OUR RESEARCH FOCUS

2025

National Cancer Center Japan
Research Institute

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Contents

Greeting
from the Director

National Cancer Center Japan
Research Institute
Director

Hiroyuki MANO, M.D., Ph.D.

国立がん研究センター
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National Cancer Center Research Institute

The National Cancer Center Research Institute (NCCRI) is one of the largest cancer research institutions in Japan, with over 350 staff, including postgraduate students and research assistants. The Institute covers 18 research areas with 9 independent units, as well as the Fundamental Innovative Oncology Core, established as a common platform serving the entire Center.

From highly original basic research to the development of therapeutic and diagnostic drugs, the Institute conducts a wide range of activities in collaboration with other units within the Center. Through a variety of sequencers and the development of unique bioinformatics, the Institute has a proven track record in cancer genome analysis. Based on these discoveries, we develop drugs and conduct clinical trials with the two hospitals of the Center.

As part of the development of specific technologies for cancer genomic medicine, we developed OncoGuide^{TM} NCC Oncopanel System, Japan's first cancer gene panel test, which is now covered by national health insurance. Currently, we are confirming the clinical usefulness of the genetic panel tests for hematopoietic malignancy and childhood cancers, which we developed and prepared with partners throughout the nation.

Our bioresources are continually expanding, with over 600 patient-derived xenograft mice and about 30,000 fresh-frozen tumor tissues in our biobank. Utilizing these resources, we will conduct joint research with academia and industries in Japan and overseas.

Commitment to Translational Research（TR）

**Kazunori AOKI,
M.D., Ph.D.**
National Cancer Center Japan
Research Institute
Deputy Director

National Cancer Center has managed the 2 frameworks (Fundamental Innovative Oncology Core and Tsukiji TR Board) to encourage TR/reverse TR in collaboration with domestic/ international Pharma companies and Academia.

FIOC：Fundamental Innovative Oncology Core

FIOC web site

FIOC has bridged basic research and clinical practice. Currently, FIOC is engaged in the following activities.

1. Development of bioresources (patient-derived cancer model)

   As cancer models for the development of antineoplastic agents, we have established PDX strains, organoid strains, and cell lines of various cancer types. Using these models, we also support the evaluation of drug efficacy.

2. Research Support as a Core Facility

   For basic and development research conducted by Pharma companies and academia, we provide various types of support, including omics analyses, immunological analyses, pathological analyses, and animal experiments.

3. Promotion of TR and reverse TR

   In collaboration with the Exploratory Oncology Research & Clinical Trial Center (EPOC), we are working on translational research (TR) from basic to clinical sciences and reverse TR from the bed to bench in the therapeutic and diagnostic development with the aim of developing antineoplastic agents and biomarkers.

3. Collaboration with Companies and Academia

   By utilizing the bioresources and various research support activities as a core facility, we've conducted many joint research programs with companies and academia.

**Wakako TOGA,
Ph.D.**
National Cancer Center Japan
Research Institute
Deputy Director
R&D support

Tsukiji TR Board (TTRB)

TTRB web site

01 Drop a request to one-stop-shop contact for your TR consultation
The one-stop-shop contact is ready for your easy access, then you don't need to seek out appropriate researchers/physicians by yourselves.

02 Have a TR consultation meeting with pre-assigned researchers/physicians
Every TR consultation request is shared within the core members in a timely manner, then appropriate researchers/physicians should be pre-assigned from the board members. Confidentiality could be maintained within only limited attendees thus.

03 Conclude a joint research agreement
Having an agreement of TR plan at the consultation meeting, a joint research agreement would be concluded between customers and researchers/physicians in charge via NCC IP and Research Alliance Section.

04 Conduct TR study in collaboration across functions in NCC Tsukiji campus
Conduct TR study effectively in collaboration with NCCH clinical department, Fundamental Innovative Oncology Core and NCCRI research divisions.

One of the TTRB's objectives is to encourage domestic/international TR activities by connecting research knowledge, technology and experiences among physicians and researchers in the hospital and the research institute collocated in the NCC Tsukiji Campus. TTRB can provide an easy access to front-line research and technologies in NCC to seamlessly support TR from a basic research to a clinical development between Pharma companies and Academia.

Molecular Pathology

Division Chief: Yasushi YATABE, M.D., Ph.D.

Passion 🔥
Working closely with the Department of Diagnostic Pathology at Hospital, we conduct researches to bridge genetic changes to practical use in diagnosis and research to find genetic abnormalities useful in diagnosis, based on questions raised in the diagnostic process.

Mission

- 💡 Analysis of molecular mechanisms that define tumor characteristics
- 💡 Analysis of early lesions of tumors and microenvironments

Innovation

Our lab aims to identify novel molecular pathogenesis by analyzing the molecular mechanisms in tumor progression based on a broad understanding of tumor characteristics. Furthermore, as we are involved in both clinical and basic research, it is also an important mission of our laboratory to promote bridging basic research and clinical practice through integration of various results in NCC hospital and research institute.

1. Molecular analysis on lung cancer development

Through a prior wide range of lung cancer research and international collaborations, we have taken a lead in the study on molecular pathogenesis of lung cancer and translational research. Our results were adapted in guidelines and expert recommendations. We also focused on high-throughput analysis over tumor types.

2021 WHO classification of tumors of the lung, Lyon
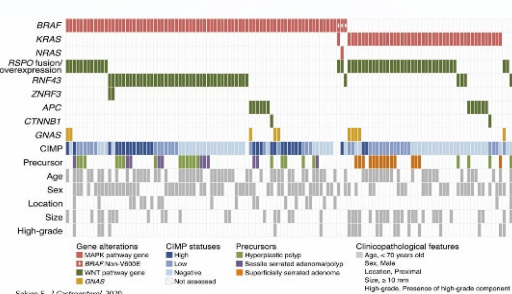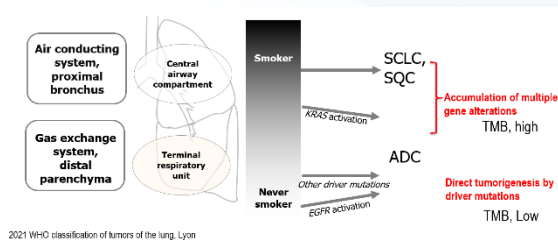
### 2. Serrated pathway in gastrointestinal tumors

Among colorectal tumors, we focus on morphological variations of colorectal tumors involving serrated pathway as a molecular pathogenesis. By analyzing familial colorectal cancers, we have shown that adenomas with serrated pathway could be developed under a genetic background of the classical APC pathway. Also, a special type of stomach tumor has been identified as proposing a new tumor entity.

Sekine S, *J Gastroenterol*, 2020

3. Secondary cancer after bone marrow transplantation

Squamous cell carcinoma of the head and neck is known to be caused by factors such as alcohol and tobacco as well as under a particular tumor microenvironment, such as immunosuppression after hematopoietic stem cell transplantation. We are investigating a novel mechanism of head and neck cancer development by analyzing genomic abnormalities in these secondary cancers.

4. Collaboration with Japan Sarcoma Genome Compositum (JSGC)

In 2014, the Japan Soft Tissue Genome Consortium (JSGC) was established to promote genomic analysis of bone and soft tissue tumors. Collaborating with the Institute of Medical Science of the University of Tokyo, we manage the consortium as an administrative office.

Cellular Signaling

Division Chief: Shinji KOHSAKA, M.D., Ph.D.
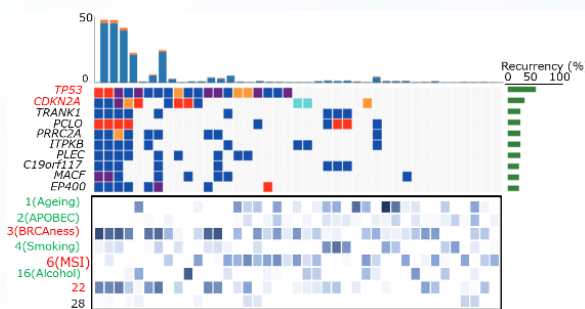
Passion 🔥 Through an approach combining high-sensitivity functional screening with next-generation sequencing analysis, we aim to elucidate the development mechanism of human tumors and develop novel molecular targeted therapies

Mission

- 💡 **Identification of tumorigenesis and development of new drugs through comprehensive genome analysis**
- 💡 **Establishment of functional assay to evaluate gene alterations**
- 💡 **Development of new computational pipeline for cancer research**

Innovation

In order to develop specific drugs for diverse cancers, it would be effective to identify essential oncogenic molecules in individual cancers and develop drugs that target them. Therefore, we are conducting comprehensive genome analysis of patient samples to elucidate tumorigenesis and identify novel targets. For example, we utilized a large-scale patient-derived tissue xenograft (PDX) model, in which patient-derived cancer tissue was transplanted into immunodeficient mice, to evaluate the drug efficacy of targeted proteolysis-inducing drugs across cancer types. We performed whole exon sequencing of PDX and identified *BRCA* and *ATM* gene mutations as predictive biomarkers of efficacy (NPJ Precis Oncol. 8:117).

Besides, we are also trying to apply new technologies to the genome medicine. We established a comprehensive assay, the Todai OncoPanel (TOP), which consists of DNA and RNA hybridization capture-based next-generation sequencing panels. A novel method for target enrichment, named the junction capture method, was developed for the RNA panel to accurately and cost-effectively detect most of fusion genes as well as aberrantly spliced transcripts involved oncogenesis in solid tumor. This comprehensive profiling panel is now applied to liquid biopsy using cell-free DNA or circulating tumor cells.

Through large-scale cancer genome projects, numerous variants of unknown significance (VUS) have been identified and their functional relevance remains uninvestigated. We developed a high-throughput method to evaluate the transforming potential and drug sensitivity of oncogenes and tumor suppressors and identified novel potential targets in VUS (Fig. 2、Sci Transl Med 9:eaan6556, Nat Commun 11:2573)

Moreover, we are establishing new computational pipeline for multi-omic analysis by ourselves to optimize for our research purpose. Our motto is "build what we need" while there are many analytical pipeline available these days. For instance, allele sprcific copy number analytical tool (for in-house use) or FFPE specific mutation error elimination tool named MicroSEC (Commun Biol 4:1396) and fusion detection tool for genome medicine (Cancer Sci 110:1464) have been developed.

Biomarker identification using PDX model
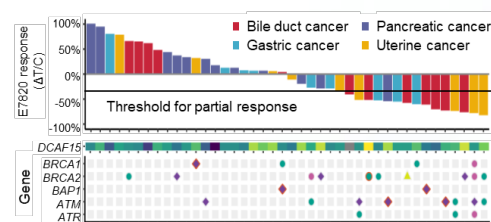
Fig.1

Gene variants correlated with drug efficacy were identified.

High-throughput functional analysis

Fig.2

Cancer Evolution
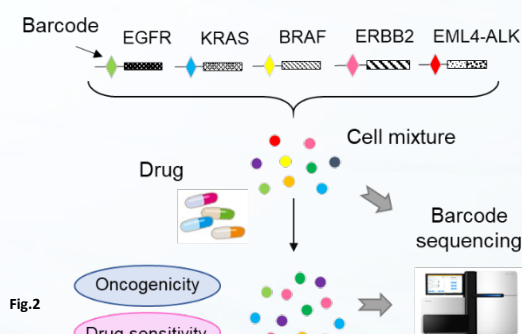
Division Chief: Kennichi YOSHIDA, M.D., Ph.D.

Passion 🔥 Thorough analyses of genetic alterations acquired in normal tissues, precancerous lesions and cancers, we are studying the genetic mechanisms of cancer development and progression.

Mission

- 💡 Study of mutations in normal tissues before cancer development
- 💡 Genetic study of cancers using novel technologies

Innovation

1. Study of mutations in normal tissues before cancer development

All cancers are caused by changes in the DNA sequence of the genomes. Therefore, it is critical to see the driver genetic alterations, which play an important role in the development and progression of cancer, to understand the pathogenesis of cancers and the identification of therapeutic targets. In past, the landscape of driver mutations was shown for most types of cancers using high-throughput sequencing and, more recently, it has been reported that normal tissues are also acquiring somatic mutations including driver mutation, which are caused by aging and environmental exposures. Our group revealed the landscape of somatic mutations in normal bronchial cells and showed the increase of mutation burden caused by tobacco smoking (**Figure 1**) and the prevalence of driver mutations, such as *TP53* and *NOTCH1* mutations (**Figure 2**), which were often acquired in early life (Yoshida et al., *Nature.* 2020).

Figure 1 Somatic mutations in normal bronchial cells
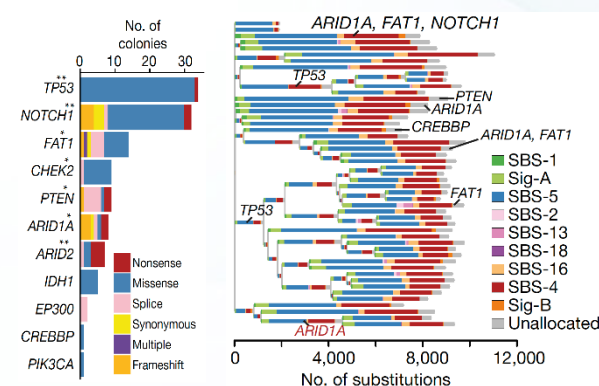
Figure 2 Driver mutations in normal bronchial cells

Our group is studying the genetic alterations in normal tissues, precancerous lesions and cancers, through which we would like to understand the mechanisms of cancer development and progression.
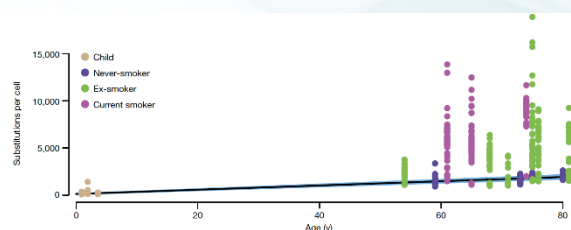

Figure 3 Complex driver rearrangement in AEL

2. Genetic study of cancers using novel technologies

Our group previously identified various driver mutations in cancers including those in RNA splicing factors in myeloid malignancies (Yoshida et al., *Nature.* 2011) (**Figure 3**) and mutations in genes associated with the cohesion complex in myeloid malignancies related with Down-syndrome (Yoshida et al., *Nat Genet.* 2013). We have also recently discovered complex rearrangement involving driver genes, such as *EPOR* and *ERG*, in acute erythroid leukemia (AEL) using whole-genome sequencing (Takeda, Yoshida et al., *Blood Cancer Discov.* 2022). We are studying the genetic alterations in various types of cancers, including hematological malignancies and rare cancers, including pediatric cancers, using novel technologies, such as whole-genome sequencing. We hope that our research will lead to the development of novel diagnostic methods and therapeutics.
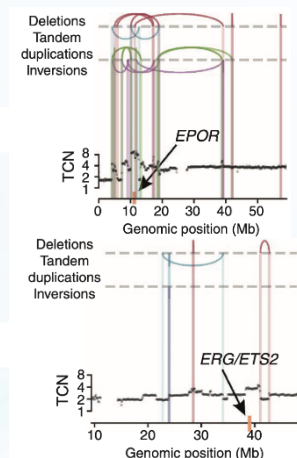
Cancer RNA Research

Division Chief: Akihide YOSHIMI, M.D., Ph.D.

Passion

Through understanding of aberrant RNA processing and the development of mRNA vaccines and nucleic acid therapeutics, we strive to deliver diagnostic and therapeutic solutions to cancer patients with RNA abnormalities.

Mission

- Understanding and targeting aberrant RNA splicing in cancers.
- Drug discovery and biomarker study using a multi-disciplinary platform.

Cancer RNA Research
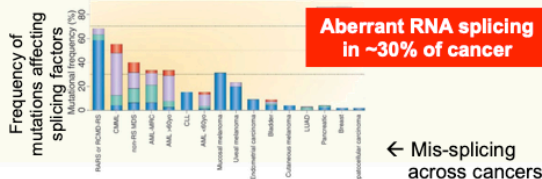The Decoding Team

Innovation

Technologies and expertise for a collaboration:

- Pan-cancer RNA splicing analysis.
- Developing nucleic acid therapeutics.
- Clinical samples (>100,000) and clinical information.
- Spatial analysis.

- Long-read/single cell sequence.
- Multi-omics analysis.
- Preclinical trials using PDX models (>600).
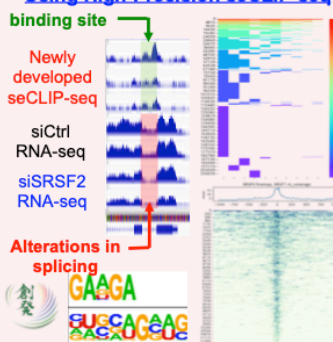- Novel therapy targeting GPCRs.

Cancer Pathogenesis and Development of Therapeutic Methods Focusing on RNA Abnormalities

RNA Splicing as a New Hallmark of Cancer

"RNA splicing" → Removal of introns from pre-mRNA

Aberrant RNA splicing in ~30% of cancer

← Mis-splicing across cancers

Tumor Microenvironment and Development of Therapeutic Methods Using NGS and Spatial Omics

Comprehensive dataset of BLCA

- *Komura K, et al. Mol Cancer. 2023*
- *Komura K, et al. Cancer Sci. 2023*
- *In preparation x4.*

Splicing Regulatory Mechanisms Using High-Precision seCLIP-seq

binding site

Newly developed seCLIP-seq

siCtrl RNA-seq

siSRSF2 RNA-seq

Alterations in splicing

GAAGA
GUGCAGAAG
GACXUGCUC

- *Yoshimi A, et al. Nature 2019*
- *Liu Z, Yoshimi A, et al. Cancer Discov. 2020*
- *In preparation.*

Therapeutic Development Focusing on Neoantigen Production Due to Splicing Abnormalities

スプライシング異

異常蛋白質

がん抗原

MHC

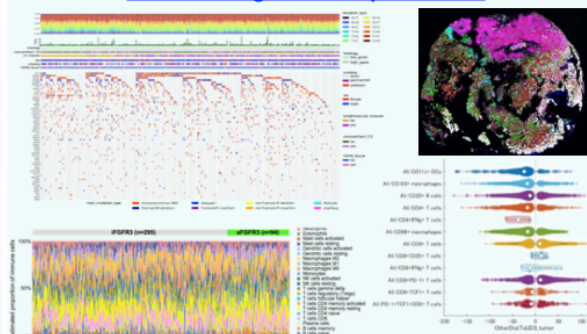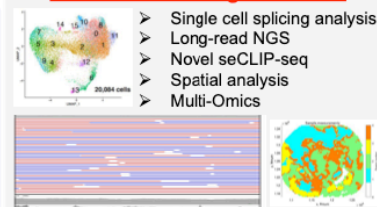腫瘍細胞

Supported by AMED   ● *Just started!*

Therapeutics targeting RNA

- Preclinical trials of a spliceosome inhibitor
- Nucleic acid treatment targeting splicing-associated variants
- Nucleic acid treatment targeting aberrant RNA modification

transcription↑

Promoter

RBP

Driver

Enhancer

Driver mRNA

stability↑   ○ : RNA modification

RBP

ASO

AMED
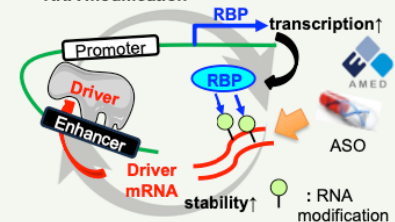
- *Seiler M*, Yoshimi A*, et al. Nat Med. 2018*
- *Shiraishi Y, Yoshimi A, et al. Nat Commun. 2022*
- *In preparation.*

Advanced technologies we have

- Single cell splicing analysis
- Long-read NGS
- Novel seCLIP-seq
- Spatial analysis
- Multi-Omics

⇒**Cancer Drug Discovery targeting aberrant RNA**

Selected publications

- Identified that aberrant splicing coordinates with epigenetic alterations to drive leukemogenesis. (Yoshimi A, et al. *Nature* 2019)
- Pan-cancer RNA splicing analysis revealed that cancer-associated mutations in *SF3B1* activate MYC and BCL2 via mis-splicing in *PPP2R5A* (Liu Z, Yoshimi A, et al. *Cancer Discovery* 2020)
- Reported a novel structural basis for ALK family receptors and their ligands. (De Munck S et al. *Nature* 2021)
- Developed a novel clinical-grade spliceosome inhibitors. (Seiler M, Yoshimi A, et al. *Nature Medicine* 2018)
- Identified splicing-associated variants by analyzing >230,000 RNA-seq data. (Shiraishi Y et al. *Nature Communications* 2022)
- Multi-Omics analysis on FGFR3 alterations and tumor microenvironment. (Komura K et al. *Molecular Cancer* 2023)

Cancer Stem Cell

Division Chief: Kenkichi MASUTOMI, M.D., Ph.D.

Passion 🔥 We conduct research aimed at elucidating the relationship between RNA-dependent RNA polymerase activity, an enzyme activity that we discovered for the first time in the world, and cancer stem cells.

Mission

- 💡 **Biochemical and molecular biological studies on the roles of RNA-dependent RNA polymerase activity in cancer progression and maintenance of cancer stem cells**
- 💡 **Development of cancer therapeutic methods targeting RNA-dependent RNA polymerase activity**

Innovation

Telomerase is a ribonucleoprotein complex that elongates telomeres. Human telomerase reverse transcriptase (TERT) is known as the catalytic subunit of telomerase and acts as an RNA-dependent DNA polymerase (RdDP), which synthesizes telomere DNA repeats from an RNA template TERC. Although the major function of TERT is believed to be telomere elongation, emerging evidence indicates that TERT exhibits various functions beyond telomere maintenance.

Reverse transcriptase activity (telomerase) → Telomere maintenance

RNA-dependent RNA polymerase activity → Tumor formation

We have reported that TERT has RNA-dependent RNA polymerase (RdRP) activity and synthesizes double-stranded RNA (dsRNA) in either a primer-dependent or primer-independent manner. Our recent studies have indicated that post-transcriptional phosphorylation of TERT enhances RdRP activity in TERT without affecting telomerase activity and that TERT RdRP negatively regulates the expression of tumor suppressor genes, eventually leading to cancer progression.

Previous studies have suggested that the constitutive expression of TERT not only stabilizes telomere length and facilitates cell immortalization but also contributes to tumor susceptibility and alters stem cell cycling in vivo even when telomere lengths are not limited.

We found that RdRP activity in TERT directly contributes to cancer progression. We further confirmed that TERT protein expression levels and RdRP activity are positively correlated in various human cancer cell lines, indicating that RdRP inhibitors can work effectively for many types of tumors with high TERT expression levels. We continue to discover and characterize novel inhibitors of TERT-RdRP activity as anticancer drugs.

Cancer cell   RdRP
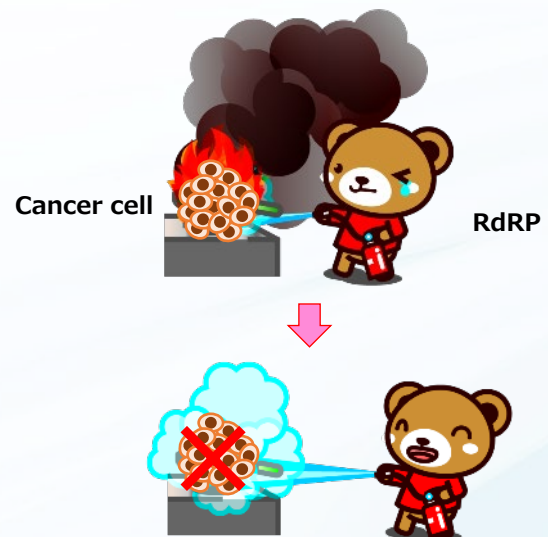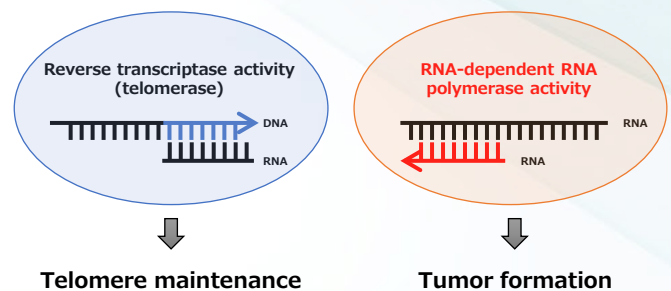
【Reference】
- Maida *et al.* **Nature** 2009
- Okamoto *et al.* **PNAS** 2012
- Maida et *al.* **Mol Cell Biol** 2014
- Yasukawa *et al.* **Nat Commun** 2020
- Matsuda *et al.* **J Pathol** 2022.
- Machitani *et al.* **Nat Cell Biol** 2024

Cancer Genomics

Division Chief: Tatsuhiro SHIBATA, M.D., Ph.D

Passion 🔥

Based on histopathological knowledge, we conduct a comprehensive analysis of cancer genome, epigenome, and gene expression, mainly targeting intractable (e.g. liver, biliary tract, gastric cancers) and rare cancers (e.g., sarcoma, adult T-cell leukemia, pediatric tumors), which are particularly important in Asia.

Mission

- 💡 **Large-scale cancer genome sequencing incl. international collaboration**
- 💡 **Clinical application of genome analysis and development to the next genome medicine**
- 💡 **Development of methods for analyzing cancer genome and epigenome information**

Innovation

The Division of Cancer Genomics is based on histopathological knowledge and utilizes the latest genome analysis technologies such as second- and third-generation sequencers to conduct comprehensive analysis of cancer genomes, epigenomes, and gene expression. We are conducting comprehensive analysis of genomes, epigenomes, and gene expression.

At the same time, we are making international contributions by participating in the International Cancer Genome Consortium (ICGC-ARGO) and the Mutographs project (Cancer Grand Challenge) as a representative group of Japan. The project is also making international contributions.

Through the identification of new cancer-related genes, novel therapeutic targets and biomarkers with a view to the immune microenvironment, estimation of carcinogenic factors by mutation signature analysis, and elucidation of the overall picture of cancer genome diversity, we are working to understand the pathology of cancer from a molecular genetic perspective and to develop personalized cancer treatment, diagnosis, and prevention using whole genome information.

Genome Biology

Division Chief: Takashi KOHNO, Ph.D.

Passion 🔥 *Our objective is to understand the genomes of cancer cells and cancer patients, and to identify seeds that can be targeted for cancer prevention, diagnosis, and treatment to improve cancer genome medicine by clarifying their biological significance and characteristics.*

Mission

- 💡 **Implementation of cancer medical seeds such as RET kinase and NCC Oncopanel test**
- 💡 **Identification of novel therapeutic and preventive target genes by whole genome and RNA sequencing analysis**

Innovation

We discovered that RET kinase gene fusions are present in 2% of lung adenocarcinomas. Furthermore, by elucidating the molecular mechanisms of resistance mutations that arise from treatment and identifying drugs that overcome these resistances, we contributed to the implementation of lung cancer therapies using RET kinase inhibitors (selpercatinib, insurance coverage as of December 2021) (1-3). Additionally, we led the insurance coverage for the NCC Oncopanel test (June 2019), establishing a foundation for cancer genome medicine (4,5). Our laboratory has also produced findings that contribute to cancer prevention and identification of high-risk groups, such as clarifying carcinogenic pathways, identifying genetic factors that predispose individuals to EGFR-mutant lung adenocarcinoma, which is common among Asians, and elucidating mutation-inducing mechanisms due to passive smoking (6-8). Currently, we are conducting research aimed at further developing cancer genome medicine based on whole-genome and RNA sequencing profiles for various cancers, including lung, breast, gynecological, and gastrointestinal cancers (9).

Promoting Cancer Genome Medicine

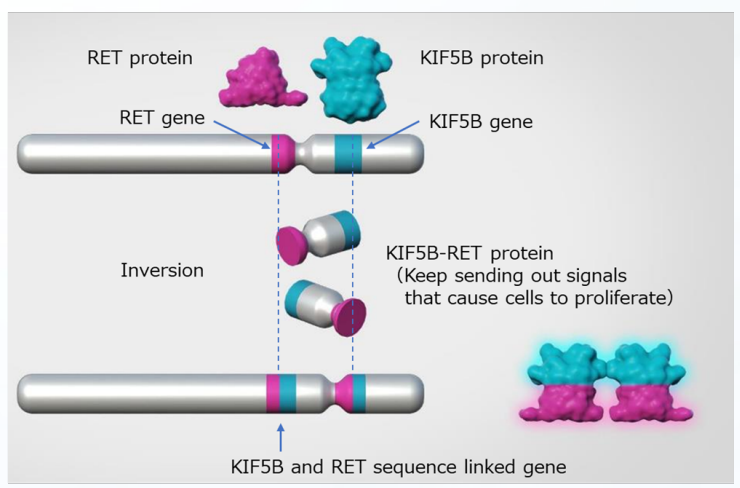**Identification of Therapeutic Targets**
- Identification of RET fusion genes
- Implementation of RET inhibitors

Promotion of Cancer Genome Medicine
- Implementation of the NCC Oncopanel test
- Mother-to-child transmission of uterine cancer

Elucidation of Carcinogenic Risk Factors
- EGFR lung cancer risk and SNPs
- Lung carcinogenesis by passive smoking

RET protein / KIF5B protein — RET gene / KIF5B gene — Inversion — KIF5B-RET protein (Keep sending out signals that cause cells to proliferate) — KIF5B and RET sequence linked gene

【Publications】

1. Kohno T et al. KIF5B-RET fusions in lung adenocarcinoma. *Nat Med*, 2012.
2. Nakaoku T et al. A secondary RET mutation in the activation loop conferring resistance to vandetanib. *Nat Comm*, 2018.
3. Tabata J et al. Novel calcium-binding ablating mutations induce constitutive RET activity and drive tumorigenesis. *Cancer Res*, 2022.
4. Sunami K et al. Feasibility and utility of a panel testing for 114 cancer-associated genes in a clinical setting. *Cancer Sci*, 2019.
5. Arakawa A et al. Vaginal transmission of cancer from mothers with cervical cancer to infants. *N Engl J Med*, 2021.
6. Shiraishi K et al. A genome-wide association study identifies two new susceptibility loci for lung ADC in the Japanese population. *Nat Genet*, 2012.
7. Shiraishi K et al. Association of variations in HLA class II and other loci with susceptibility to EGFR-mutated lung adenocarcinoma. *Nat Comm*, 2016.
8. Mochizuki A et al. Passive smoking-induced mutagenesis as a promoter of lung carcinogenesis. *J Thorac Oncol*, 2024.
9. Haga Y et al. Whole-genome sequencing reveals the molecular implications of the stepwise progression of lung adenocarcinoma. *Nat Comm*, 2023.

Passion

Our lab sequences several types of malignant tumors to reveal how these tumors form and why some of the tumors are refractory to current therapies. We are working on the sequencing analysis of brain tumors and other solid cancers to lead to the development of novel therapies.

Mission

- Investigating the molecular pathogenesis of brain tumors through whole-genome sequencing
- Elucidating the mechanism of U1 snRNA mutations in medulloblastoma
- Unraveling Intratumoral Heterogeneity in Malignant Glioma through Multi-omics Analysis
- Development of Molecular-Based Diagnostic Approaches for Brain Tumors
- Understanding the Biology of Solid Tumors with Multi-omics Approaches

Innovation

Our lab is analyzing sequencing data to reveal the pathogenesis of brain tumors and other solid tumors. We are performing multi-omics to detect therapeutic targets underlying their pathogenesis and therapy resistance.

1. Investigating the molecular pathogenesis of brain tumors through whole-genome sequencing

We revealed the mutational landscape of glioma and medulloblastoma. Those findings are now used in the WHO classification (Suzuki, H. Nat Genet ,2015). We join the national sequencing project as a team of rare cancer where our lab is conducting multi-omics analysis of brain tumors. Our lab is seeking novel targets using the world's largest sequencing data from brain tumors.
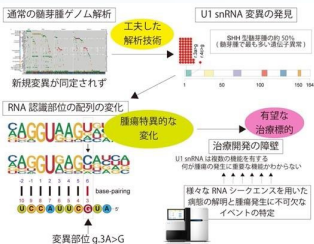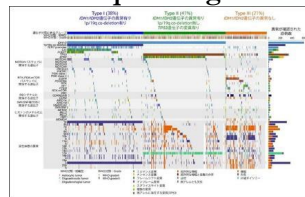
2. Elucidating the mechanism of U1 snRNA mutations in medulloblastoma

Medulloblastoma is the most common pediatric malignant brain tumor. We discovered a novel recurrent mutation in U1 small nuclear RNA using a unique method which can analyze repetitive elements. To reveal the detailed mechanism of U1 snRNA mutations in medulloblastoma, we are analyzing several types of RNA-seq. (Suzuki, H. et al. Nature, 2019)

3. Multi-omics analysis of intratumoral heterogeneity in glioma

Intratumoral heterogeneity contributes to therapy resistance and tumor progression. To reveal the heterogeneity in gliomas, we are analyzing single-cell multi-omics sequencing data. Our analysis would detect the vulnerability of tumor progression which can be a good therapeutic target.
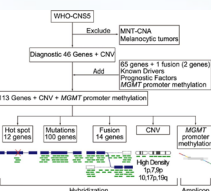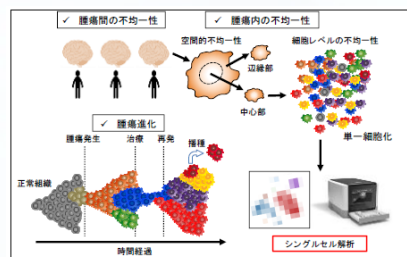
4. Development of Molecular-Based Diagnostic Approaches for Brain Tumors

Our laboratory is actively developing diagnostic methods tailored to brain tumors. We aim to establish systems that can be implemented in clinical settings using these new diagnostic tools.

5. Understanding the Biology of Solid Tumors with Multi-omics Approaches

We are providing bioinformatic analyses to other projects that analyze several solid cancers. We performed extensive genomic analyses, especially urologic cancers. We are analyzing multi-omics data for those tumors and developing non-invasive molecular diagnoses.

Mutational subtypes

Hyper-mutated	TP53/MDM2	RAS	FGFR3	Triple negative
5.5%	37.7%	15.1%	35.2%	6.5%
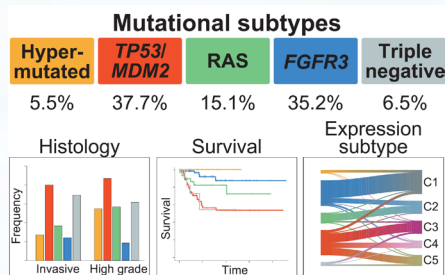
Passion 🔥 By combining genomics with molecular and functional approaches, we aim to 1. genetically dissect the molecular pathogenesis of human cancers; 2. identify novel potential therapeutic targets and/or biomarkers; and 3. establish clinical relevance of genetic alterations.

Mission

- 💡 **Genetic dissection of molecular pathogenesis of human cancers**
- 💡 **Elucidation of roles of genetic alterations in cancer immunity**
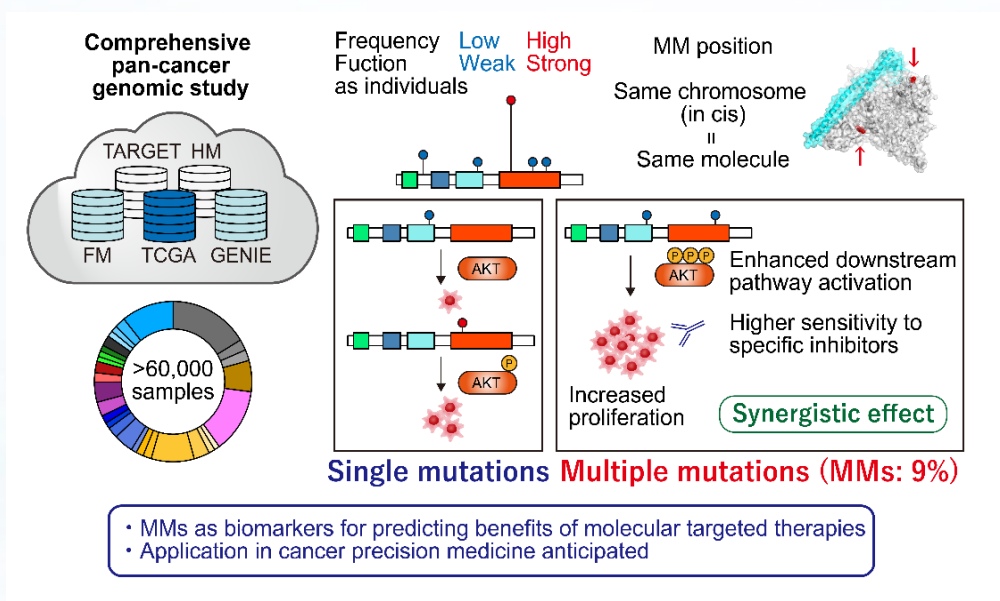- 💡 **Clinical sequencing of hematologic malignancies**

Innovation

Using the above-mentioned approaches, in recent years, we have revealed the genetic portrait of adult T-cell leukemia/lymphoma (ATL) (K Kataoka, Nat Genet. 2015; K Kataoka, Blood. 2018). In addition, we have performed whole-genome sequencing (WGS) of 150 ATL cases to reveal the overarching landscape of genetic alterations, including structural variations and non-coding mutations in ATL (Y Kogure, Blood. 2020).

In addition, by performing pan-cancer analysis based on this study, we identified PD-L1 genetic alterations leading to cancer immune evasion in many cancers (K Kataoka, Nature. 2016). We also performed another pan-cancer analysis and identified a new mechanism whereby multiple mutations in the same oncogene cooperatively drive oncogenesis (Y Saito, Nature. 2020; illustrated in the following figure)

Recently, we have developed a new analytical technique, enabling the combined analysis of transcriptome, surface markers, and T/B-cell receptor repertoires at a single-cell level and characterized premalignant cells in human T-cell leukemia virus type-1 (HTLV-1) infection and the multicellular ecosystem in ATL (J Koya, Blood Cancer Discov. 2021).

As shown in the above, we aim to delineate the entire picture of genetic aberrations in human cancers using NGS. Based on the genetic findings, we will identify novel potential drug targets and/or biomarkers and clarify the molecular pathogenesis underlying the development and progression of cancers. In addition, we will establish clinical significance of these alterations, which can help cancer precision medicine.

Comprehensive pan-cancer genomic study

TARGET HM
FM TCGA GENIE
>60,000 samples

Frequency / Fuction as individuals — Low/Weak, High/Strong

MM position — Same chromosome (in cis) = Same molecule

AKT

AKT — P

Increased proliferation

Enhanced downstream pathway activation

Higher sensitivity to specific inhibitors

Synergistic effect

Single mutations   Multiple mutations (MMs: 9%)

- MMs as biomarkers for predicting benefits of molecular targeted therapies
- Application in cancer precision medicine anticipated

NCCRI / Division of
Genome Analysis Platform Development

Division Chief: Yuichi SHIRAISHI, Ph.D

Passion 🔥

Utilizing information technology, we aim to "decode the dark matter regions of the cancer genome" and "explore new forms of knowledge acquisition.

Mission

- 💡 Development of algorithms and software for cancer genome reconstruction
- 💡 Development of a large-scale genome data analysis platform
- 💡 Contribution to cancer genome medicine

Innovation

Due to recent advances in high-speed data processing technology, it has become possible to comprehensively investigate the diverse mutations in cancer. At the same time, the development of software that accurately identifies abnormalities within vast amounts of data and the creation of data analysis platforms that efficiently process large volumes of information have become significantly more important. Our laboratory aims to develop a genome analysis data processing platform using cutting-edge information technologies such as machine learning, cloud computing, and large language models (LLMs), to gain a deeper understanding of cancer genomes.

1: Development of an Information Analysis Platform for Cancer Genome Reconstruction and Interpretation

We have developed various algorithms and software for cancer genome analysis, including the detection of somatic mutations using Bayesian statistical theory (EBCall, Shiraishi et al., Nucleic Acids Research, 2013), the exploration of splicing mutations (SAVNet, Shiraishi et al., Genome Research, 2018; PCAWG Transcriptome Core Group et al., Nature, 2020), and pattern mining of mutations based on machine learning (Shiraishi et al., PLoS Genetics, 2015). In recent years, we have been advancing the development of software for detecting highly complex forms of structural abnormalities using long-read sequencing data (Shiraishi et al., Nucleic Acids Research, 2023; Nakamura et al., npj Genomic Medicine, 2024). Additionally, we are leading the world in decoding previously largely unexplored genome regions (dark matter regions) such as centromeres.
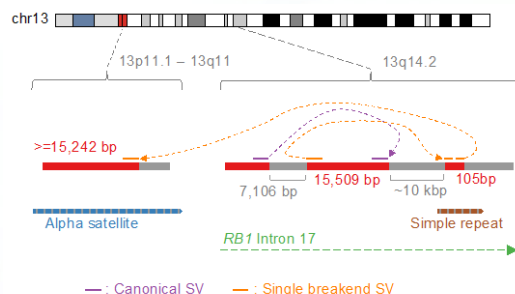

Fig1: Complex structural variation identified by long-read sequencing analysis (Nucleic Acids Research, 2023)

2: Knowledge Discovery from Large-Scale Public Data Analysis

As the implementation of genomic medicine progresses, various omics analyses are actively conducted not only in research but also in medical settings. This has led to the accelerated accumulation of omics data, and discussions on its efficient utilization are ongoing worldwide. We aim to develop a system that autonomously acquires knowledge from large-scale data, bringing innovation to science and medicine. Specifically, we are developing new screening methods for pathogenic mutations using transcriptome data from hundreds of thousands of samples (Shiraishi et al., Nature Communications, 2022; Iida et al., Nature Communications, 2025) and advancing these medical applications in collaboration with our research partners. Additionally, we are exploring new forms of research through large language models (LLMs).
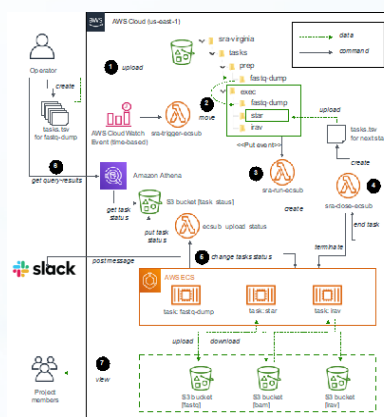

Fig2: Large-scale transcriptome analysis platform on cloud (Nature Communications, 2022).

国立がん研究センター
研究所
National Cancer Center Research Institute

Bioinformatics

Division Chief: Mamoru Kato, Ph.D.

Passion 🔥 Bioinformatics is an emerging academic discipline that combines biology and informatics. This discipline explores living organisms exclusively through computer-assisted experimental data analysis.

Mission

- 💡 **Bioinformatics in genomic cancer medicine**
- 💡 **Pioneering a future cancer genome medicine by numerical simulation**
- 💡 **Data mining for cancer genomics and advancement of bioinformatics**

Innovation

Our laboratory investigates the discipline of "biological informatics," also known as "bioinformatics," which is an emerging academic discipline that combines "biology" and "informatics." This discipline exclusively uses computers to analyze experimental data for studying living organisms. In our laboratory, we are developing bioinformatics approaches ranging from fundamentals to applications, focusing on cancer.

1. Bioinformatics in genomic cancer medicine investigates the diverse technologies required for cancer genomics and genome-based medicine. Current genomic cancer medicine is mainly based on gene panel testing of hundreds of genes. In contrast, we are developing information processing technology for whole-genome and AI for gene abnormality detection software. In collaboration with the Center for Cancer Genomics and Advanced Therapeutics (C-CAT), we are also developing a data format for standardizing data from various cancer genome tests, called the CATS format, and the programs to handle the data, called catstools.

2. In genomic cancer medicine, the application of molecular-targeted medications follows the detection of gene abnormalities, although they do not always result in a satisfactory response. To predict the response of each patient more accurately, we are studying a new type of cancer genome medicine where we simulate to culture cancer cells in a computer and predict drug response, just like a numerical simulation forecast for weather forecasting.

3. We strongly promote collaborative research with experimental laboratories. We are conducting data-mining research that analyzes a large amount of cancer data generated by experimental laboratories to make innovative discoveries. In addition, we are developing bioinformatic technologies that incorporate the perspective of machine learning and process data from new technologies developed by experimental laboratories.

We are a unique bioinformatics laboratory that conducts research keeping in mind the perspective of clinical practice, unlike other researchers who tend to lose this perspective when conducting research. We are establishing our research themes without fear of criticism while encouraging collaborative research that contributes to the mainstream of the field. We intend to develop novel cancer bioinformatics from a global perspective while actively incorporating the most cutting-edge experimental and analytical technologies.

Googol

詳しくは、「生物情報学」と検索！

生物情報学 ×

検索

Passion — We aim to develop optimal cancer therapies by focusing on genetic abnormalities and finding optimal therapeutic targets based on genetic abnormalities characteristic of each cancer patient.
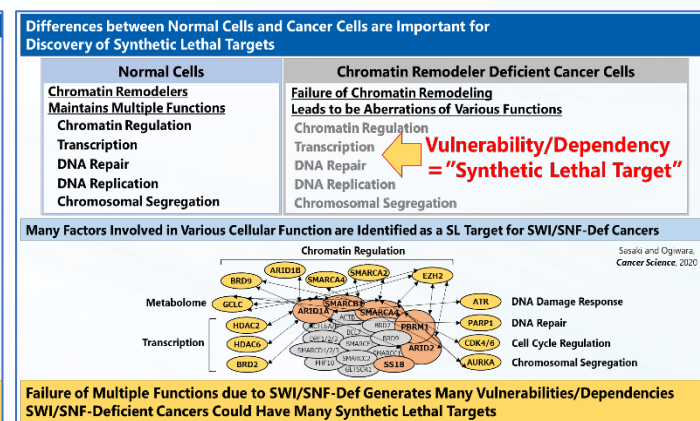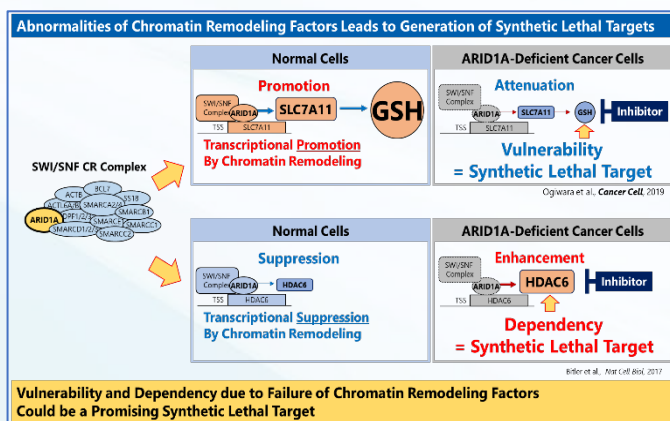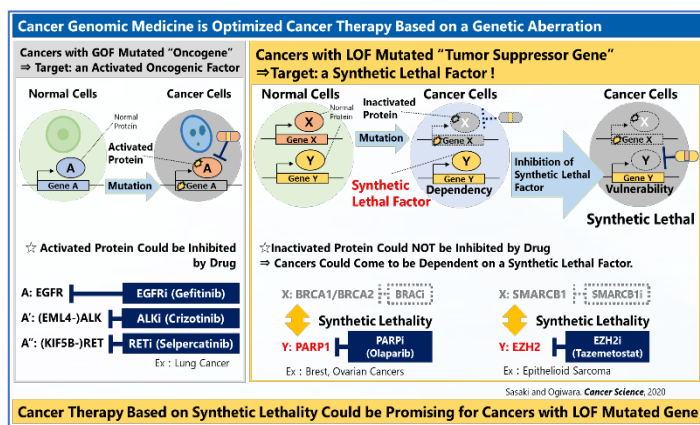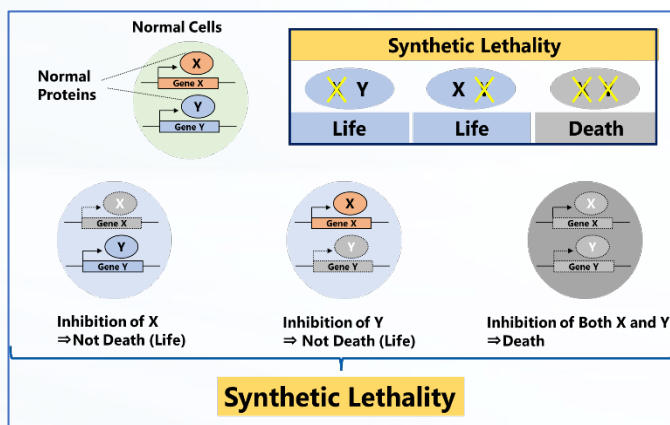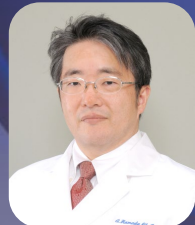
Mission

Identification of promising therapeutic targets for loss-of-function mutated cancers

Innovation

"Cancer Genomic Medicine" is an optimized cancer therapy based on gene aberrations. An oncopanel system using "NCC OncoPanel" became covered by insurance in June 2019. Cancer Genomic Medicine has started in earnest in Japan. Synthetic Lethal Therapy is promising for cancer with the Loss-Of-Function (LOF) gene mutation and is promising due to high cancer specific. Strategy for LOF gene mutated cancers is targeting vulnerability, including such as addiction to complemental genes or functional pathways.

We have been proposed therapeutic strategies for cancer cells. We aim to develop methods for cancer therapy based on gene aberrations in each cancer patient. Specifically, we focus on the development of therapeutic methods for cancer patients with loss-of-function mutations of chromatin regulator genes.

Synthetic Lethality

Cancer Genomic Medicine is Optimized Cancer Therapy Based on a Genetic Aberration

Sasaki and Ogiwara. *Cancer Science*, 2020

Cancer Therapy Based on Synthetic Lethality Could be Promising for Cancers with LOF Mutated Gene

Abnormalities of Chromatin Remodeling Factors Leads to Generation of Synthetic Lethal Targets

Ogiwara et al., *Cancer Cell*, 2019

Bitler et al., *Nat Cell Biol*, 2017

Vulnerability and Dependency due to Failure of Chromatin Remodeling Factors Could be a Promising Synthetic Lethal Target

Differences between Normal Cells and Cancer Cells are Important for Discovery of Synthetic Lethal Targets

Sasaki and Ogiwara, *Cancer Science*, 2020

Failure of Multiple Functions due to SWI/SNF-Def Generates Many Vulnerabilities/Dependencies SWI/SNF-Deficient Cancers Could Have Many Synthetic Lethal Targets

Passion 🔥 Clinical pharmacology & molecular pharmacology section serve as a bridge from bench to bed side and connect the gap between medical practice and laboratory science especially in drug development.

Mission

- 💡 **Development of methods for measuring blood concentrations of antibody drugs using mass spectrometry technology**
- 💡 **Research on the use of molecular imaging**
- 💡 **Development of drug discovery research methods using the Patient derived xenograft (PDx) mode**

Innovation

In phase I clinical trials of anticancer drugs, clinical pharmacology research includes various kinds of analyses such as pharmacokinetics (PK), pharmacodynamics (PD), pharmacogenomics (PGx), toxicology, drug-drug interaction, transporter, and so on. These clinical pharmacological analyses are indispensable for connecting the "Death Valley" between pre-clinical and clinical trials.

In the PK study, it is important to establish analytical methods for drug concentrations in order to understand the movement of drugs in vivo.

In the drug development, the pre-clinical screening model is the key to success in development. The Japanese Cancer Patient-derived Xenograft (J-PDX) Library Program aims to create and serve a high-quality library for PDX models, including clinical information for use in the pharmaceutical industry.

Pharmacology and Therapeutics for accelerating translational research

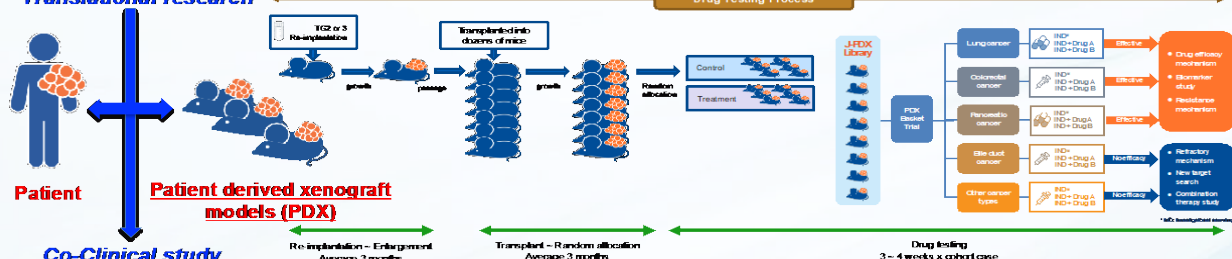**STEP 1** — **PDX with clinical information across cancer types**

STEP 2 — **Developing conventional PK and Imaging PK analysis method**

STEP 3 — **Pharmacokinetic/Pharmacodynamics/Pharmacogenomics**
- Decision support "Go" or "No-go" in a pre-clinical study
- Estimation of optimal dose in a clinical study by receptor occupancy

STEP 4 — **Early phase clinical trial**
- Recruit PDX donor patients to a clinical trial (Co-Clinical study)
- Collect biopsy sample in donor patients
- Estimate the optimal dose and therapeutic effect by receptor occupancy
- Omics analysis by NCC investigators

Rare Cancer Research

Division Chief: Tadashi KONDO, M.D., Ph.D.

Passion 🔥 We investigate the biomarker candidate for diagnosis and personalized medicine and the therapeutic targets in various rare cancers such as sarcomas, GIST, neuroendocrine tumors, and brain tumors.

Mission

- Establishment of fundamental research system for rare cancer
- Sarcoma research
- Reverse innovation

Innovation

A rare cancer is defined as "a malignant tumor with an annual incidence of less than 6 cases per 100,000 population". Due to the small number of cases, rare cancers present various challenges in diagnosis and treatment. The establishment of standard diagnostic and therapeutic methods, the promotion of research and development and clinical trials, and the establishment of a medical care system are important issues for rare cancers.

Despite its name, rare cancers are not rare. Nearly 200 types of cancers are considered rare cancers because "rare cancers" are defined by their extreme low frequency of occurrence. As a result, approximately 15% of all newly diagnosed cancers in Japan are classified as rare cancers. Therefore, it can be said that research on rare cancers is socially important research that targets a larger number of patients than any other cancer.

We will introduce our approach to the issues of rare cancers below.

[Research applicable to rare cancers in general: construction of research infrastructure]

Due to the difficulty in obtaining clinical specimens for rare cancers, the basic tools necessary for research have not been developed. For example, patient-derived cancer models are essential tools for developing new therapies, but are rarely available for rare cancers. We have constructed a patient-derived cancer model as a research base necessary for research on rare cancers, and have it used by researchers and companies upon request. I would like to generalize the know-how of model system construction obtained in the process and use it to promote rare cancer research.

[Research on specific rare cancers: development of biomarkers]

We are developing biomarkers that are useful for determining treatment strategies such as indications for anticancer drugs. Specifically, we are identifying molecules involved in therapeutic efficacy and resistance based on molecular background data obtained through proteogenomics. As part of such activities, we participate in the International Cancer Proteogenomics Consortium (ICPC). At the ICPC, Japan is in charge of sarcoma, and we are trying to build an international joint research system by promoting data sharing.

[Reverse Innovation]

The problem of "difficulty in obtaining clinical specimens hinders research" is not limited to rare cancers. Even for common cancers, stratification of patients based on molecular background will eventually lead to rare fractions. In that situation, the know-how of rare cancer research would be useful. We are developing various technologies and applications, keeping in mind the application to other cancers.

Cancer Immunology

Division Chief: Hiroyoshi NISHIKAWA, M.D., Ph.D.

Passion 🔥 By integrating various omics analyses such as basic immunology, genomics, and metabolism, we are elucidating the true nature of antitumor immune responses in the cancer microenvironment while conducting basic to translational research for the development of new cancer immunotherapies.

Mission

- 💡 Elucidating nature of cancer immune responses using multi-omics immunological analysis
- 💡 Developing novel immune cell therapies that is sustainably effective in the solid tumor microenvironments

Innovation

Elucidation of essential antitumor immune responses and identification of biomarkers in cancer immunotherapy

We have elucidated multiple mechanisms by which cancers could be resistant against immuno-therapies, and identified biomarkers that can identify responders to the specific immune therapies using multi-omics analysis including multicolor flow cytometry, mass cytometry, imaging mass cytometry, and single-cell transcriptome analysis (Figure). These findings are highly valuable as clinically applicable biomarkers and as therapeutic targets for the new drug discovery.

Establishing transparent mouse models that enable visualization of immune cell distribution in the TME

To further analyze how host immune cells works in the TME, we have established transparent mouse models that can visualize dimensional distribution of immune cells in the host tumors and organs. We are now analyzing how immune cells infiltrate to, exert functions and sustain in the TME using a brain tumor mouse model.

Developing novel CAR/TCR gene modified T cell therapies for solid tumors.

From above comprehensive immunological analysis, we have identified multiple targetable factors that has dominant role to limit sustained activity of host-immune reactions. By targeting these therapeutic findings, we are developing novel CAR/TCR T cell therapies. Some of our CAR/TCR T cell pipelines are under preclinical testing aiming for the first-in-human trial.

Kobayashi T, Nishikawa H, et al. *STAR Protocols* Sep 16 2022
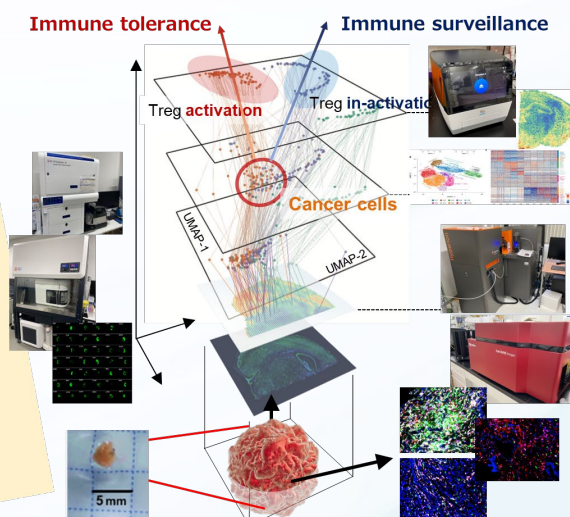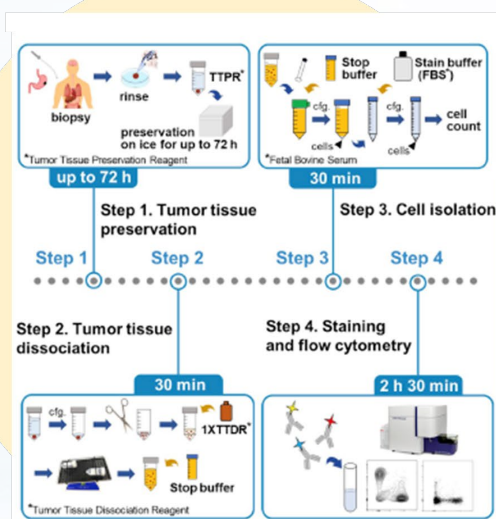
NCCRI / Division of
Medical AI Research and Development

Division Chief: Ryuji HAMAMOTO, Ph.D.

Passion 🔥 Using latest artificial intelligence technology, we engage in the development and research of new cancer diagnosis systems, support systems to realize personalized medicine, and novel drug discovery design systems.

Mission

- 💡 **Development of AI-equipped medical devices for clinical application.**
- 💡 **Multi-omics analysis using machine learning for integrated understanding of cancer.**
- 💡 **Construction of an integrated database system as a foundation for medical AI R&D.**

Innovation

Expectations for artificial intelligence (AI) technology have been increasing in recent years due to advances in machine learning technology, especially deep learning, the development of inexpensive and high-performance GPUs, and the expansion of public databases, which has enabled the utilization of big data. In fact, AI technology is already widely used in society, for example, in facial recognition at airports, automatic translation, and self-driving. The medical field is no exception, with more than 1000 AI-equipped medical device programs approved by the U.S. FDA, and several AI-equipped medical device programs, including our own, have received regulatory approval in Japan. In Japan, the Fifth Science and Technology Basic Plan approved by the Cabinet in January 2016 announced the concept of a new society called "Society 5.0," and clearly stated that AI technology will be used as a fundamental technology to achieve this goal. The government's policy is to utilize AI technology as one of the key areas of focus.

Under these circumstances, in 2016, we launched a large-scale medical AI R&D project, "Development of an Integrated Cancer Care System Using Artificial Intelligence," as the pioneering project of its kind in Japan. This research project was promoted as one of JST's CREST projects, and has been developed into a public-private investment expansion program (PRISM) led by the Cabinet Office from 2018, and a bridge program between R&D and Society 5.0 (BRIDGE) led by the Cabinet Office from 2023, In 2023, the program will be expanded to include the Cabinet Office-led BRIDGE program, which bridges research and development with Society 5.0. During this period, we have developed a world-leading real-time endoscopic diagnosis support system using AI, and have published several important research results, including the construction of a large-scale integrated database for lung cancer oriented to AI analysis.

In particular, we have already achieved multiple results in clinical applications, such as obtaining pharmaceutical approval for a real-time endoscopic diagnosis support system using AI as a controlled medical device (Class II) in 2020 (Japan: 3 cases of pharmaceutical approval, 1 case of certification based on the Pharmaceutical Affairs Law; Europe: 2 cases of CE marking).

Our priority is to always conduct "research for patients" without falling into "research for research's sake". We publish original papers in high quality international journals, and at the same time, we place great importance on clinical applications.

Division of Medical AI Research and Development
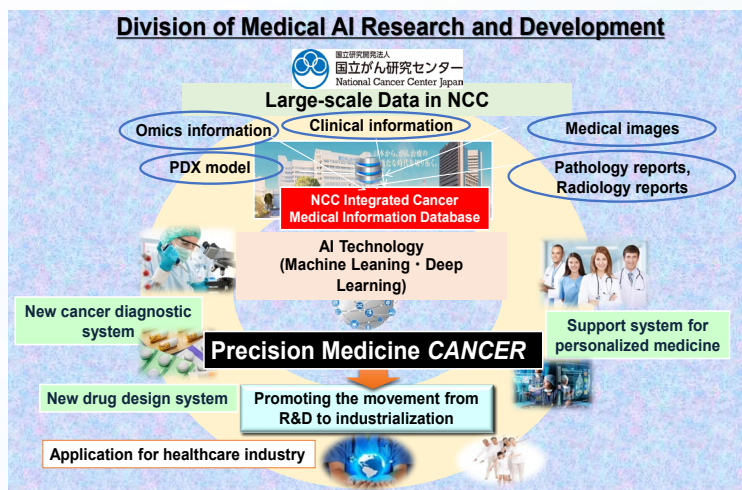
Passion 🔥 We perform single-molecule imaging of oncogenic products and receptors in living cells to elucidate how these molecules function and to develop new therapies.
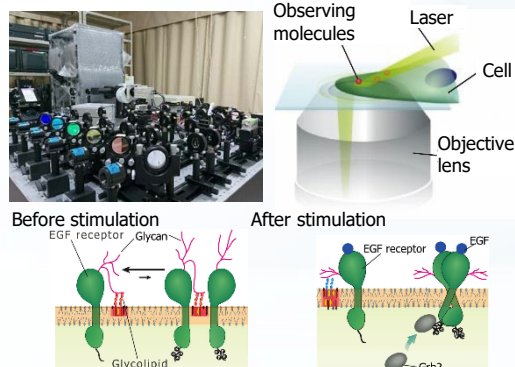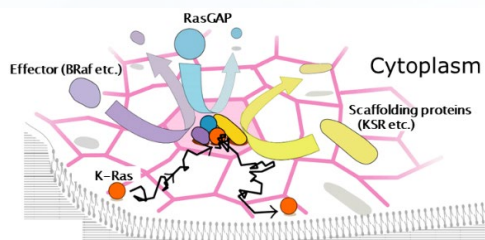
Mission

- Unraveling of oncogenic signaling mechanisms by single-molecule and super-resolution microscopy
- Visualization analysis of signaling platforms such as lipid rafts and liquid-liquid phase separation
- Unraveling of mechanisms of target cell modification by tumor-derived small extracellular vesicles
- Development of novel microscopic systems

Innovation

Intracellular molecules undergo thermal motion and molecular interactions occur stochastically for short periods. To elucidate dynamic molecular mechanisms in cells, we follow the behaviors of each individual molecule. (Tanaka et al., Nat. Methods, 2010; Suzuki et al., Nat Chem. Biol, 2012; Komura et al., Nat Chem Biol. 2016; Morise et al., Nat. Commun., 2019; Kemmoku et al., Nat. Commun., 2024; Hirosawa et al., Nat. Commun., 2025). In particular, we attempt to understand the essential nature of events by performing simultaneous multi-color, ultra-fast, single-molecule/super-resolution microscopic observation of oncogenic products and receptors in living cells.

1. Unraveling of oncogenic signaling mechanisms by single-molecule and super-resolution microscopy

By simultaneous single-molecule observation of receptor-type tyrosine kinase and oncogenic products such as Ras, we attempt to elucidate the signaling mechanisms at the molecular level in living cells. For example, we demonstrated that after activation, K-Ras clusters are localized in specific lipid domains in the inner leaflet of the plasma membrane, and the downstream signaling molecules such as Raf and RasGAP are recruited to K-Ras in the lipid domain.

2. Visualizing analysis of signaling platforms

Cellular structures such as lipid rafts and liquid-liquid phase separation, are supposed to be keys for oncogenesis and the efficacy of anticancer drugs. However, their entity is not well understood due to their small and dynamic nature. We attempt to elucidate these structures and functions by single-molecule and super-resolution microscopy.
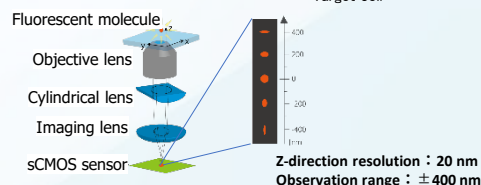
3. Unraveling of mechanisms of target cell modification by cancer-derived small extracellular vesicles (sEVs)

Cancer-derived sEVs are reported to play critical roles in the metastasis of the cancer cells. However, the mechanisms of the binding, uptake, and function of sEVs in the target cells remain enigmatic. We attempt to elucidate the mechanisms by single-molecule and super-resolution microscopy.
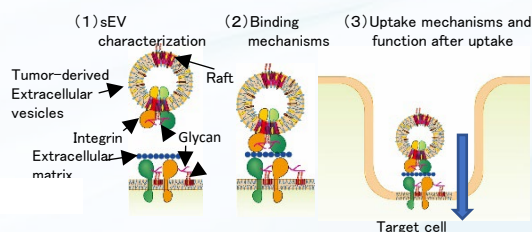
4. Development of novel microscopic systems

We attempt to improve the 3D, single-molecule imaging and super-resolution microscopy at high resolution. This allows us to track interactions and changes in more diverse molecules and structures within the cells.

Z-direction resolution：20 nm
Observation range：±400 nm

NCCRI / Division of
Integrative Cancer Research
Division Chief: Tomotaka UGAI, M.D., Ph.D.

Passion 🔥 Collaborating with international research institutions, we conduct a variety of large-scale population science studies, to elucidate the carcinogenic mechanisms and to develop personalized preventive and treatment strategies.

Mission

- 💡 Elucidate the carcinogenic mechanisms affected by a variety of intrinsic and extrinsic factors

- 💡 Develop scientific evidence to develop precision oncology

Innovation

【**Global Descriptive Epidemiology**】

We are investigating global cancer incidence and mortality trends using global cancer databases. We particularly focus on early-onset cancers, incidence of which has increased worldwide.

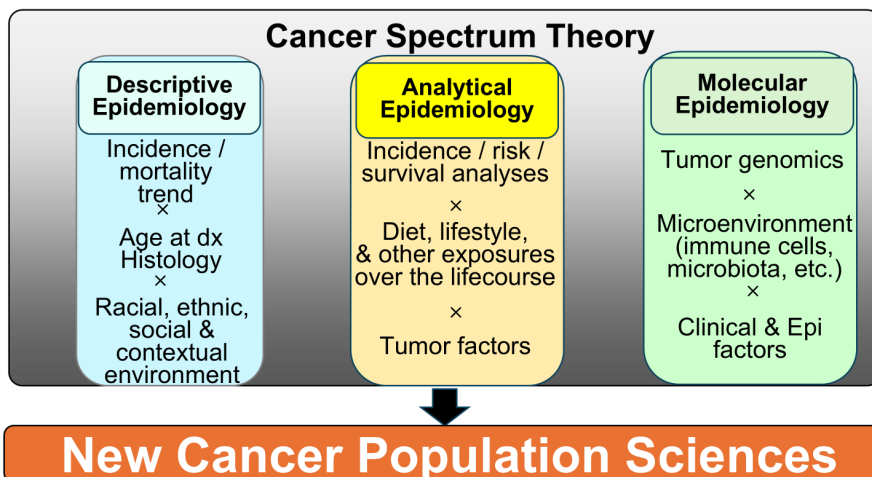【**Integrative Analytical Epidemiology**】

We elucidate causality in the association between exposures and disease risk by integrating biomarkers into large-scale population studies. We have been examining interactions of diet (nutrition), medication use, lifestyle variables, and tumor molecular, microbial, and immune characteristics in relation to the incidence and mortality of cancer.

【**Integrative Molecular Epidemiology**】

We have been analyzing germline and somatic genomics, epigenomics, tumor-infiltrating immune cells, and microbiota in human tumors.
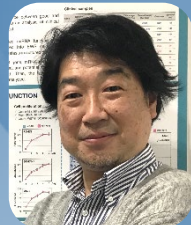
We are recruiting new lab members who are interested in integrating multiple fields and leading interdisciplinary population sciences in novel directions.

Integrative Cancer Spectrum Approach

Cancer Spectrum Theory

Descriptive Epidemiology	Analytical Epidemiology	Molecular Epidemiology
Incidence / mortality trend × Age at dx Histology × Racial, ethnic, social & contextual environment	Incidence / risk / survival analyses × Diet, lifestyle, & other exposures over the lifecourse × Tumor factors	Tumor genomics × Microenvironment (immune cells, microbiota, etc.) × Clinical & Epi factors

New Cancer Population Sciences

【Key publications】
- Ugai T et al. Is early-onset cancer an emerging global epidemic? Current evidence and future implications. Nat Rev Clin Oncol. 2022 Oct;19(10):656-673.
- Lee H, … Ugai T. The Cancer Spectrum Theory. Cancer Discov. 2024 Apr 4;14(4):589-593.
- Ugai S, … Ugai T. Long-term yogurt intake and colorectal cancer incidence subclassified by Bifidobacterium abundance in tumor. Gut Microbes. In press.
- Ugai T et al. Molecular Characteristics of Early-Onset Colorectal Cancer According to Detailed Anatomical Locations. Am J Gastroenterol. 2023 Apr 1;118(4):712-726.

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National Cancer Center Research Institute

Molecular Carcinogenesis

Lab Chief: Naoto TSUCHIYA, Ph.D

Passion

By focusing on microRNAs and knowing their functions, we develop an understanding of the molecular mechanisms of carcinogenesis while conducting basic research that contributes to new cancer therapies and diagnostic methods.

Mission

- Regulatory mechanisms of intracellular networks through microRNA structural diversity
- Analysis of tumor Microenvironment regulation and metastasis induced by microRNAs
- Development of Cancer Diagnostic Biomarkers Using MicroRNAs

Innovation

Our genome contains information for thousands of non-coding RNAs. These RNAs play essential roles in normal development. Dysfunction in these molecules is closely linked to the onset of various human diseases, including cancer.

Our research unit focuses on small RNAs called microRNAs. In normal cells, the precise function of microRNAs is crucial for regulating complex molecular networks. However, in cancer cells, these functions become disrupted. By understanding the intracellular networks governed by microRNAs, we aim to gain deeper insights into cancer biology. Our findings have the potential to contribute to the development of novel cancer therapies.
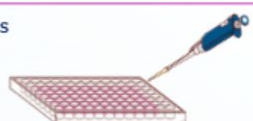
MicroRNAs undergo structural diversification during their intracellular biosynthesis, resulting in the production of multiple structural isoforms. However, the relationship between these isoforms and their functions remains unclear. Our laboratory has discovered that abnormalities in the synthesis of microRNA structural isoforms play a critical role in determining the malignant properties of cancer. Furthermore, we have identified IGF2BP3, an oncofetal gene, as a key molecular factor involved in this process. We are conducting fundamental research to uncover the mechanisms underlying microRNA dysregulation in cancer cells. Our findings could provide new insights into the mechanisms of gene expression abnormalities in cancer malignancy and pave the way for the development of diagnostic and therapeutic agents.

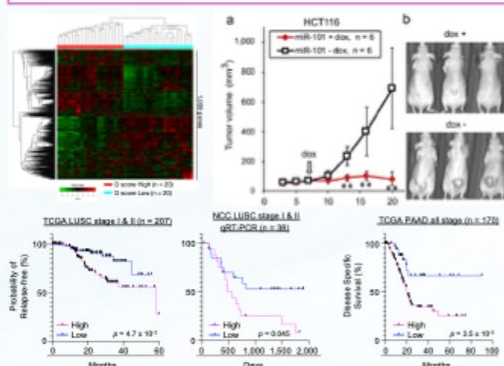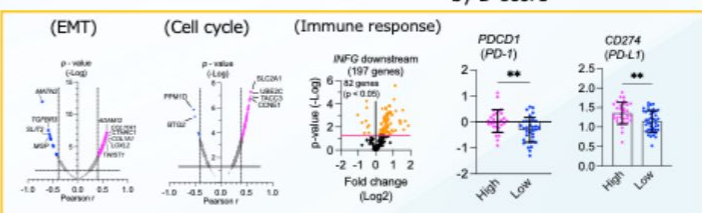**Passion** 🔥 Research on the p53 gene will greatly contribute to elucidating the nature of cancer and its clinical application.

Mission

💡 We will elucidate the novel function of the tumor suppressor gene p53, which is the most well-known tumor suppressor gene and the most frequently mutated gene in human cancers.

Innovation

Elucidation of the functions of the tumor suppressor gene p53 and its target genes

p53 responds to a variety of stresses on the cell and its job is to ensure that these cells do not become cancerous. In addition, in cases where p53 cannot adequately counter these stresses, it can instruct the cells to die by apoptosis. p53-deficient mice are extremely cancer-prone with 75% dying within half a year, underlying the significance of p53 in cancer. p53 is a transcription factor that activates the transcription of various genes depending on the intensity and type of stress to which the cells are subjected. p53 halts the cell cycle and prevents overgrowth, and as mentioned above can also trigger apoptosis in some cases. Advances in technology, such as gene expression analysis using microarrays and analysis of the DNA sites to which p53 protein binds in the cell, have enabled a comprehensive analysis of p53 and the identification of now 235 genes regulated by p53. p53 is very well-known and accordingly, many researchers around the world have performed analyses similar to ours. We, therefore, focused our functional analyses on genes whose functions were unknown at the time, and this has helped us become one of the world leaders in research on the regulation of cancer by p53 (Cell, 136, pp. 535-550, 2009 , PNAS, 111, E2404-E2413, 2014, PNAS, 122, No. 6, e2413126122, 2025).

Newly discovered tumor suppressor gene PHLDA3

PHLDA3 is one of the genes with unknown functions found through an exhaustive search for potential p53 target genes. We have shown that the PHLDA3 protein, which is induced by p53, regulates oncogenic signals by inhibiting the cancer-promoting function of the protein product of the Akt oncogene (Cell, 136, pp. 535-550, 2009). When p53 is mutated, PHLDA3 is not expressed, and therefore Akt is not suppressed. As we mentioned earlier, half of all cancers have a mutation in p53, and among the half in which p53 is not mutated, some have been found to lack PHLDA3 function.

This discovery was a key to understanding pancreatic neuroendocrine tumors, a disease that caused the death of Apple founder Steve Jobs. The pancreatic islets of Langerhans secrete hormones such as insulin. When these islets become cancerous, we often observe a loss of PHLDA3 gene function and hyper-activation of AKT, a phenotype that indicates a poor prognosis for the patients (PNAS, 111, E2404-E2413, 2014). PHLDA3-deficient mice exhibit abnormal proliferation of the islets of Langerhans, although this alone does not result in cancer in these animals. The relationship between the loss of PHLDA3 function and the promotion of cancer is found not only in the pancreas but also in tissues such as the lungs and large intestine, which are also endocrine tissues. Thus, PHLDA3 may be a universal tumor suppressor gene for endocrine tissues.

NCCRI / Independent Unit of

Molecular Genetics

Lab Chief: Haruna TAKEDA, Ph.D.

Passion 🔥 Using genetic approaches such as genetically modified mice, SB transposons, and CRISPR-Cas9, we explore the molecular mechanisms that regulate cancer.

Mission

- 💡 Understanding the cancer microenvironment driving CRC metastasis
- 💡 Elucidate the mechanism of CRC promoted by inflammation or high-fat diet intake
- 💡 Development of novel therapeutic approaches focusing on the metabolic characteristics of CRC

Innovation

Our research focuses on colorectal cancer, aiming to establish novel therapeutic and preventive methods. We have identified a number of CRC-related genes (Nat Genet, 2015) and gastric cancer-related genes (PNAS, 2016) using our unique Sleeping Beauty (SB) transposon-based in vivo screening method. This approach allows us to identify genes that are found in human cancers (Figure 1).

Recently, we performed SB screening in a colitis model and showed that malignant progression is induced by cellular plasticity in the inflammatory microenvironment (Nat Commun, 2023; BMC Cancer, 2025) . In the study, we succeeded in creating a spontaneous CRC metastasis model, and are now using this model to search for therapeutic targets using state-of-the-art expression analysis technology (Figure 2).

Since the obesity population is increasing worldwide, we have developed an obesity model and are conducting SB screening to clarify the relationship between obesity and colorectal cancer at the molecular level. The findings from this research will lead to the establishment of cancer prevention methods.

Fig. 1. Sleeping Beauty transposon screening
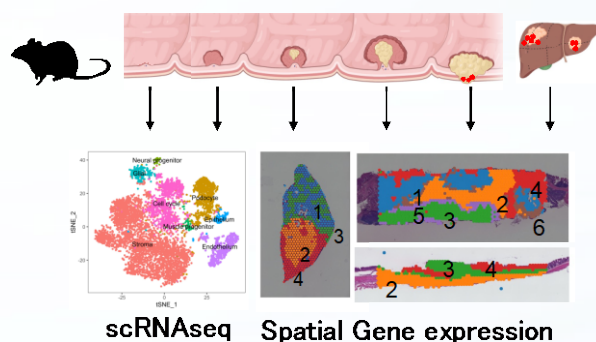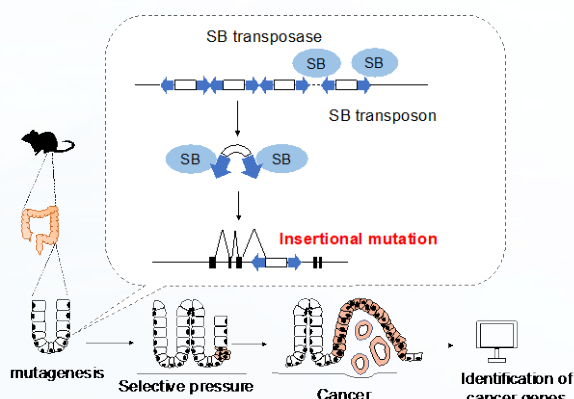

scRNAseq   Spatial Gene expression
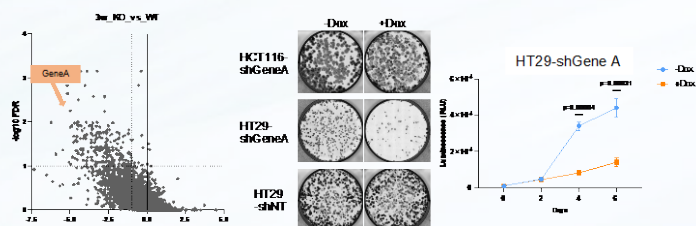
Fig.2 Identification of metastasis-specific markers using our SB models

Furthermore, we have found that some CRC cell lines have vulnerabilities in metabolic pathways through comprehensive CRISPR knockout screening, and we hope to use these unique findings to establish new therapeutic methods.

Fig3. Knockdown of GeneA susceptible to growth suppression in APC-mutant CRC cell lines

NCCRI / Independent Unit of
Genome Stability Maintenance

Lab Chief: Ken-ichi YOSHIOKA, Ph.D.

Passion — Most cancers are inevitably developed with genomic instability. This implies a possibility of cancer prevention with genome stability maintenance. Our major aim is innovation of cancer-prevention drugs and supplements.

Mission

- Characterization of a cellular state risking genome stability
- Study of regulation for genome stability maintenance
- Innovation of cancer-prevention drugs and supplements
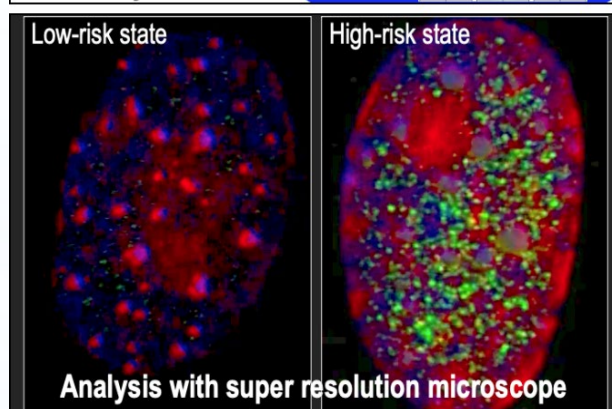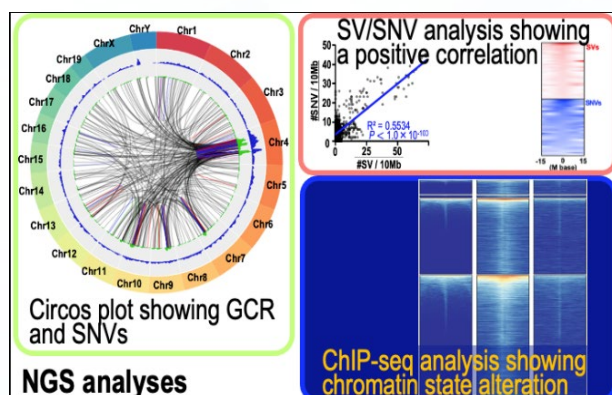
Innovation

Cancer is widely developed with genomic instability. Our previous studies revealed that oncogenic clonal evolution can be caused with genomic instability, in which gross chromosomal rearrangements (GCR). GCR induction is usually caused by replication stress-associated DNA double strand breaks (DSBs) through the resulting erroneous repairs. Such GCR is further correlated with single nucleotide variant (SNV) induction. Those correlated GCR and SNV inductions are widely seen in cancer cells. These lines of knowledge pose an attractive hypothesis: cancers caused with genomic instability might be preventable with genome stability maintenance. However, still a question is how risk of genome stability is elevated and regulated, because many cancers developed with GCR do not show any background mutations in repair systems. We have developed an *in vitro* model system and are studying (1) factors risking genome stability and (2) regulations enabling genome stability maintenance.

(1) Factors risking genome stability

Our recent studies revealed that (1) risk of genome stability arises upon replication stress-associated DSBs when cells express senescence-associated phenotypes (Cancer Sci. 2021, 112: 515), (2) clonal evolution of cells with mutation in the ARF/p53 pathway is induced with genomic instability (Nature Com. 2019, 10: 3925), and (3) risk of genome stability elevates with exogenous stresses, such as radiation exposure (iScience 2021, 24: 102313). We are currently studying the effects of epigenetic regulation, cellular senescence, and UV exposure.

(2) Regulations enabling genome stability maintenance

We previously revealed that (1) cells at high-risk state still have a pathway to transiently activate DSB repair systems (Cell Rep. 2015, 13: 2728) and (2) polyphenols that reveal cancer-prevention phenotype induce DSB repair and the effects of genome stability maintenance (Sci. Rep. 2020, 10: 5388). We are currently pursuing the screening of compounds that induce the effect of genome stability maintenance and studying those effective points and the cancer prevention effect using animal models. Here, our aim is the innovation of cancer prevention drugs and/or supplements.

Circos plot showing GCR and SNVs

SV/SNV analysis showing a positive correlation

NGS analyses

ChIP-seq analysis showing chromatin state alteration

Low-risk state

High-risk state

Analysis with super resolution microscope

Cancer Cell Systems

Lab Chief: Keisuke SEKINE, Ph.D.

Passion 🔥 Through a cell biology approach focusing on organoid technology, we conduct research aimed at elucidating the cancer cell society and developing novel therapies.

Mission

- 💡 Establish patient-derived cancer organoids
- 💡 Model human cancer tissue and metastatic tissue in vitro
- 💡 Elucidate and control cancer ecosystems using artificial cancer tissue

Innovation

Background

Cancer ecosystems, the cancer cell society in cancer tissue, include not only cancer cells, but also various stromal cells such as mesenchymal and vascular endothelial cells. To analyze cancer cell-stromal cell interactions and to accurately assess drug susceptibility, a culture system capable of recapitulating cancer ecosystems is essential.

Modeling human primary and metastatic cancer tissues in vitro

It is an urgent issue to understand the characteristics of intractable cancers such as pancreatic cancer and develop treatments. In recent years, it has become clear that stromal cells have a significant effect on treatment resistance of cancers. It is important to reproduce cancer microenvironments including metastatic cancer tissue microenvironments in vitro. Therefore, using the artificial reconstitution method of normal tissue with stroma (Nature, 2013, Nature 2017), we established a culture system to reproduce the cancer microenvironment using primary cancer cells isolated from patients.
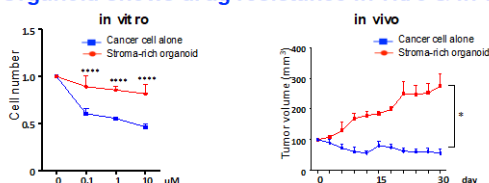
Elucidation and control of the cancer ecosystem using artificial cancer tissue

We are conducting research using organoid technology by a cell biological approach to elucidate cancer ecosystems. We are elucidating the dynamics, interactions, and metastasis mechanisms by comprehensive gene expression analysis at the single cell level, genomic analysis, drug responses, and modification technology using our human organoid culture technology that recapitulates the cancer ecosystem. Additionally, we are analyzing animals (in vivo studies) and patient specimens, and performing comparative studies in vitro. Ultimately, we are trying to save the lives of cancer patients through basic cancer research.
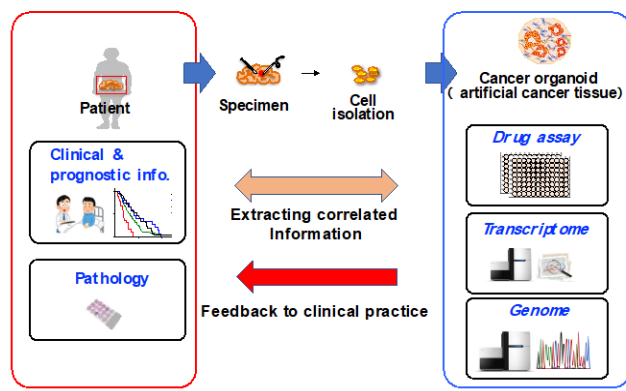

Generation of pancreatic cancer tissue recapitulating tumor micro-environment
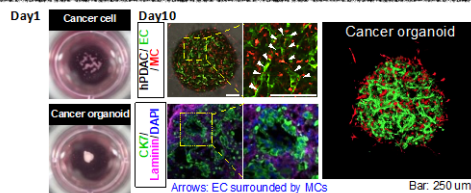
Organoid shows drug resistance in vitro & in vivo

Elucidation and control of cancer ecosystem using artificial cancer tissue

NCCRI / Independent Unit of
Integrative Oncology

Lab Chief: Yusuke YAMAMOTO, Ph.D.

Passion 🔥 Our research focuses on cancer diversity and micro-environment through genetically engineered carcinogenesis models and primary cultures of patient-derived cells.

Mission

- 💡 Develop Cancer Therapeutics Based on Gene Mutations
- 💡 Understand Cancer Diversity by Single-cell Approaches
- 💡 Develop Novel Diagnostic Tools by miRNAs and Exosomes

Innovation

The Laboratory of Integrative Oncology aims at elucidating the diversity of cancer cells and the microenvironment within tumors. As is the case with cancer biology and pathology, the nature of cancer cells is complex and full of diversity. To understand these characteristics of cancer cells, it is essential to take a multifaceted approach, which requires technological innovation and imaginative research ideas. Specifically, we use bio-imaging, single cell expression analysis, screening with compound libraries, and tissue stem cell culture techniques. Based on our accumulated experience in these areas, we are constantly challenging to develop new therapeutic and diagnostic strategy as well as elucidating cancer biology.

### 1. Develop Cancer Therapeutics Based on Gene Mutations

We search for novel therapeutic targets against cancers with specific genetic mutations and rare cancers for which few treatments are available, e.g. the identification of drugs with selective antitumor effects against lung cancer cells with KRAS mutations (Cancer Lett. 2019; JCI Insight. 2021) and the validation of novel therapeutic agents for uterine leiomyosarcoma (Clin Cancer Res. 2022).

2. Understand Cancer Diversity by Single-cell Approaches

Gene expression analysis at the single cell level is used to analyze cellular diversity within tumors and the cells within the cancer microenvironment. We showed drug resistance mechanisms in breast cancer (Cancer Res. 2019), analysis of early cancer diversity (Cancer Res. 2022), examination of smoking effects on lung (Cancer Res Commun. 2023), and inflammatory diseases (ARJCMB. 2022).

3. Develop Novel Diagnostic Tools by miRNAs and Exosomes

Intercellular communication by exosomes has attracted much attention for its impact on cancer biology. We have been working to analyze the function of exosomes secreted by cancer cells (Nat Commun. 2017; Oncogene. 2019) and to elucidate the mechanisms of their secretion from cancer cells (Sci Adv. 2020; Cell Rep. 2024).

Intracellular Traffic & Oncology

Lab Chief: Yuuki OBATA, Ph.D.
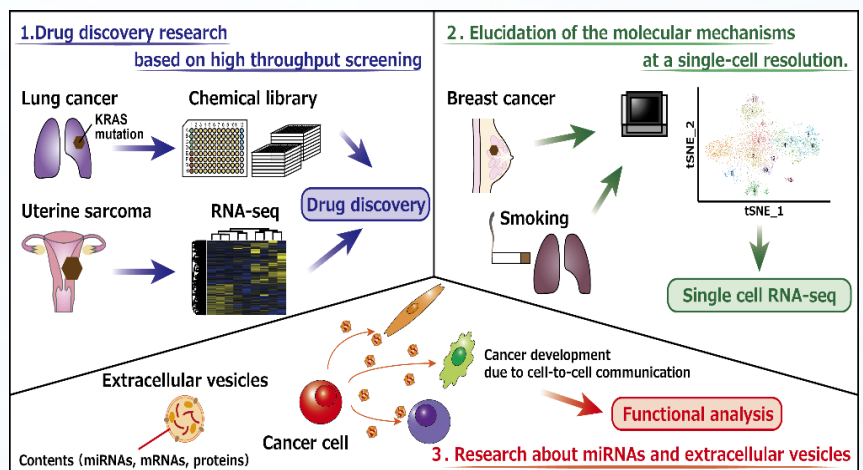
Passion 🔥 Intracellular localization of signaling molecules in cancer cells is strikingly different from that in normal cells. We investigate the mechanism of aberrant localization of cancer-causing mutants to develop a new strategy for the inhibition of oncogenic signaling.

Mission

- 💡 Spatio-temporal analysis of mislocalization of cancer-causing RTKs
- 💡 Identification of cancer-specific intracellular trafficking mechanisms
- 💡 Development of a novel strategy for the inhibition of oncogenic signals

Innovation

Gain-of-function mutations in receptor-type tyrosine kinases (RTKs) are critical drivers for cancerization. Considering that in normal cells, wild-type RTKs are localized to the plasma membrane to send signals, RTK mutants have been thought to be distributed on the cell surface membrane. However, we found that mutant RTKs, such as KIT and FLT3, are aberrantly localized in the intracellular compartments such as the Golgi apparatus and endosomes. These predominantly cause downstream activations in the endomembranes. Our investigations have also identified the presence of other mutant proteins in organelles. Therefore, **mislocalized growth signals in organelles are a characteristic feature of cancer-causing RTK mutants**. Our primary aim is to clarify the molecular mechanism underlying RTK retention in organelles and to develop a new strategy for the suppression of oncogenic RTK signaling.

### 1. Mislocalization of oncogenic RTKs in cancer cells

Recently, we found that in gastrointestinal stromal tumors (GISTs) and leukemia, mutant RTKs localize in intracellular compartments where they generate oncogenic signals (*Nature Commun.* 2014; *Oncogene,* 2017; *CCS,* 2019; *Sci. Rep.* 2021). We are investigating whether other mutants of signaling molecules also cause oncogenic signaling on organelles in various cancers.

2. Mechanism of aberrant localization of RTKs

We recently found that KIT RTK is retained in the Golgi region in a manner dependent on PKD2 (*Cell Rep.* 2023). Identification of molecules that result in aberrant localization of mutants in other cancers is also in progress (*bioRxiv,* 2025).

3. Development of a new strategy for inhibition of RTKs through trafficking inhibition

We recently reported that the blockade of RTK trafficking to a signal platform inhibits oncogenic signaling (*PLoS ONE,* 2017; *Cancer Lett.* 2018; *CCS,* 2019; *Sci. Rep.* 2021; *J. Biol. Chem.* 2024). Furthermore, induction of RTK destabilization in organelles with an HSP90 inhibitor results in inhibition of growth signals (*BJC,* 2020; *IJC,* 2023). Currently, we are developing a novel strategy for the blockade of RTK signaling through trafficking inhibition.

Computational Life Science

Lab Chief: Yasuhiro KOJIMA, Ph.D.
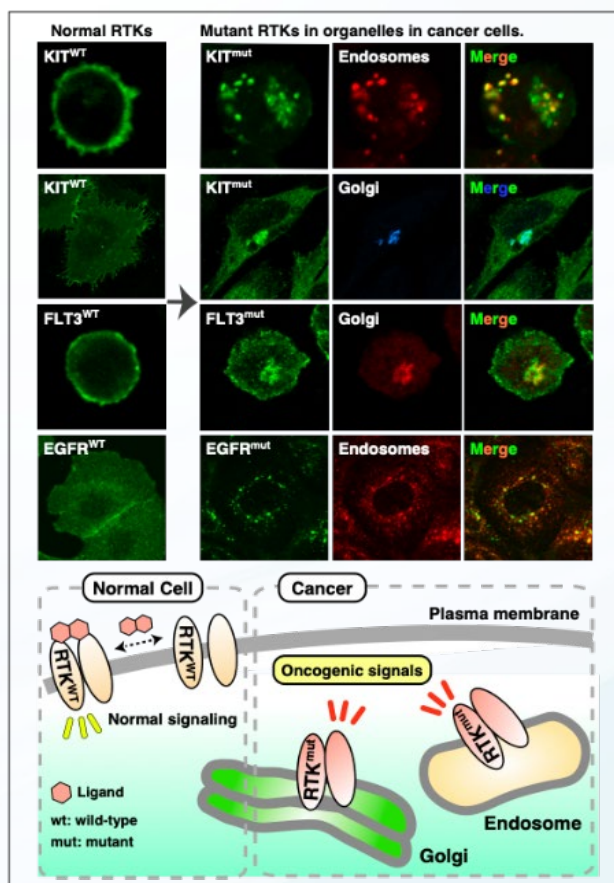
Passion — Developing innovative computational methodologies that integrate machine learning/mathematical modeling with cutting-edge omics data. Using these technologies, we aim to capture the spatio-temporal dynamics of omics profiles in the progression of cancer and contribute to cancer treatment.

Mission

- Development of computational methodologies for advanced omics analysis
- Data-driven exploration of tumor enhancing cellular communications
- Revealing spatiotemporal omics dynamics behind tumor progression

Innovation

This lab innovates computational methods for advanced omics techniques like single-cell and spatial omics. We blend deep learning with mathematical modeling, grounded in biological understanding, to devise new computational strategies. Our focus lies in unraveling the spatiotemporal dynamics of molecular profiles tied to tumor development, with a goal to enrich cancer treatment through discovering influential cell interactions within the tumor microenvironment.

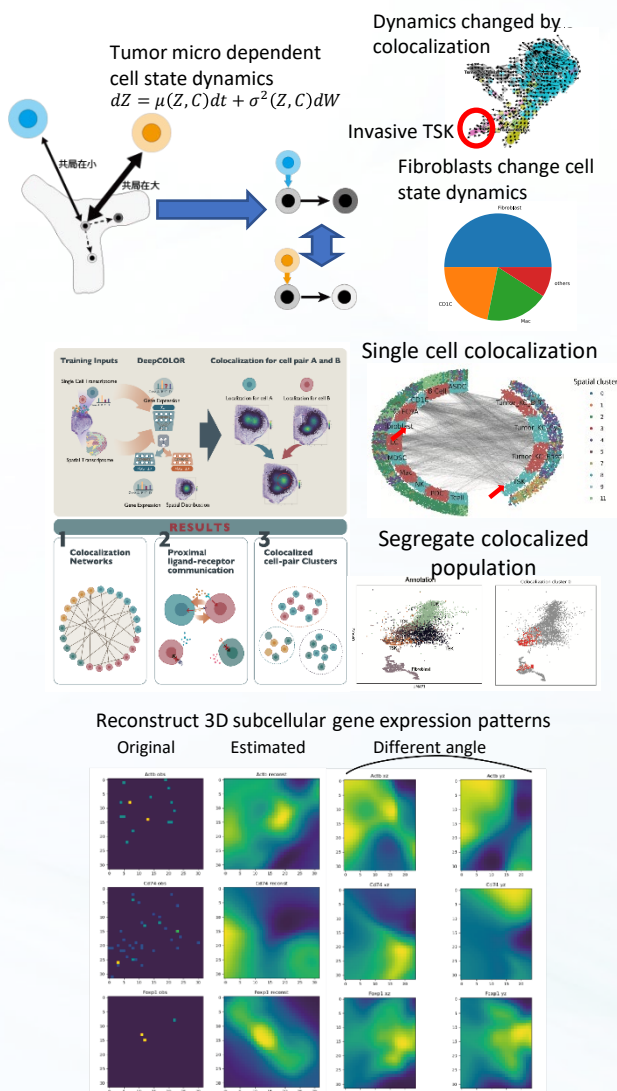### 1. Cell state dynamics inference by deep generative model

Many omics observations, like single-cell transcriptome studies, are invasive and offer only momentary insights. We're formulating a method to uncover cellular state dynamics through combining splicing math models with deep generative models. Our aim is to clarify molecular mechanisms driving cell state transitions, especially during the creation of highly malignant tumor cells, and suggest molecular interventions to hinder cancer progression.

2. Cell-cell interaction analysis by single cell colocalization

Understanding cell-cell interactions and their molecular underpinnings is crucial in finding cancer treatment targets. We've created an analytical method, leveraging a deep generative model, to combine spatially resolved and single-cell transcriptomes to decipher cell-cell colocalization and interaction mechanisms. By employing this data-driven method, we provide an all-inclusive perspective of possible interactions for potential cancer treatment targets.

3. Computational methodologies for subcellular omics

Recently, spatial omics observation resolution has vastly improved, allowing detailed molecular profiling within cells. However, analysis technologies for subcellular-resolution omics profiles are still insufficient for utilizing this resolution. We're developing a method to reconstruct three-dimensional spatial patterns within single cells from this type of data using deep learning. This will help us decode the molecular profiles within cell compartments due to phenomena like liquid-liquid phase separation.

Tumor micro dependent cell state dynamics
$$dZ = \mu(Z,C)dt + \sigma^2(Z,C)dW$$

Dynamics changed by colocalization

Invasive TSK

Fibroblasts change cell state dynamics

Single cell colocalization

Segregate colocalized population

Reconstruct 3D subcellular gene expression patterns

Original Estimated Different angle

Passion 🔥 The Laboratory of Cancer Pathophysiology performs fundamental research to establish next-generation cancer supportive care and cancer palliative care focusing on improvement of the quality of life in cancer patients.

Mission

- 💡 The study of neuron-immune cell-tumor cell interactions through brain-peripheral connections based on "Cancer Neuroscience"
- 💡 Global analysis of neuron-associated tumor properties based on brain-peripheral linkage
- 💡 The clinical development of novel non-narcotic analgesics that have a high safety window against side effects for pain relief
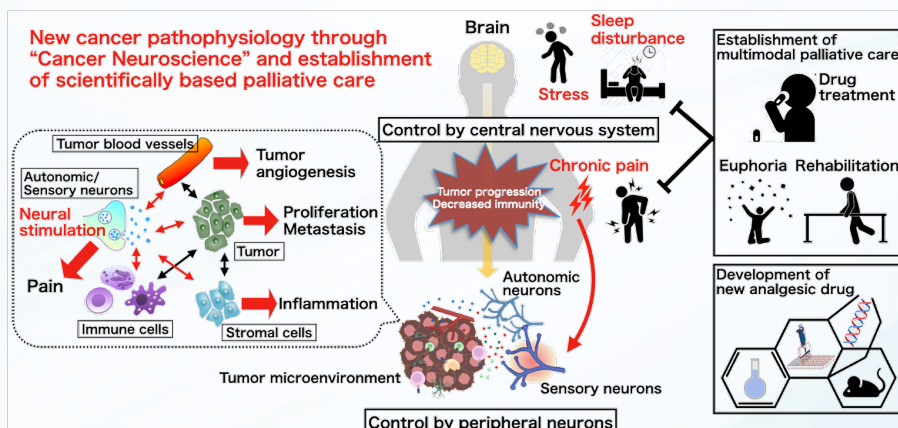
Innovation

Recent improvements in cancer treatment have resulted in an increasing number of cancer survivors each year. Thus, a new cancer treatment is strongly needed not only for the eradication of cancer cells, but also for the establishment of cancer supportive care and palliative care under the presence of cancer. To promote effective cancer treatment with high-quality cancer supportive care, it is critical to understand the influence of the underlying basic health condition on cancer pathology, because most cancer patients are integrally affected by non-cancer diseases such as pain disorders, sleep disturbance, diabetes, movement disorder, cognitive impairment, etc. The Laboratory of Cancer Pathophysiology has been analyzing the underlying health conditions associated with a cancer pathology and performing fundamental research on cancer pathophysiology to establish prospective next-generation cancer supportive care and palliative care with a view to improving the quality of life in cancer survivors.

On the other hand, new cancer research fields such as "Cancer Neuroscience" and "Pain Oncology" have recently emerged, and these research studies have revealed findings about the regulatory mechanisms of cancer growth via neuronal connections. It is well known that tumor cells grow by interacting with surrounding immune cells, stromal cells and vascular cells. However, it is also possible that tumor cells directly interact with peripheral neurons (autonomic neurons and sensory neurons) in the tumor microenvironment to take up nutrients and use them for growth and metastasis. Actually, large-scale clinical trials have shown that treatment of severe pain with the hypersensitive reaction of sensory nerves enhances anti-tumor immunity and supports cancer treatment.

As in the saying "Your mind controls your body, i.e., disease begins in the mind", the role of altered brain function in the mechanism of cancer modification is gradually becoming clear. Thus, it is important to study the influence of the "nervous system" on tumor cells to understand the essence of cancer pathophysiology.

Globally, Laboratory of Cancer Pathophysiology has been studying comprehensive cancer pathophysiology through "Cancer Neuroscience" and "Pain Oncology", and has been establishing a new evidence-based palliative care