Inquiry on collaborative research
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Introduction

In 2015, based on the “Research Center for Innovative Oncology (RCIO),” which was established in the National Cancer Center Hospital East (NCCH E) at the Kashiwa Campus in 2005, doctors and researchers in the research and development of drugs and medical devices, the National Cancer Center (NCC) opened a new organization, “Exploratory Oncology Research & Clinical Trial Center (NCC-EPOC),” through the integration of RCIO with the “Exploratory Oncology Research & Clinical Trial Center (EPOC),” which was founded in 2012. This integration has enabled drug discovery seed research, biomarker discovery, and diagnostics and laboratory test development in collaboration with the National Cancer Center Research Institute (NCCRI), and provided seamless transitions to clinical studies conducted by the NCCH and NCCE via early phase clinical development and research activities in the NCCH and NCCE. In addition to the intramural collaboration with NCC institutions, NCC-EPOC is collaborating with a wide variety of organizations and businesses domestically and internationally in various fields from academic institutions to drug makers, diagnostic and medical device developers, and regulatory authorities, with the aim of creating newly shared values and serving as the driving for the development of new drugs and medical devices in Japan.

We are actively involved in the provision of research funds and consultation services for promising research ideas, concept and primitive materials in the NCC and in the introduction of the cultivated idea, concept and primitive materials to Japanese and overseas academic institutions and companies. This brochure describes the studies undertaken by researchers in Kashiwa, Kashiwa, and Tsuruoka Campuses of the NCC-EPOC, with a focus on potential drug or medical device candidates that can be provided by the NCC-EPOC researchers include candidate treatments for so-called personalized medicine, such as peptide vaccine treatment and alpha-ray treatment, platforms to create candidates, animal models and their evaluation methods, and seeds related to delirium and dementia, covering a wide range of research fields. Joint research and development with the NCC-EPOC allows you to develop the research ideas and concept into drugs or medical devices that can be applied in actual medical practice (hospital) in a seamless manner. We would like to work together with you to promote the development of novel medicines for global cancer care.

Dr. Atsushi Ochiai
Director
Exploratory Oncology Research & Clinical Trial Center, National Cancer Center
Aiming for the therapeutic intervention for pancreatic cancer cachexia
One-stop service for the basic researches and TRs related to cancer cachexia

- Basic researches on cancer cachexia
- Establishment of the model mice of pancreatic cancer nerve invasion
- Development of a method for extracting true cancer cachexia patients

**Research background**
Cancer cachexia is the clinical condition in which the skeletal muscle mass and body weight gradually decrease due to the continuous malnutrition associated with the aggravation of disease condition. In particular, patients with pancreatic cancer have a high risk of developing cancer cachexia, and cancer cachexia is reported as a poor prognostic factor for them. Our division developed novel model mice exhibiting pathological features similar to those of human pancreatic cancer specimens and developing cancer cachexia. Moreover, we developed a method for extracting true patients, whose disease condition is found to worsen due to cancer cachexia, from pancreatic cancer patients diagnosed with cancer cachexia and improved the infrastructure for the future therapeutic drug development researches for cancer cachexia.

**Research characteristics**
In the GAPFREE Project by AMED, we conducted multi-layer omics analysis on the tumor microenvironment of pancreatic cancer and created a database. Moreover, we identified the factor that causes the inflammatory environment of pancreatic cancer and conducted and completed an investigator-initiated clinical trial. After inoculation of pancreatic cancer cell lines into the sciatic nerve of a mouse, the cancer cells are increased by nerve compression. This model mouse is a unique model animal exhibiting morphological features similar to those of the specimens from human patients with pancreatic cancer and developing cancer cachexia. Moreover, we established a method for identifying true cachexia patients based on the metabolites and amino acid composition in the blood of pancreatic cancer patients diagnosed with cachexia.

**Potential research technical cooperation**
- Technologies for the production of model mice of pancreatic cancer nerve invasion
- Methods to stratify patients with pancreatic cancer cachexia
- Joint researches by using the cachexia-related clinical indicator data, blood samples, tumor-derived proteins, and tumor-derived nucleic acids obtained from about 200 patients with pancreatic/biliary tract cancer

**Future research prospects**
Although it is well known that cancer cachexia worsens the prognosis of pancreatic cancer patients, there are no therapeutic drugs effective for cachexia. We have improved the infrastructures to produce therapeutic drugs, including model mice developing cachexia, methods to stratify patients, and specimens obtained from pancreatic cancer patients. In the future, we would like to develop therapeutic drugs for cancer cachexia in collaboration with companies and deliver them to patients as fast as we can.

**Propose for the development of anti-cachexia therapy**
The advantages of biomarker based clinical trial
- Enrichment of SOC (standard of care)-refractory cachexia → Decrease of a bias from SOC
- Exclusion of patients with extremely poor prognosis → Keeping a duration for evaluation

Our proposal : 2nd sieve for the enrichment of cachexia

- Diagnosed as cancer
- Diagnosed as cancer cachexia

The appropriate population for the evaluation of anti-cachexia therapy

**Nerve invasion model using human pancreatic cancer cell**

*PDAC in patients*  
*Tumor invasion along nerve*  
*Cachexia*  
*Pain*

*Model*
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

► 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.
Overcoming Resistance to Cancer Therapy

Understanding of mechanisms of resistance using human cancer specimens

- 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 activities

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 assets

- 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 perspectives

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

- 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 vulnerability). We aim to develop novel cancer therapeutics and innovative therapeutic strategies on chromosomal instability-mediated cancer vulnerabilities.

Research activities

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 assets

- 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 prospectives

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

- 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 activities

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 assets

- 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 prospectives

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.

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)
Expansion of the indication for genomic medical care
Development of the panel tests for pediatric cancer/sarcoma and analysis on special cases

- Development of NCC Oncopanel test and expansion of panel tests to pediatric cancer/sarcoma
- Gene abnormality/gene expression profile researches on various types of sarcoma
- Search for gene alteration in the cases which followed interesting clinical courses

Genomic medicine, in which therapeutics are selected based on genomic information, is evolving. In Japan, two gene panel tests were approved in 2019. Our division has been developing one of these tests, the NCC Oncopanel test. Meanwhile, rare cancers, such as pediatric cancer and sarcoma, are known to be associated with the gene alterations different from major adult cancers and such genomic information is useful for the diagnosis and prognosis prediction. However, the development of the panel tests corresponding to the diagnosis and prognosis prediction is slow. Apart from this, some patients follow the interesting clinical courses which cannot be explained by their known information, and there may be potential seeds of development of novel therapies.

Research background
Genomic medicine, in which therapeutics are selected based on genomic information, is evolving. In Japan, two gene panel tests were approved in 2019. Our division has been developing one of these tests, the NCC Oncopanel test. Meanwhile, rare cancers, such as pediatric cancer and sarcoma, are known to be associated with the gene alterations different from major adult cancers and such genomic information is useful for the diagnosis and prognosis prediction. However, the development of the panel tests corresponding to the diagnosis and prognosis prediction is slow. Apart from this, some patients follow the interesting clinical courses which cannot be explained by their known information, and there may be potential seeds of development of novel therapies.

Research activities
With the Chief of our division, Dr. Takashi Kohno, we played a significant role in the development of the NCC Oncopanel test. Currently, we are engaged in the development of the panel tests for pediatric cancer/sarcoma. Moreover, we are investigating the gene alterations and gene expression in sarcoma and recently identified novel mutated genes, prognosis-correlated gene alterations, etc., from dedifferentiated liposarcoma and granular cell tumor. In addition, I am responsible for the Genomic Core Facility as the Chief of the Department of Clinical Genomics of the National Cancer Center Research Institute; as part of this business, I am implementing the "Do-it-now Section" project, in which the causative gene alterations are quickly searched from the patients exhibiting super response to molecular-targeted drugs, rapid resistance to therapies, and other things.

Potential research assets
- Genome/transcriptome analysis technologies using FFPE specimens
- Results of the gene abnormality/gene expression analyses on various types of sarcoma
- Know-how of the development of gene panel tests

Future research prospectives
We would like to work for the development of the panel tests that are more suitable for pediatric cancer/sarcoma patients who are unable to sufficiently receive the benefits of genomic medicine with the current gene panel tests. In addition, we are expecting that the quick finding of gene alterations related to therapeutic efficacy through the activities of the "Do-it-now Section" project will lead to the development of novel therapeutics.

Genomic profiling of dedifferentiated liposarcoma
The causative gene alterations are quickly searched from the patients exhibiting super response to molecular-targeted drugs, rapid resistance to therapies, and other things.

“Do-it-now Section” project
Drug discovery based on translational informatics
Establishment of integrated database of non-coding RNA

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

Future research prospectives
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.

Analysis for Translational informatics
Non-coding RNA analysis with enhanced DB

- High quality clinical and research data
- Experimental data
- Our databases
- Public databases
- Integrated databases
- melina version 1.1
- Original tools for bioinformatics analysis for non-coding RNA, metagenome
- Data processing with statistics, informatics and AI techniques
- Elucidation of novel biomedical knowledges

- Many cancer related RNA data
- RNA mapping
- Co-expression network
- mRNASDB
- Annotations for mRNA
- Annotations for non-coding RNA
- Normal annotation for mRNA
  - Differentially expressed genes
  - GO, KEGG, REACTOME
- Whole transcriptome knowledges by integrated analysis of mRNA + non-coding RNA

- Integrated non-coding RNA DB
- mRNASDB
- IncRNA
- Cancer related non-coding RNA
- Public DBs
- Neo-antigen
- Predicted ORF
- Estimated function for non-coding RNA
- Cell adhesion, immune response
- Non-coding RNA (non-coding sequence element)
- Non-coding RNA (non-coding sequence element)
Development of New Patient Stratification Techniques and Drugs
Establishment of analysis techniques for immune cells that reflect the tumor microenvironment

- 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)

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 background
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 technique, 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 energy) and are committed to the development of new cancer immunotherapy.

Research characteristics
- 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

Potential research technical cooperation
- Techniques for examining immune cells in the tumor microenvironment
- Identification 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.

Immuno-genome assay
Sufficient amount of cells can be prepared for Immuno-genome assay
Establishment of the methods to search for novel immunotherapeutic targets

Identification of novel immunotherapeutic targets by separating cells bound to antibodies

- 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 research.
Application of PDX derived from Japanese cancer patients to drug discovery
Support for the industrial use of the PDX library linked to clinical information

- 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

- 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 heterogeneous 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.
Actions for the establishment of pathological assessment method for tumor regression
Residual tumor areas as an objective pathological assessment method of tumor regression

- 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 pathologists. 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.

Pathological assessment method of tumor regression across the organ
Area of residual tumor (ART) Grade using the field of the microscope.

Grade 1  Grade 2  Grade 3  Grade 4

PATHOLOGICAL ASSESSMENT OF CANCER PHYSIOLOGY AND GENE EXPRESSION ANALYSIS
Cancer stroma regulate it's physiology
Genes associated with cancer physiology can be therapeutic target

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EPOC Researchers Catalog
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

- 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.

Research summary

Multi-omics Analysis and Molecular Profiling

Clarification of the differences in genes, biomolecules and metabolites between PBMC-T and TIL-T via multi-omics analysis (mass spectrometry) and molecular profiling

The list of the genes, biomolecules and metabolites for the induction from PBMC-T to TIL-T that should be created

Development of induction method from PBMC-T to TIL-T

Various research of T-cell-based technology and its therapeutic application

Various researches of T-cell-based technology and its therapeutic application

T cell chemotaxis

Local proliferation and activation of T cells

Regulation of T cells and cytokine storm

Redirection of T cell activity towards cancer cells via BsAb

Immunogenic cell death and T cell activation

Bi-Ab

T cell activation and its off-target effect

Preventing cytokine storm
T Cell Therapy Targeting Unique Cancer Antigens

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

- 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 no treatment was needed in children suffered from multiple times relapses of intractable cancers).

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.

Peptide vaccines targeting common antigens such as GPC3 and HSP105
Development of immune cell medication for cancer treatment
Establishment of an off-the-shelf-type immune cell platform

- 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

- 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 works 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

- 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.
High-field MRI to strongly support drug discovery researches
Selection of development candidates via high-throughput MRI examination for multiple animals

- 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.

Multiple animal MRI for four orthotopic hepatoma-bearing rats

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.

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

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

- 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.
Actions for the development and popularization of BNCT

Expansion of indication of BNCT to new cancer types by a hospital-installed compact accelerator

- Development of hospital-installed BNCT system
- Promotion of the clinical studies of BNCT
- Production of novel boron drugs

Research background

Boron neutron capture therapy (BNCT) is a treatment in which cancer cells are selectively destroyed by the α-particles and Li atomic nuclei produced by the reaction of the boron (10B) compounds that are specifically taken by cancer cells and the neutron irradiated from the outside of the body. Since the range of the α-particles and Li atomic nuclei produced by this nuclear reaction is about a diameter of one cell, the DNA of cancer cells can be cleaved, and only the tumor cells can be destroyed with a minimal adverse effects on the normal cells surrounding the tumors. To develop and popularize BNCT, our division is promoting BNCT-related basic and clinical researches in collaboration with the relevant sections.

Research characteristics

Performing BNCT requires the incorporation of boron into cancer cells and the neutron irradiation system by an accelerator or a nuclear reactor. To predict in advance the amount of boron incorporated into cancer cells, we are developing/improving the 18FBPA PET examination method. We are also working for the joint development of a compact accelerator which can be installed in a hospital and started a single-institutional clinical trial of BNCT for the patients with malignant melanoma and angiosarcoma in collaboration with the Department of Radiation Oncology and Department of Medical Physics of the National Cancer Center Hospital.

Potential research technical cooperation

- Utilization of hospital-installed compact accelerator
- 18FBPA PET examination method
- Development of novel boron drugs

Future research prospects

The cancer types indicated for BNCT are determined by the amount of boron drugs taken by tumor cells. We would like to develop novel boron drugs as a replacement of the existing BSH and BPA and expand the range of indication for BNCT. Moreover, after conducting the single-institutional clinical trial, we will obtain an official approval of the neutron radiation device for BNCT, and perform multicenter clinical studies, with the aim of establishing and expanding the clinical indications of BNCT.
Seeds cultivation by endoscopists

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

- 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.
Endoscopic device development in anticipation of exit strategies

Establishment of an endoscopy development framework based on medical needs in collaboration with companies

- Development of endoscopic diagnostic and therapeutic devices
- Development of endoscopic procedure training system
- Development of AI system supporting endoscopic diagnosis/therapy

Research background

Endoscopy is mainly used for the purposes of “observation/diagnosis” and “treatment” of the lesions. However, the diagnosis still focuses on morphological features of the lesions, and the detectability and diagnostic accuracy of the lesions are limited. In addition, problems still exist, including the existence of difficult-to-treat lesions, complications associated with the treatment and limited number of certificated endoscopists. Our efforts will be focused on the developments of new endoscopic diagnosis and treatment, as well as an effective training system with industry-academia collaboration.

Research characteristics

Our division is working for endoscopic device development in anticipation of exit strategies after extracting the medical needs related to endoscopy development and prioritizing them. As an ongoing project, in collaboration with Olympus Corporation, we are developing innovative endoscopic diagnostic, therapeutic and training equipment at Olympus Lab in the National Cancer Center Research Institute (NCCRI). In addition, the performance of artificial intelligence (AI) has recently been dramatically improved by the combination of deep learning and backpropagation and expected to be utilized in the fields of medical care. We are also progressing the development of AI system supporting endoscopic diagnosis/therapy.

Potential research technical cooperation

- Endoscopic device development meeting the medical needs for clinicians
- Endoscopic device development based on high-quality clinical data from a large number of cases

Future research prospects

By visualizing the characteristics of cancer through the combination of new technologies, such as molecular imaging and functional imaging, beyond the current endoscopic diagnosis focusing on morphological features of the lesions, our efforts will be focused on the developments of new endoscopic diagnosis, which leads to new therapeutic strategies, and more advanced endoscopic treatments, such as full thickness resection.
Equalization and efficiency improvement of surgical treatments in Japan
Reduction of the gaps between sites and operators by information-powered surgery

- 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.

Overall Structure of the S-access JAPAN Project

Contributing to Develop Information Rich Platform for the Quality- Consistency, Safety and Efficiency of the Endoscopic Surgery
Joint-Development with OLYMPUS by the Japan Agency for Medical Research and Development Subsidiary Program

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Drug Discovery by Co-Clinical Trials

Assessment of anticancer drugs using PDX models or cancer organoids

▶ 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

Clinical trial/Practice
- Sample collection
- Entry to the clinical trials
- Progression
- Entry to future clinical trials
- Drug A
- Drug B

Prospective Novel pre-screening system
- Drug sensitivity

Parallel Novel drug evaluation system
- Pharmacokinetics
- Mode (Mechanism) of Action

Non-clinical models from same patients
- Organoid models
- PDX organoid models
- Perfusable organoid models

Assessment
- Prospective
- Parallel

Common
- Model establishment rate

Individual
- Tumor growth rate
- Concordance rate
- Establishment of evaluation systems
Utilization of 3D organoids in drug development researches

Establishment of cell growth assessment system using colorectal cancer organoids

- 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.
Development of novel therapeutic drugs for leukemia
From the understanding of molecular mechanism to molecular-targeted drugs

- 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 nucleic acid biosynthesis pathway inhibitors

Development of novel therapeutics inhibiting nucleic acid recycle pathways

- 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.

Development of a novel therapy inhibiting nucleic acid recycle pathway

Antifolate-sensitivity in HPRT1-knocked out SCLC cells
Basic information

Foundation September 1st, 2012
Director Dr. Atsushi Ochiai

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.

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