## OUR RESEARCH FOCUS

### Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greeting from the Director</td>
<td>3</td>
</tr>
<tr>
<td>Commitment to Translational Research</td>
<td>4</td>
</tr>
<tr>
<td><strong>[Research Division]</strong></td>
<td></td>
</tr>
<tr>
<td>Molecular Pathology Division</td>
<td>5</td>
</tr>
<tr>
<td>Cellular Signaling Division</td>
<td>6</td>
</tr>
<tr>
<td>Cancer Biology Division</td>
<td>7</td>
</tr>
<tr>
<td>Cancer Evolution Division</td>
<td>8</td>
</tr>
<tr>
<td>Cancer RNA Research Division</td>
<td>9</td>
</tr>
<tr>
<td>Hematological Malignancy Division</td>
<td>10</td>
</tr>
<tr>
<td>Cancer Stem Cell Division</td>
<td>11</td>
</tr>
<tr>
<td>Cancer Genomics Division</td>
<td>12</td>
</tr>
<tr>
<td>Genome Biology Division</td>
<td>13</td>
</tr>
<tr>
<td>Brain Tumor Translational Research Division</td>
<td>14</td>
</tr>
<tr>
<td>Molecular Oncology Division</td>
<td>15</td>
</tr>
<tr>
<td>Genome Analysis Platform Development Division</td>
<td>16</td>
</tr>
<tr>
<td>Bioinformatics Division</td>
<td>17</td>
</tr>
<tr>
<td>Cancer Pathophysiology Division</td>
<td>18</td>
</tr>
<tr>
<td>Cancer Therapeutics Division</td>
<td>19</td>
</tr>
<tr>
<td>Molecular Pharmacology Division</td>
<td>20</td>
</tr>
<tr>
<td>Rare Cancer Research Division</td>
<td>21</td>
</tr>
<tr>
<td>Cancer Immunology Division</td>
<td>22</td>
</tr>
<tr>
<td>Medical AI Research and Development Division</td>
<td>23</td>
</tr>
<tr>
<td>Advanced Bioimaging Division</td>
<td>24</td>
</tr>
<tr>
<td><strong>[Independent Research Unit]</strong></td>
<td></td>
</tr>
<tr>
<td>Molecular Carcinogenesis Unit</td>
<td>25</td>
</tr>
<tr>
<td>Fundamental Oncology Unit</td>
<td>26</td>
</tr>
<tr>
<td>Molecular Genetics Unit</td>
<td>27</td>
</tr>
<tr>
<td>Genome Stability Maintenance Unit</td>
<td>28</td>
</tr>
<tr>
<td>Cancer Cell System Unit</td>
<td>29</td>
</tr>
<tr>
<td>Genomic Stress Signaling Unit</td>
<td>30</td>
</tr>
<tr>
<td>Integrative Oncology Unit</td>
<td>31</td>
</tr>
<tr>
<td>Intracellular Traffic &amp; Oncology</td>
<td>32</td>
</tr>
<tr>
<td>Computational Life Science</td>
<td>33</td>
</tr>
</tbody>
</table>
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 20 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™ 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.
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.

4. **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.

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.
Mission

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

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.

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.

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.

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.
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

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.

We aim at identifying essential growth drivers in every cancer and developing new molecularly-targeted therapy, by taking advantage of our functional screening system coupled with the next generation sequencing technologies.

We recently performed a comprehensive multi-omic analysis of malignant ascitic fluid of advanced gastric cancer and identified potentially targetable gene alterations approximately half of all cases (Fig.1, Nature cancer 2:962).

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 specific 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.
We aim to develop new methods for cancer prevention, and treatment, and contribute to a healthy and long-lived society by applying a new concept of “membrane-less organelles” involved in mitochondrial quality control, which we discovered for the first time in the world.

**Mission**

- Analysis of membrane-less organelles involved in p53/Mieap-regulated mitochondrial quality control
- Targeting cancer specific abnormal mitochondria by activating membrane-less organselles

**Innovation**

Accumulation of unhealthy mitochondria in cells leads to a variety of mitochondrial dysfunctions that cause cancer, neurodegenerative diseases, and aging. However, the mechanism for mitochondrial quality control (MQC) remains unclear.


In the process of this project, we have succeeded to discover the most important p53 target gene, designated Mieap. In this novel function, Mieap forms mitochondrial liquid droplets that function as membrane-less organelles (MLOs) to compartmentalize and facilitate cardiolipin (CL) metabolism (doi.org/10.1101/2020.10.26.354365) (Droplets of life, 2022, Elsevier).

The p53/Mieap MQC is frequently inactivated in human clinical colorectal cancers (Oncogenesis. 5: e181, 2016). Mieap-deficient ApcMin/+ mice show strikingly high rates of intestinal tumor development, and advanced graded adenomas and adenocarcinomas (Scientific Reports. 5: 12472, 2015). Defects in p53/Mieap-regulated MQC lead to accumulation of abnormal mitochondria in human colorectal cancers and Mieap-deficient ApcMin/+ tumors, which exhibit a spherical shape and remarkable decrease of cristae structure. Cancer-specific abnormal mitochondria contribute to cancer development and aggressiveness through inhibition of apoptosis and altered metabolism. Therefore, activation of Mieap-regulated MLOs for CL metabolism in cancer cells could be a new strategy for cancer therapy to target cancer specific abnormal mitochondria.

As a scaffold protein, activation of Mieap alone is able to drive formation of MLOs in mitochondria to activate CL metabolism. Utilizing a new concept of “membrane-less organelles”, our efforts could develop novel therapeutic strategies to conquer human cancer.
Thorough analyses of genetic alterations acquired in normal tissues, precancerous lesions and cancers, we are studying the genetic mechanisms of cancer development and progression.

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).

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.

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.
Understanding and targeting aberrant RNA splicing in cancers.

Drug discovery and biomarker study using a multi-disciplinary platform.

Aim to understand and target aberrant RNA processing in cancer to bring medical solutions for cancer patients harboring RNA abnormalities.

Technologies and expertise for a collaboration:

- Pan-cancer RNA splicing analysis.
- Abundant experience in developing nucleic acid therapeutics.
- Clinical samples (>100,000) and clinical information.
- Multi-omics analysis.
- Preclinical trials using PDX models (>15,000)
- Novel biosensors targeting GPCRs.
- Animal models/Molecular biology.

Selected publications

- Reported a novel structural basis for ALK family receptors and their ligands. (De Munck S et al. Nature 2021)
- Identified splicing-associated variants by analyzing >230,000 RNA-seq data. (Shiraishi Y et al. Nature Communications 2022)
NCCRI / Division of Hematological Malignancy
Division Chief : Issay KITABAYASHI, M.D., Ph.D.

Mission

🌟 Our mission is to establish new therapeutic methods by identifying molecular targets that is essential for maintenance of hematological malignancy, especially AML stem cells.

Passion🔥

As we elucidate the molecular mechanisms of epigenomic and metabolic regulation, which are essential for maintaining cancer stem cells, we are developing novel therapies targeting mechanisms.

Innovation

Cancer cells alter their flux through various metabolic pathways to meet the increased energetic and synthetic demand as well as oxidative stress required for cancer cell proliferation and survival. Cancer driver mutations coupled with environmental nutrient availability control flux through these metabolic pathways. Mutations in isocitrate dehydrogenase (IDH) 1 and 2 are frequently observed in various cancers. While wild-type IDHs convert isocitrate to α-ketoglutarate (α KG), mutant IDHs convert α KG to oncometabolite 2-hydroxylglutarate (2HG), which dysregulates a set of α KG-dependent dioxygenases, such as TETs. We have found that mutant IDHs are essential for tumor growth with IDH1 mutation in acute myeloid leukemia, glioma and chondrosarcoma. The recent approval of drugs that target mutant IDHs in acute myeloid leukemia (AML) provides a milestone in targeting cancer metabolism with precision and establishes that metabolic therapy can be highly effective.

Acute myeloid leukemia is a genetically heterogeneous clonal malignancy characterized by a variety of chromosomal abnormalities and gene mutations. Recurrent chromosome translocations are observed in about half of AML patients, which lead to expression of fusion genes. NPM1 mutations represent the most common genetic lesion in adult AML. Mutations in genes of the cohesin complex and CTCF are recurrent in AML with a strong association with NPM1 mutation. Upregulation of HOXA genes is commonly observed in a subset of AML patients either with the NPMc mutation or with the chromosomal abnormalities involving either MLL, MLL, CALM, NUP98 or MOZ genes. HOXA upregulation is critical for development of these type of AML. Histone modifying enzymes such as TIP60, MOZ, MLL and DOT1L are required for the expression of HOXA and development of AML. Tip60 acetylated H2A.Z, thereby promoting Hoxa9 gene expression. Conditional deletion of Tip60 prevented the development of MLL-fusion-induced leukemia, indicating that Tip60 is indispensable for the leukemogenic activity of the MLL-AF10 and MLL-ENL-fusions. The small molecules that disrupt interactions between MLL and MENIN reduced proliferation of AML cells in mice and PDX models. We have also demonstrated that RING1A/B and enhancer of zeste homolog 1/2 (EZH1/2), which are catalytic subunits of polycomb repressive complexes 1/2, are essential for maintenance of leukemic stem cells in AML. The EZH1/2 dual inhibitor selectively reduced the number of cancer stem cells and prevented tumor progression in preclinical models of acute leukemia, multiple myeloma, lymphomas and colon cancers. Clinical trials of the inhibitor are ongoing for malignant lymphoma and acute leukemia.
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

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.

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. 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.

[Reference]
- Okamoto et al. PNAS 2012
- Maida et al. Mol Cell Biol 2014
- Yasukawa et al. Nat Commun 2020
NCCRI / Division of Cancer Genomics
Division Chief: Tatsuhiro SHIBATA, M.D., Ph.D

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

Passion

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

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.
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.

Significance of mutations in diverse genes that occur in cancer cells, such as RET kinase

Identification of novel therapeutic and preventive target genes by whole genome sequencing analysis

Division of Genome Biology has identified seeds for promoting genomic medicine for lung, breast, gynecological, gastrointestinal, and other cancers by understanding genomic alterations in cancer cells and cancer patients; and clarifying their significance.

We discovered that RET gene fusions are present in 2% of lung adenocarcinomas, and we also identified the molecular mechanism of resistance mutations caused by treatment and drugs to overcome resistance. These findings contributed to the implementation of a RET kinase inhibitor-based lung cancer therapy (Selpercatinib covered by insurance from December 2021). Currently, we are identifying genetic alterations by in silico analysis of whole genome sequencing data from lung cancer and breast and gynecological cancers; and elucidating the pathological and clinical significance of genetic mutations by experiments with purified proteins and cells and molecular dynamics simulations using supercomputers.

Polymorphisms and mutations exist in each person’s genome. Our lab has found that the HLA-DPB1 genotype is associated with susceptibility to lung adenocarcinoma with EGFR mutations, which is common among Asians. We are currently conducting whole genome sequencing analysis of for young-onset lung, breast, gynecological, and gastrointestinal cancers to identify genes that can be used to identify high-risk groups, prevent cancer, and detect cancer early.

[Publications]
Genetic analysis of brain tumors and solid tumors

Functional analysis of U1 snRNA mutation in medulloblastoma

Multi-omics analysis of intratumoral heterogeneity in glioma

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

Genetic analysis of brain tumors and solid tumors

Functional analysis of U1 snRNA mutation in medulloblastoma

Multi-omics analysis of intratumoral heterogeneity in glioma

Passion

Innovation

Our lab is analyzing sequencing data to reveal the pathogenesis of brain tumors and other solid tumors. We are performing multi-omics analyses including genomics, transcriptomics, post-transcriptomics, and epigenomics. Our purpose is to detect therapeutic targets underlying their pathogenesis and therapy resistance.

1. Genetic analysis of brain tumors

Recent advances in sequencing technology enable us to classify brain tumors based on their molecular features leading to precision medicine. Until now, 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. Functional analysis of U1 snRNA mutation 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. Genetic analysis of solid tumors

We are providing bioinformatic analyses to other projects that analyze several solid cancers. We performed extensive genomic analyses, especially urologic cancers including renal cancer and upper urinary tract urothelial carcinoma. We are analyzing multi-omics data for those tumors and developing non-invasive molecular diagnoses.
Mission

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

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.

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.
Development of information analysis pipeline for detection and interpretation of cancer genome mutations.

Development of infrastructure for large-scale data analysis using cloud computing

Integrated analysis of genome and transcriptome

Mission

Through the development of practical cancer genome analysis platforms, we will support cancer researchers while becoming users ourselves to elucidate new cancer mechanisms.

Innovation

Recent developments in high-throughput measurement technology have made it possible, in principle, to comprehensively detect various mutations occurring in cancer. At the same time, the importance of informatics technology has increased dramatically, including the development of algorithms and software to accurately and sensitively detect abnormalities in noise, and the technology to implement programs on supercomputers, cloud computing, and other computational platforms to process large amounts of data. Our laboratory aims to support cancer researchers through the development of infrastructures for information analysis that can contribute to new discoveries, while also deepening new biological and medical knowledge through large-scale analysis ourselves.

1: Development of information analysis infrastructure for detection and interpretation of cancer genome mutations

We have developed a practical cancer genome sequencing pipeline (Genomon) and associated acquired mutation detection (Shiraishi et al., NAR, 2013) and structural aberration detection tools Shiraishi et al., Nucleic Acids Research, 2023). In addition, we have developed methodologies for pattern mining of mutations based on machine learning (Shiraishi et al., PLoS Genetics 2015), screening methods for splicing mutations based on Bayesian models (Shiraishi et al., Genome Research, 2018 ), and have been involved in large-scale cancer genome analysis projects (PCAWG Transcriptome Core Group et al., Nature, 2020) using these methodologies. We will contribute to the elucidation of cancer pathology through the development of new analytical methods by incorporating information technologies such as long read sequencing, machine learning, and cloud computing, which will continue to develop in the future.

2: Knowledge Discovery from Large-Scale Public Data Analysis

With the implementation of genomic medicine, various omics analyses are being actively performed not only in research but also in medicine, and the accumulation of various types of data is accelerating. We have developed a new screening method for pathological mutations using transcriptome data of several hundred thousand samples in the cloud to further enhance the effectiveness of omics data (Shiraishi et al., Nature Communications, 2022). We aim to make it feasible to screen various types of mutations, and to apply this method to therapeutic use such as antisense oligonucleotides therapeutics.
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.
The Division 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

- Advanced research on non-cancer disease-complexed Cancer Pathology as the Basis for Comprehensive Cancer Supportive Care
- Global analysis of neuron-associated tumor properties based on brain-peripheral linkage
- Analysis of neurological disease-specific immune variability

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 diabetes, movement disorder, cognitive impairment, etc. The Division 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, recent 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, Divisions of Cancer Pathophysiology have been studying comprehensive cancer pathophysiology by elucidating “neuron-tumor cell interaction” in vivo and in vitro.
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.

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.
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.

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 occupany

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 occupany
- Omics analysis by NCC investigators
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.

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.
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

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

Passion

Innovation

Elucidating nature of cancer immune responses and identifying biomarkers in cancer immunotherapies

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 (CyTOF® Helios), imaging mass cytometry (CyTOF® Hyperion), 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.

Figure. Investigation of the dynamic immune state in cancer patients
Using 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.

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 100 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 the JST's CREST projects, and in 2018, the project "Development of Artificial Intelligence to Accelerate New Drug Discovery" was added to the Public/Private R&D Investment Strategic Expansion Program (PRISM) project led by the Cabinet Office. This project has been ongoing to date. 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 the world's largest integrated database for lung cancer, which is oriented toward AI analysis.

In particular, our AI-based real-time endoscopic diagnostic support system received regulatory approval as a controlled medical device (Class II) in 2020 (approval number: 30200BZX00382000), and in Europe, it complies with the CE mark requirements, the standard for medical device products, and is already in clinical use in Japan and Europe.

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.
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

Passion

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 Chem Biol., 2019). 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.
Mission

- Oncogenic molecular network(s) regulated by miRNAs
- Regulation of tumor-microenvironment by miRNAs
- Molecular mechanisms for the secretion of specific miRNAs

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.

Innovation

Over ten thousands of genes, encoding protein non-coding RNAs, are presented in the human genome. They have essential functions for the normal development of tissues and bodies. Their functional abnormalities are closely associated with the induction of various human diseases, including cancer.

Our research unit focuses on small RNAs called microRNAs. The precise function of microRNAs is necessary for the regulation of complex molecular networks formed in normal cells, but their dysfunction occurs in cancer cells. We are challenging to uncover the nature of cancer cells by understanding the intracellular networks governed by microRNAs. We believe that our findings can contribute to understanding the molecular mechanisms of cancer development and the development of new cancer therapies.

Recently, extracellular microRNAs secreted from cancer cells in various forms is a major interest for their molecular functions and application for diagnosis. The secreted microRNAs are thought to regulate the tumor-microenvironment (TME), leading to maintaining the malignant properties of cancer cells and cancer tissue. In other words, secreted microRNAs are taken up by surrounding non-cancerous cells and alter the gene expression program of those cells to create the TME favorable to cancer cells. Our research projects aim to uncover the functions of intracellular microRNAs using molecular, cellular, and biochemical techniques to understand their relationship with cancer development. We also aim to clarify the pathways through which microRNAs are secreted to extracellular spaces and how secreted microRNAs function. The final goal of our research is to clarify the relationship of the microRNA system to carcinogenesis, and the application of the findings of basic research for the development of novel cancer medicine.

[Cellular]

Basic: Molecular mechanisms of carcinogenesis
- Molecular, Cellular & Biochemistry
- Functional screening of miRNAs
- Phenotype analysis
- Network analysis
- Clinical samples
- Identification of cellular network(s)
- Animal experiments

[Extracellular]

Basic: Molecular connection of intercellular networks
- Cancer specific extracellular RNA profile
- Mechanisms for miRNA secretion
- Biological significances
- Serum miRNA profiles
- Diagnostics and therapeutics
- Detection of cancer patients at early stage
- Rapid diagnosis
- Securing safety

Mission

- Oncogenic molecular network(s) regulated by miRNAs
- Regulation of tumor-microenvironment by miRNAs
- Molecular mechanisms for the secretion of specific miRNAs

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Basic: Molecular connection of intercellular networks
- Cancer specific extracellular RNA profile
- Mechanisms for miRNA secretion
- Biological significances
- Serum miRNA profiles
- Diagnostics and therapeutics
- Detection of cancer patients at early stage
- Rapid diagnosis
- Securing safety
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.

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.

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

Mission

- Identification of genes involved in colorectal cancer metastasis by Sleeping Beauty (SB) transposon screening
- Functional analyses of candidate genes using organoids

Passion

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

Innovation

To understand the molecular mechanisms promoting colorectal cancer (CRC) metastasis, we have performed SB mutagenesis screening. SB mutagenesis is a powerful tool to identify cancer driver genes in mice (Fig. 1). We have reported many CRC driver genes including Apc, Smad4, Fbxw7 and Rspo2 (Nat. Genet. 2015) and gastric cancer driver genes (PNAS 2016).

Using this genetic tool, we are modeling metastatic CRC, inflammatory CRC and CRC resistance to anti-cancer drugs (Fig. 2). Our study will identify key molecules regulating metastasis and help understanding how cancer genomes adapt to the cancer microenvironment.

To functionally validate candidate genes identified from SB screens, we established an experimental system using organoids expressing Cas9 and custom gRNA libraries (PNAS 2016). Using the system, we have generated several knockout organoids and performed detailed analyses such as drug screening and RNA-seq.

Our study will identify new therapeutic targets to develop anti-cancer drugs.
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.
Establish patient-derived cancer organoids
Model human cancer tissue and metastatic tissue in vitro
Elucidate and control cancer ecosystems using artificial cancer tissue

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

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.
Tumor development by DNA Replication Stress Response

Drug resistance regulated by genomic stress response

Activation and signaling analysis of ATR, the master kinase regulating DNA replication stress response

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**Innovation**

The main cause of cancer has long been discussed to be stress on genomic DNA, the blueprint of human cells. Genomic stress can be caused by environmental factors, genetic factors (e.g., BRCA1 mutations), and DNA replication factors (unlucky mistakes in DNA replication), which harms the information in genomic DNA (e.g., DNA mutations).

The DNA mutations often lead to activation of oncogenes and inactivation of tumor suppressors. Repeated proliferation under such conditions causes additional genomic stress (DNA replication stress) during DNA replication. DNA replication stress is thought to induce DNA replication errors as well as loss, amplification, or translocation of DNA (genomic instability), which may promote cancer development. We are exploring “Genome Stress Signaling,” which ask how cells respond to such genomic stresses and how cell fate is determined.

In particular, we focus on DNA replication stress and ask how normal cells evolve into cancer cells, and we aim to find “Achilles’ heels of cancer” based on these studies and to develop novel cancer treatment strategies. Genomic stress response mechanisms are a double-edged sword closely related to cancer development and cancer treatment. Our focuses are on molecular biological and biochemical analyses using cell models, validation studies using animal models, and TR studies that bridge the results obtained at the bench to the bedside. We are working toward a "cancer-free" or "cancer-curable" future.

1) “How does cancer starts and grows?”

When oncogenes are activated in normal cells, DNA replication stress is induced. We have found that when the expression of ATR kinase, which responds to this stress, is elevated, cancer cells develop more frequently. We are currently conducting a detailed analysis to elucidate the mechanism underlying DNA replication stress driven cancer development.

2) “Achilles’ heels of cancer”

Cancer cells suffer from higher levels of DNA replication stress than normal cells due to lack of homeostasis caused by the various mutations. We have found that cancer cells with mutations in SMARCA4, a chromatin remodeling factor, exhibits particularly high levels of DNA replication stress and shows susceptibility to ATR inhibitors (Kurashima et al. NAR Cancer 2020). Collaboration works with Pharmas for ATR inhibitor therapy are on going.
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 (BioRxiv. 2021), and inflammatory diseases (MedRxiv. 2020).

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; Cancer Sci. 2020).
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; Cell Commun. Signal., 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
   What is the cause of mislocalization of RTK mutants? Identification of molecules that result in aberrant localization of mutants is also in progress.

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; Cell Commun. Signal., 2019; Sci. Rep., 2021). Furthermore, induction of RTK destabilization in organelles with a HSP90 inhibitor results in inhibition of growth signals (BJC, 2020). Currently, we are developing a novel strategy for the blockade of RTK signaling through trafficking inhibition.
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.