishment of high-quality surgical video database for industrial use**
- ▶ **Development of the medical devices and implementation for clinical needs**

Research background

From the viewpoint of patient QOL improvement, the number of endoscopic surgeries is increasing annually. Meanwhile, due to the shortage of surgeons in Japan and the requirement of advanced surgical facility and highly skilled operators in endoscopic surgeries, the gaps of surgical performance between the sites and operators have become emerging problems. With the aim of establishing an environment in which advanced surgeries can be performed at every medical institution, our division is developing an information-powered surgical system in collaboration with external entities. In addition, we are teaming up with multiple academic institutions for the establishment of surgical video database. We are promoting the development of medical devices in Japan and are also accepted as "Support Program on Collaborative Innovation Networks for Medical Device" by the Japanese Agency for Medical Research and Development (AMED).

Research characteristics

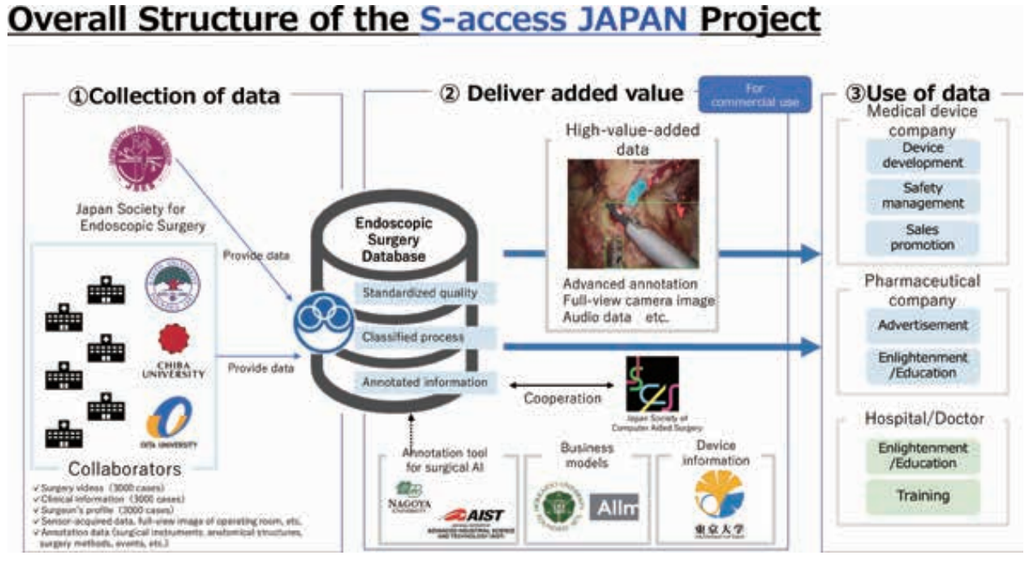
In Japan, with the expected increase in the number of cancer patients in the future, the shortage of the absolute number of surgeons is a major concern. Therefore, we consider that the currently facing issues are surgical education/training and efficiency of surgical procedures. We are establishing an information-powered surgical system in collaboration with Olympus Corporation and multiple academic institutions. Moreover, to transform physicians' tacit knowledge to objective database, we are establishing surgical video database available for industrial use in collaboration with multiple universities and medical institutions. Also, as the AMED Collaborative Innovation Networks for Medical Device, we are promoting human resource development/PoC (Proof of concept) acquisition in animal trials/business and regulatory strategies.

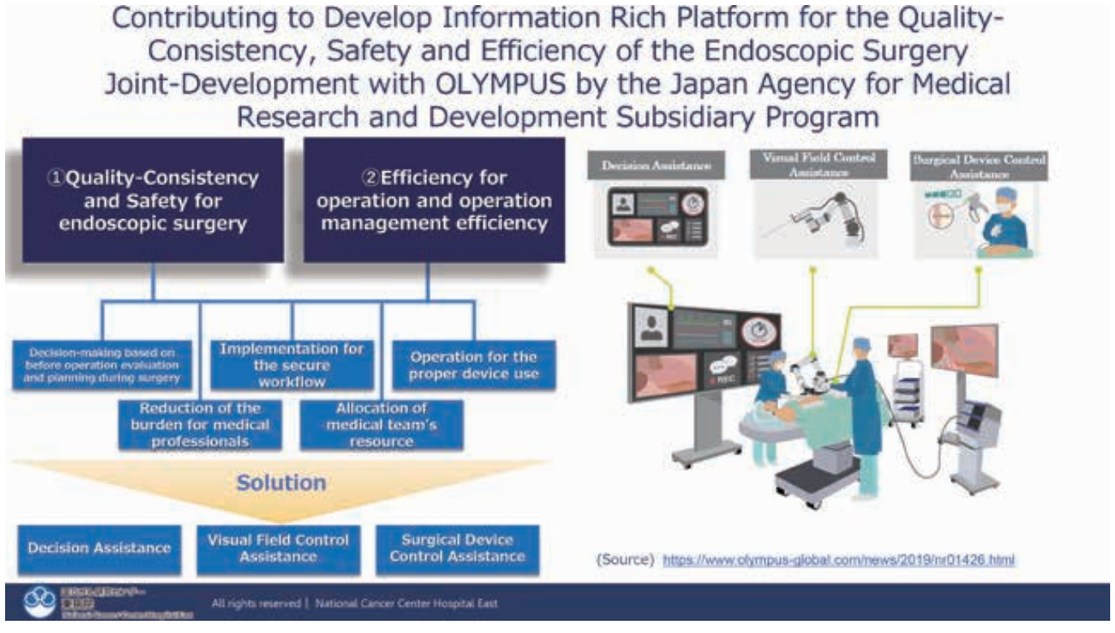
Potential research technical cooperation

- ◆ High-quality surgical video database available for industrial use
- ◆ Development of medical devices based on clinical needs and support for regulatory affairs
- ◆ Fostering entrepreneurship in surgeons

Future research prospects

Through the development of surgical video database and information-powered surgical system, surgical robots accurately following the surgeons' intention are likely to be produced in the future, which ultimately leads to autonomous surgery. These initiatives will fill the gaps between the sites and operators. Improvement effects on the quality of surgery are expected.





Drug Discovery by Co-Clinical Trials

Assessment of anticancer drugs using PDX models or cancer organoids

Yoshikatsu Koga, MD, PhD
Section of Experimental Animals　Head

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- ▶ PDX models or cancer organoids using human cancer tissues
- ▶ Drug discovery support by co-clinical trials
- ▶ Assessment of new nonclinical models, such as perfusable cancer organoids

Research background

Although cancer cell lines and transplant models have been used for the development of anticancer drugs for a long period of time, there is a growing need for patient-derived nonclinical models, such as the patient-derived xenograft (PDX) models, in which the patient-derived cancer tissues are transplanted to immunocompromised mice, and organoid models, in which 3D culture is performed on the gel which contains extracellular matrix. The Section of Experimental Animals is working together with US Beth Israel Deaconess Medical Center and National Institute of Advanced Industrial Science and Technology to develop an infrastructure for PDX models, system for cancer organoids (3D culture system), and co-clinical trials (concurrent clinical studies).

Research characteristics

The Section of Experimental Animals investigated the actual use, application, and trend of PDX models for drug discovery in Japan and overseas to report the issues and the points to consider. Our analysis of the points to consider revealed that the issues were the establishment of PDX models capable of the reproduction of the human cancer microenvironment in the mouse body and the low efficiency of PDX model establishment, which took a long time. To contribute to the promotion of drug development, we are working on the basic studies of PDX models using human cancer tissues and cancer organoids, as well as the standardization of quality control procedures for these parameters and establishment of co-clinical trial framework.

Potential research technical cooperation

- ◆ Provision of PDX models
- ◆ Provision of cancer organoids
- ◆ Drug development and research support using co-clinical trials

Future research prospects

We will make the best use of PDX models derived from human cancer tissues, genetically modified animals, and cancer organoids and will establish a co-clinical trial system to reduce the time and cost required for clinical trials and deliver drugs to patients as soon as possible.

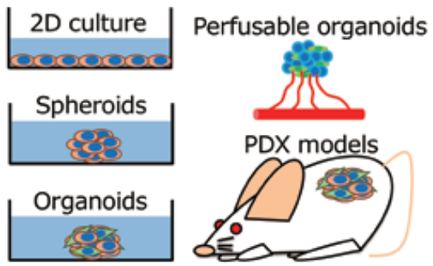
Non clinical model for drug development

in vitro/ex vivo

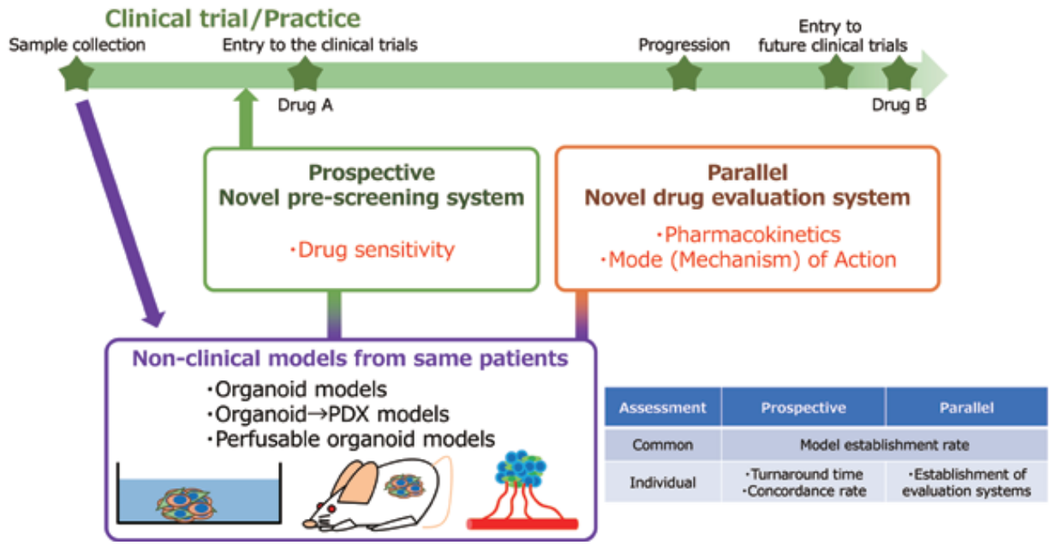
- ・2D culture
- ・Spheroids
- ・Organoids
- ・Perfusable organoids

in vivo

- ・Mouse cell-line derived allograft model
- ・Genetically engineered mouse model (GEMM)
- ・Human cell-line derived xenograft (CDX) model
- ・PDX (Patient-derived xenograft) model



Co-clinical trial



Assessment	Prospective	Parallel
Common	Model establishment rate	
Individual	・Turnaround time ・Concordance rate	・Establishment of evaluation systems

Utilization of 3D organoids in drug development researches

Establishment of cell growth assessment system using colorectal cancer organoids

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Section of Support of Animal Experimentation (Tsukiji) Head

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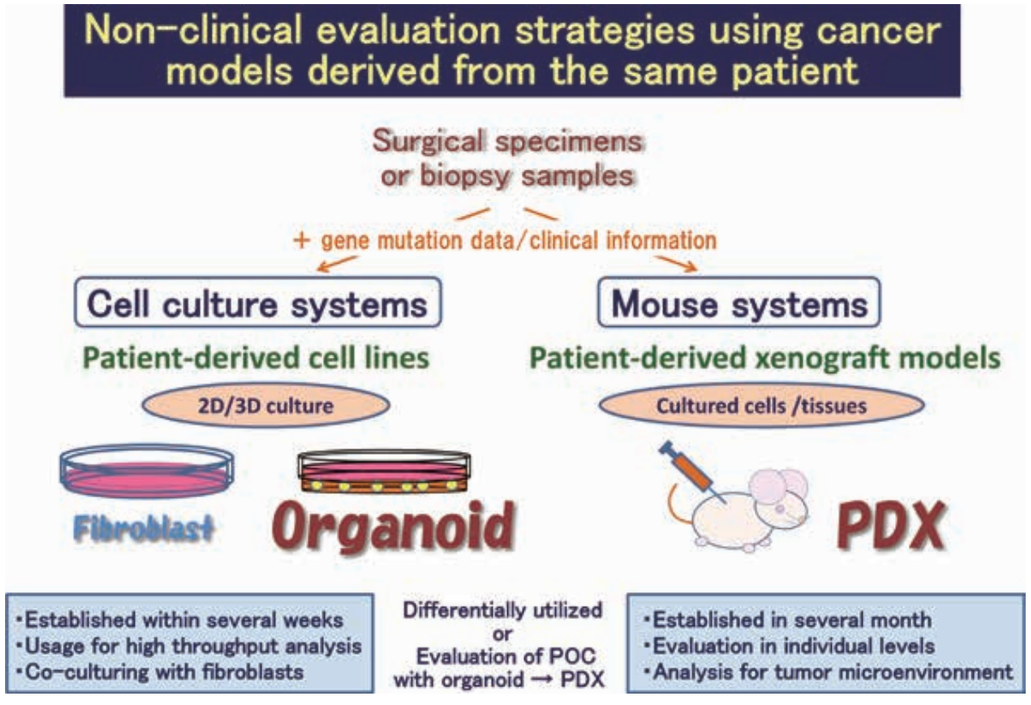
- ▶ **Cultivation techniques of 3D organoids using surgical specimens of colorectal cancer**
- ▶ **Cell growth evaluation system using colorectal cancer-derived organoids**
- ▶ **Co-culture system of cancer organoids with cancer-associated fibroblasts**

Research background

In the development researches of anticancer drugs, various established human cancer cell lines have been used. Recently, in addition to the existing cell lines, organoid models, in which patient-derived cancer cells are cultured in vitro, and patient-derived xenograft (PDX) models, in which patient-derived cancer tissues are cultured in vivo, are increasingly used. However, researches using organoids and PDXs only have a short history, and they are not sufficiently used in drug development researches. Our section has promoted drug development researches by utilization of 3D organoids using residual surgical specimens.



Research characteristics

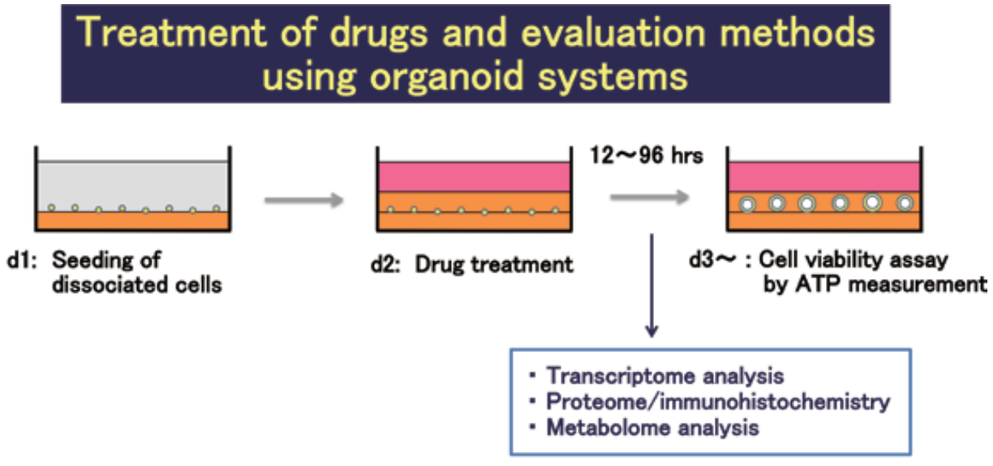
In comparison with 2D cell lines, 3D organoids have diverse component cells and maintain basic intercellular structures and gene expressions. Our section established pharmacological evaluation system by utilizing the organoids derived from surgical specimens of colorectal cancers. Moreover, we successfully established a co-culture system of the colorectal cancer organoids with cancer-associated fibroblasts derived from the same patient. We can also establish cancer organoids corresponding to the cancer types required by pharmaceutical companies or academic institutions. For PDX models, we are improving research infrastructures in collaboration with the Division of Clinical Pharmacology and Translational Research.

Potential research technical cooperation

- ◆ Organoid cultivation techniques
- ◆ Cell assay system using organoids
- ◆ Co-culture system of cancer organoids with cancer-associated fibroblasts

Future research prospects

By co-culturing of cancer organoids with cancer-associated fibroblasts, vascular endothelial cells and/or lymphocytes, linked to patient information (including genetic panel analysis data and drug reactivity data), we reconstruct the in vivo cancer micro-environment of cancer patients, with the aim of establishing novel organoid evaluation systems to assess various types of anticancer drugs including those for immunotherapy.



- ✓ **Individual evaluation of cytotoxic/molecularly targeted anticancer drugs for each patient (using gene mutation data /clinical information)**
- ✓ **Cell type-based reaction analysis to anticancer drugs using a chamber system in co-culturing of organoids with mesenchymal cells**
- ✓ **Possible application for not only cancer-associated fibroblast but also tumor endothelial cells and tumor infiltrating lymphocytes**

Development of novel therapeutic drugs for leukemia

From the understanding of molecular mechanism to molecular-targeted drugs

Akihiko Yokoyama, PhD
Yokoyama Project, Tsuruoka Metabolomics Laboratory　Team Leader

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- **Basic research utilizing the leukemia-developing mouse models induced by MLL fusion genes**
- **Identification of novel therapeutic targets based on the molecular mechanism of leukemia**
- **Epigenome analysis using original chromatin immunoprecipitation methodologies**

Research background

Leukemia is a major type of pediatric cancer. As it cannot be surgically resected, the development of molecular-targeted drugs with few adverse side-effects is strongly desired. Recently, oncogenesis-related gene alterations have been studied by exhaustive genome analysis, which realized the selection of therapeutic drugs and prediction of therapeutic efficacy for each gene alteration. In addition, leukemia subtypes prone to be refractory or exhibit resistance are also elucidated. By using the mouse leukemia model induced by MLL fusion gene which mimics human refractory leukemia, we are working to elucidate the mechanism of leukemia and develop novel molecular-targeted drugs.

Research characteristics

Our team examines the function of individual oncogenes by using the hematopoietic precursor cells to which various oncogenic driver genes are introduced. In particular, we have studied the molecular mechanism of leukemia caused by MLL fusion genes and also identified the key MLL target genes for drug discovery. In addition, since the driver genes of leukemia often code for transcriptional regulators, we developed highly sensitive chromatin immunoprecipitation methodologies, which are greatly useful for the promotion of epigenome research. Moreover, in collaboration with Keio University, we also conduct an exhaustive metabolome analysis.

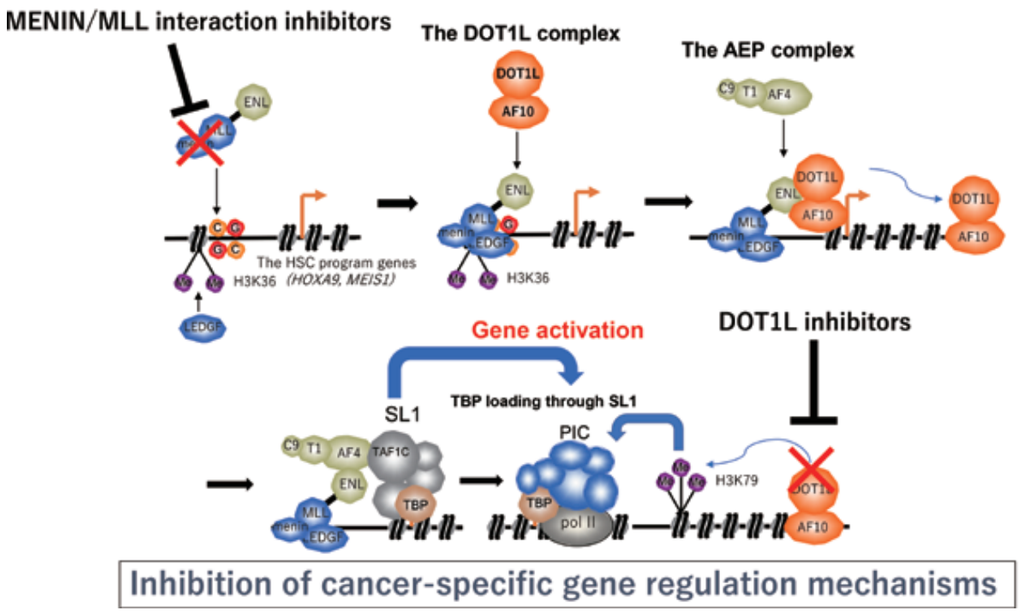
Potential research technical cooperation

- ◆ Leukemia model in normal immune mice
- ◆ Ex vivo culture system using primary mouse bone-marrow precursor cells
- ◆ Original highly-sensitive chromatin immunoprecipitation methods

Future research prospects

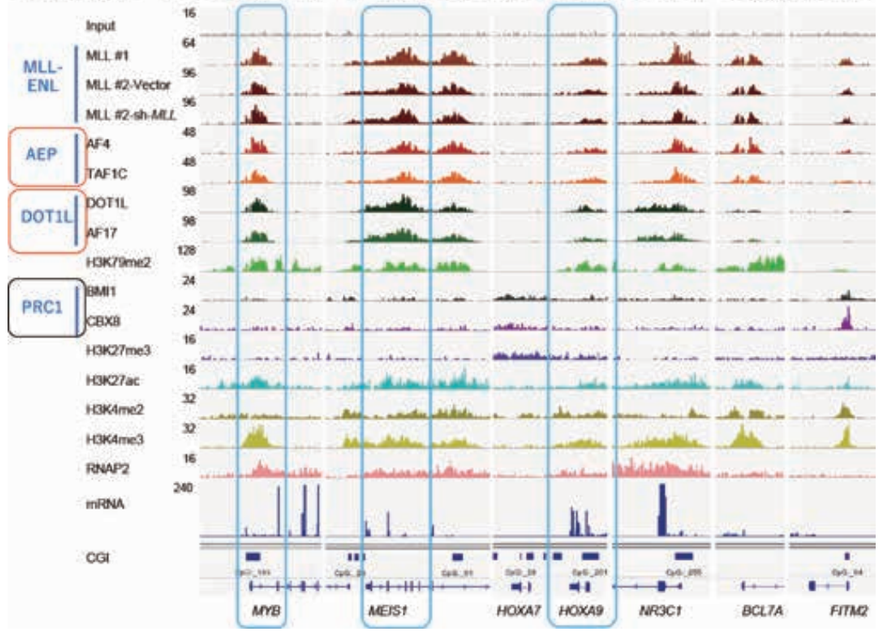
We established mouse leukemia models by using the primary hematopoietic cells to which various oncogenic driver genes are introduced. By clarifying the detailed mechanisms through the full use of our original technologies, we aim to produce novel therapeutic drugs for highly malignant leukemia which cannot be treated completely with the current therapeutics.

Development of molecular-targeted drugs for MLL-rearranged leukemia



Inhibition of cancer-specific gene regulation mechanisms

Genomic localization of various transcriptional regulators



Development of nucleic acid biosynthesis pathway inhibitors

Development of novel therapeutics inhibiting nucleic acid recycle pathways

Hideki Makinoshima, PhD
Makinoshima Project, Tsuruoka Metabolomics Laboratory　Team Leader
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- ▶ Identification of the target genes inhibiting nucleic acid recycle pathways
- ▶ Analysis of the expression level of target genes in the cases of small-cell lung cancer
- ▶ Validation of inhibition of target genes in tumor-bearing mice

Research background

There are two known kinds of nucleic acid biosynthesis pathway: new biosynthesis pathway and recycle pathway. While folic acid metabolism antagonists inhibiting new biosynthesis pathways are approved as pharmaceutical products, no pharmaceutical products inhibiting recycle pathways have been approved. In addition, the blood nucleic acid level in cancer patients is high, and the nucleic acids released from dead cancer cells are introduced into and recycled in their surrounding cancer cells; therefore, the development of nucleic acid recycle pathway inhibitors is desired. By using the cell lines, tumor-bearing mice, and clinical specimens of small-cell lung cancer, our team is conducting researches aimed at developing novel therapeutics which inhibit nucleic acid recycle pathways.

Research characteristics

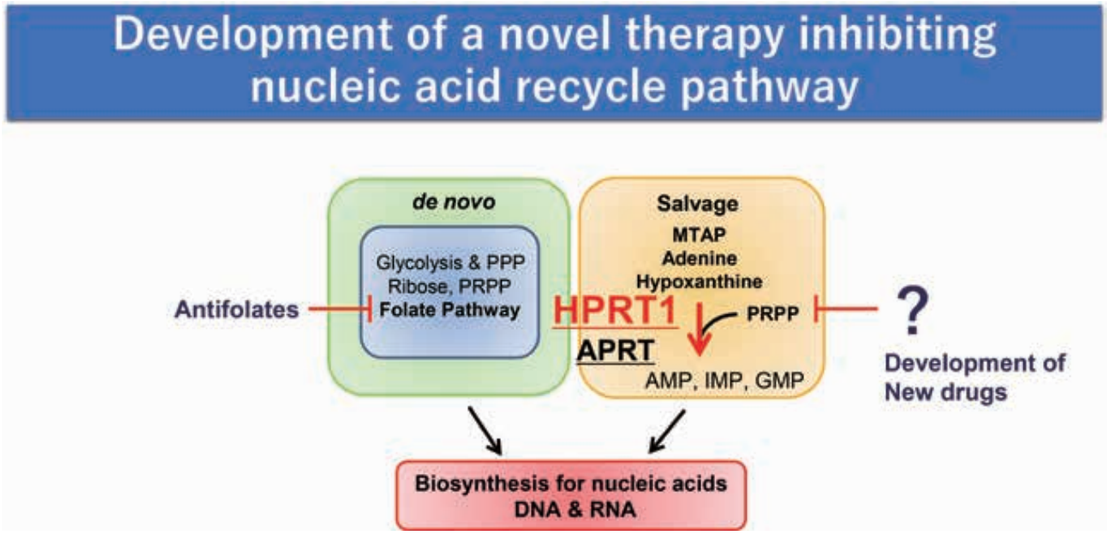
Analysis of the clinical specimens of small-cell lung cancer (SCLC) through immunohistochemical staining revealed that the cases with high expression of HPRT1, which plays a role in a recycle pathway, accounted for 86% of all cases. On the SCLC cell lines on which a single-agent administration of a folic acid antagonistic inhibitor exhibited no effects, the folic acid antagonistic inhibitor exhibited effects following HPRT1 knockout. Moreover, in the tumor-bearing mice of HPRT1 knockout cell lines, a marked cell proliferation inhibition effect was observed after the administration of a folic acid antagonistic inhibitor. These results revealed the importance of the simultaneous inhibition of the two kinds of nucleic acid biosynthesis pathway.

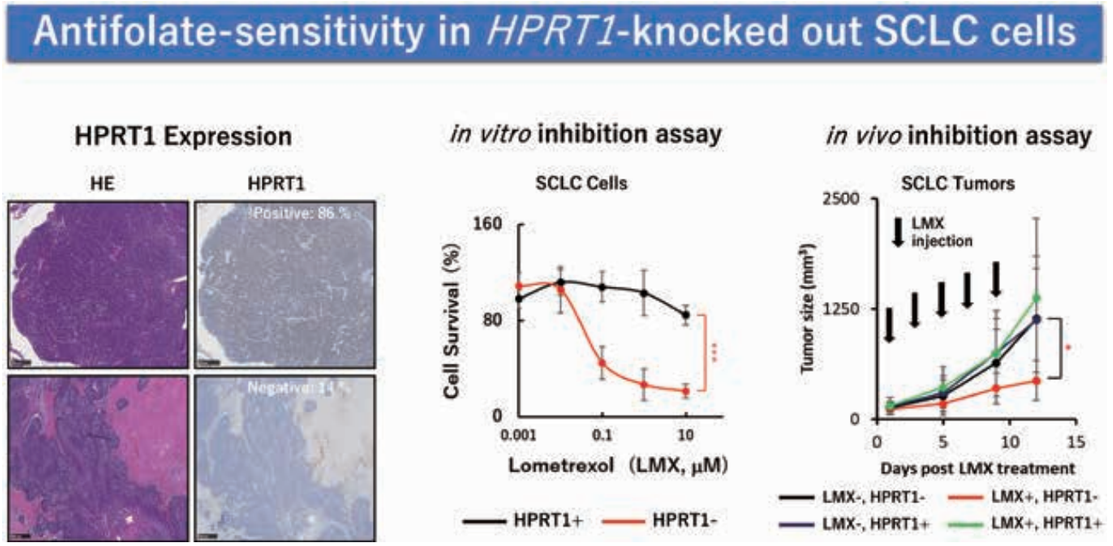
Potential research technical cooperation

- ◆ HPRT1 knockout SCLC cell lines
- ◆ Metabolome analyses by using GC-MS

Future research prospects

Researches on nucleic acid biosynthesis recycle pathway are not highly advanced. With progressing further verification on the target validity of HPRT1, we would like to link the outcomes of the previous cancer metabolome researches to the clarification of the mechanism of anticancer drug resistance acquisition and development of pharmaceutical products inhibiting recycle pathways.





Basic information

Foundation　September 1st, 2012

Director　Dr. Toshihiko Doi

History

October 2005 Research Center for Innovative Oncology was established in National Cancer Center Hospital East.

April 2008 Office of Clinical Research was opened at the center. A support system for investigator-initiated clinical studies was organized.

July 2011 National Cancer Center was selected as a center of the “Project for Organization of Early/Exploratory Clinical Trial Centers,” and Phase 1 Center was established as a center of new cancer drug development in close cooperation between National Cancer Center Hospital East/Research Center for Innovative Oncology and Center Hospital/Research Institute. Several development studies were initiated, including sponsor- and investigator-initiated first-in-human studies.

July 2012 Office of Translational Research was opened. A full-scale support system for translational research (TR) was established.

September 2012 Exploratory Oncology Research & Clinical Trial Center (EPOC) was established.

April 2015 Research Center for Innovative Oncology was integrated into EPOC. Atsushi Otsu (current Director, National Cancer Center Hospital East) was appointed as the Director of this center.

May 2016 EPOC reorganization was performed to focus on nonclinical studies aiming at demonstrating concepts of drug discovery and early and exploratory clinical TR studies. Atsushi Ochiai was appointed as the Director of this center.

May 2019 Memorandums on research cooperation were concluded with Shonan Health Innovation Park (iPark) and Cancer Center at Beth Israel Deaconess Medical Center, Boston, the U.S.A., respectively.

June 2019 A master agreement was concluded with Miraca Holdings Inc. and Mitsui Fudosan Co., Ltd., for cooperation and collaboration for development of next-generation medical techniques and healthcare services.

November 2021 Memorandum on research cooperation was concluded with Frederick National Laboratory of Cancer Research, USA.

April 2022 Toshihiko Doi was appointed as the Director of this center.

Activities　We consistently support new idea, concept and primitive materials designed to become approved as cancer drugs or medical devices with an aim of **“Conquer and Cure Cancer (3C).”**

- ◆Establishment of a system to promote cross-sectional TR studies among National Cancer Center Hospital East, Central Hospital and Research Institute
- ◆Promotion of TR studies using quality-controlled clinical samples associated with clinical information
- ◆Elucidation of the fundamental mechanism of intractable or refractory cancer
- ◆Exploration of therapeutic targets and development of medical devices for supportive therapy
- ◆Drafting clinical development plans for drug or medical device candidates derived from within and without National Cancer Center Japan
- ◆Acceleration of an effective industry–academia cooperation
- ◆Education of global human resources involved in medical development

Location/Access

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