

Exploratory Oncology
Research & Clinical Trial Center

Preface

In 2011, the National Cancer Center was selected as one of the five designated centers for early/exploratory clinical trials. In 2012, with budget support from the Japanese Ministry of Health, Labour and Welfare (MHLW), we organized “the Exploratory Oncology Research and Clinical Trial Center” (NCC-EPOC) through the Kashiwa and Tsukiji campuses, which focus on early/exploratory clinical trials and translational research (TR). The NCC-EPOC was actually activated in April 2013 consisting of a phase I unit in each campus, a central/data center function unit for clinical trials, and a translational research (TR) unit. The TR unit additionally included the immunotherapy division in July 2013. As for drug developments from Japan, three missions are focused on in the NCC-EPOC: to conduct first-in-human (FIH) trials, investigator-initiated trials (IITs) with unapproved agents, and TRs during early clinical studies. In addition to drug development, EPOC was integrated with the Research Center for Innovative Oncology (RCIO) in 2015 and has started developing medical equipment and accelerating higher quality TR in the NCC. The activities in each unit in 2015 are described as follows:

- 1) Group for Clinical Research: The Department of Experimental Therapeutics consisting of several medical oncologists with backgrounds in each organ department was newly organized in both hospitals in order to conduct all-comer-type FIH/phase I studies. A regular weekly teleconference is held to collaborate with the two groups in each hospital. In 2015, several FIH trials including three IITs have been achieved in total at both hospitals. The number of phase I studies in the NCC means it is ranked as the largest academic center in Asia. New seed subjects from outside academic research organizations have been introduced.
- 2) Group for Innovative Center Treatment: We organized and co-developed several new seeds including newly developed antibodies, an antibody-drug-conjugate (ADC), a peptide vaccine, immune cell therapy and drugs for supportive care in both campuses. In 2015, two venture businesses, a new immune therapy business at the Tsukiji campus and a new antibody development business at the Kashiwa campus, have been launched to organize quick introduction to early clinical trials. With collaboration with the Seeds selection committee, we support early non-clinical seeds for quick introduction to early clinical development and follow them up.
- 3) Group for Translational Research: Nationwide genome screening network (SCRUM Japan). Several pharmaceutical companies, which conducted similar new agent development studies for tiny populations with driver gene alterations, joined this network under contract with the NCC. A similar screening system for some driver genes has also started in colorectal cancers using an originally developed screening panel, followed by an organization of nationwide genome screening academia-industry consortium (SCRUM-JAPAN) using a cutting-edge pan-cancer NGS panel. A total of 15 pharmaceutical companies are collaborating with the consortium for more than 2,500 new patients per year with lung and gastrointestinal cancer genome screening in association with more than 30 agent studies. This study will contribute to making a public database of genome profiling and the distribution of precision medicine in Japan. The TOP-GEAR study aiming to establish genome information-driven standard treatment has started in collaboration with the in-house genome sequencing laboratory (SCI Lab), in which QA/QC is regulated according to the CLIA law in the Department of Pathology and Clinical Laboratories, Hospital at Tsukiji campus
- 4) Group for Innovative Diagnostic and Therapeutic Device: Four fields concerning development of endoscopy, surgical equipment, functional imaging and proton therapy have innovated new medical equipment and introduced them to clinical trials for obtaining approval as medical equipment. We established “C-square” jointly with Chiba prefecture chambers of commerce and local manufacturing companies in the Tohkatsu area to establish industry-academia cooperation. We are aggressively developing new radiation therapies as intensity modulated radiation therapy and boron neutron capture therapy (BNCT) and are planning for clinical introduction in both campuses.

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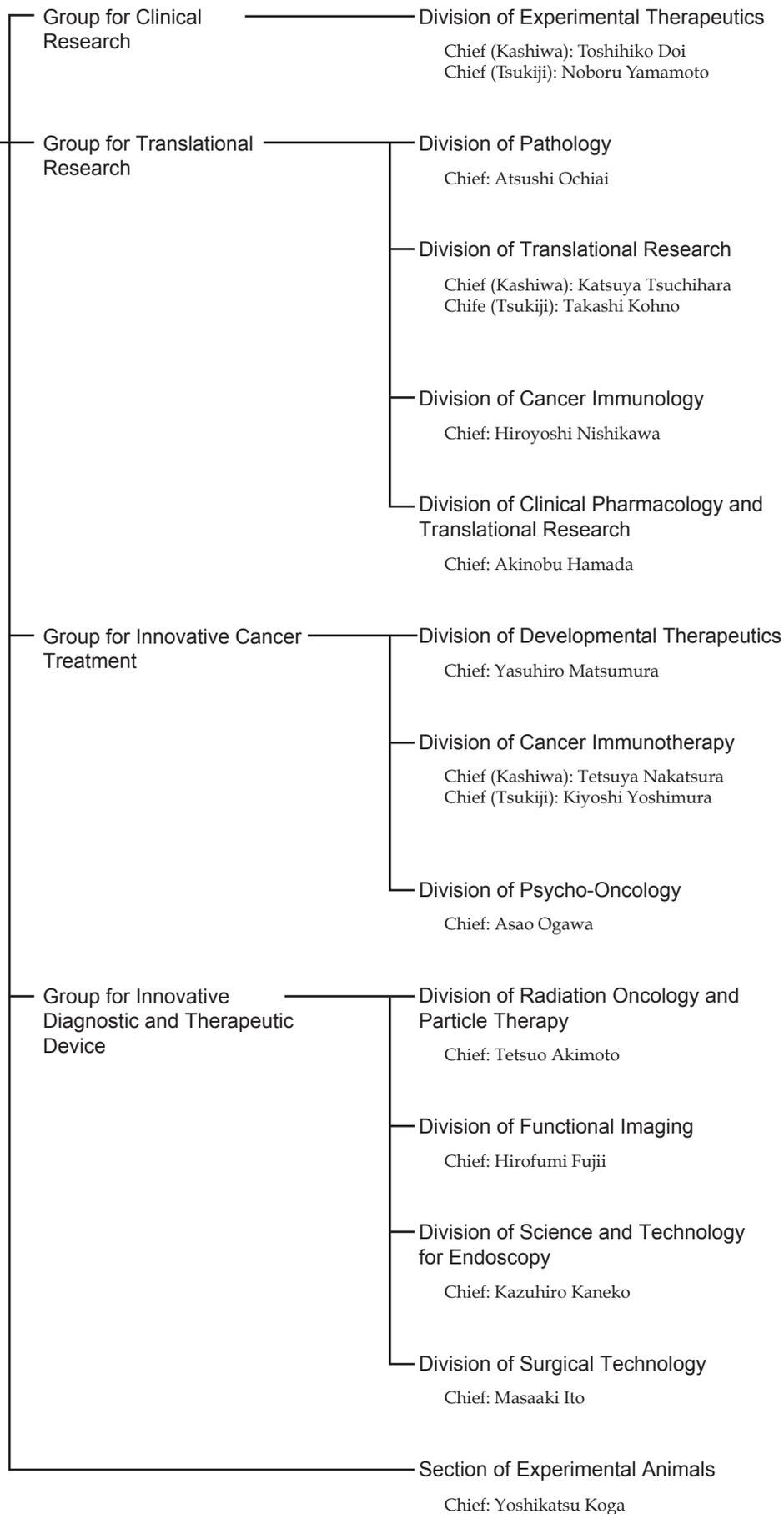
Organization

President:

Tomomitsu Hotta

Director:

Atsushi Ohtsu



Activities of the Divisions

DIVISION OF EXPERIMENTAL THERAPEUTICS

[Kashiwa Campus] Toshihiko Doi, Kiyotaka Yoh, Yoichi Naito, Takahiro Kogawa, Kohei Shitara, Hideaki Takahashi, Tomoko Yamazaki, Yasutoshi Kuboki
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Introduction

The Division of Experimental Therapeutics supports efforts toward the creation of new drugs and other products from breakthroughs originating from academic institutions by achieving results at the level of basic research. We evaluate and discover excellent research and development proposals, and provide integrated management of the program so that basic research outcomes are linked through to clinical research and clinical trial for approval. We have conducted several IITs as applications for approval and also have promoted research and development in the field of medicine.

Routine activities

Engaging in medical R&D and establishment/maintenance of medical research environment

Research activities

We promote the following activities for appropriate conducting of research and trials.

- To plan the clinical trial as IIT for achieving POC of new academic seeds
- Explanation meetings for researchers and office employees on compliance of laws, ordinances and guidelines
- To consider development design to create a new with the goal of creating innovative drugs, medical devices, as well as ensuring that research projects on promising results proceed more rapidly and in greater depth

Clinical trials

We have conducted several IITs using unapproved drugs from academia and pharmaceutical companies (Table 1).

Table 1. Experimental Therapeutics 2015 Number of Investigator-Initiated Trials

| Phase I | Phase I (FIH) | Phase Ib | Phase II | Phase IIa | EAP |
|---------|---------------|----------|----------|-----------|-----|
| 1 | 3 | 2 (1) | 9 (4) | 1 (1) | 3 |

* () Pharmaceutical company grant

List of papers published in 2015

Journal

(Kashiwa Campus)

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DIVISION OF PATHOLOGY

Atsushi Ochiai, Genichiro Ishii, Satoshi Fujii, Motohiro Kojima, Takeshi Kuwata, Masato Sugano, Chisako Yamauchi, Syuichi Mitsunaga, Akiko Nagatsuma, Kazuyoshi Yanagihara, Yuka Nakamura, Tomofumi Miura, Ken Hatogai, Naoki Sakuyama, Masayuki Ishibashi, Hiroko Hashimoto, Sachiko Fukuda, Tamae Hanai, Ayumi Iwaya, Aya Endo, Natsuko Maruyama, Yuki Iino, Teruo Komatsu, Motoko Suzaki, Yoshiko Onuma, Youichi Higuchi, Anna Abe, Yoshitaka Suda, Tomoyuki Miyashita, Yusuke Asai, Syota Yamazaki

Introduction

The major contribution of the Division of Pathology to both the Research Center for Innovative Oncology (RCIO) and the National Cancer Center Hospital (East) [NCCH-E] includes four major activities: 1) Basic and translational research in the cancer field; 2) Pathological diagnoses in the NCCH-E; 3) Clinical resident training for diagnosis and translational research (TR); and 4) Establishment and maintenance of the NCCH-E tissue bank (Bio-bank) system.

Routine activities

The staff members of the Division of Pathology are responsible for basic and translational research in the cancer biology and cancer treatment fields. Members are also involved in all routine pathological and cytological diagnosis in the NCCH-E with the collaboration of staff pathologists of the Department of Pathology and Clinical Laboratories of the NCCH-E. The Division participates in the training of clinical residents in pathological diagnosis and translational research using clinical samples from NCCH-E, in addition to participating in clinicopathological conferences and research meetings between the NCCH-E and the RCIO.

Research activities

The goal of the research at the Division of Pathology is to explore the cause of the cancer and to develop novel diagnostic and therapeutic methods for cancer patients. The research activities of the Division of Pathology start with the detection of cancer-specific pathological conditions closely

associated with clinical outcomes. The appropriate *in vitro* and *in vivo* models are required to solve the molecular mechanism of the relevant issues. Research is further confirmed in final validation studies using human samples. The following are the major research results of this year.

- 1) Podoplanin-positive cancer-associated fibroblasts play an important role in promoting cancer cell invasion (16, 22). Moreover, these fibroblasts can cause primary resistance to chemotherapy in lung adenocarcinoma patients (20, 28).
- 2) In the head and neck carcinomas, carcinomas with neuroendocrine features were found to have an aggressive clinical course, which corresponded with the Ki-67 index and mitotic count (35). Genes involved in cancer-related pathways were frequently affected not only by genetic but also by epigenetic alterations in HER2-positive breast cancer (36).
- 3) Peritoneal invasion in colon cancer is an important prognostic factor and the cancer microenvironment formed by both cancer cells and subperitoneal fibroblasts is involved in the promotion of tumor growth and metastasis (4, 5, 17).
- 4) Approximately two-thirds of patients with gastric adenocarcinoma exhibited the expression of at least one tyrosine kinase receptor and would be candidates for targeted therapies. Moreover, one-third of at least one RTK over-expressing cases showed multiple RTKs expression, which may be useful for selecting the most suitable patients for each targeted therapy (21, 25, 26).
- 5) High serum IL-6 was related to advanced age, the presence of hepatic metastasis, a large tumor burden in the liver, severe fatigue, high

carcinoembryonic antigen, high C-reactive protein, and anemia in patients with treatment-naïve advanced pancreatic cancer (9).

Prognostic factors and clinicopathological characteristics of various cancers have also been investigated in collaboration with the NCCH-E Diagnostic Pathology Section and other institutions.

These include lung cancers (7, 10, 18, 27, 29, 30, 31), colon cancers (8, 12, 13, 14), gastric cancers (2, 24, 38), pancreatic cancers (15, 19, 39), breast cancers (11, 16), esophageal cancers (1, 34) and head and neck cancer (32).

Clinical trials

Central pathological diagnosis in a global trial (gastric cancer).

List of papers published in 2015

Journal

1. Sugimoto M, Takahashi S, Kobayashi T, Kojima M, Gotohda N, Satake M, Ochiai A, Konishi M. Pancreatic perfusion data and post-pancreaticoduodenectomy outcomes. *J Surg Res*, 194:441-449, 2015
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11. Nishida Y, Kuwata T, Nitta H, Dennis E, Aizawa M, Kinoshita T, Ohtsu A, Ochiai A. A novel gene-protein assay for evaluating HER2 status in gastric cancer: simultaneous analyses of HER2 protein overexpression and gene amplification reveal intratumoral heterogeneity. *Gastric Cancer*, 18:458-466, 2015
12. Haruki T, Aokage K, Miyoshi T, Hishida T, Ishii G, Yoshida J, Tsuboi M, Nakamura H, Nagai K. Mediastinal nodal involvement in patients with clinical stage I non-small-cell lung cancer: possibility of rational lymph node dissection. *J Thorac Oncol*, 10:930-936, 2015

Education

The Division participates in the pathological training of clinical residents in NCCH-E. Moreover, staff members give professional guidance for doctoral students of Juntendo University, Keio University, Tokyo Medical and Dental University and the Graduate School of Frontier Sciences, University of Tokyo.

Future prospects

We are strengthening particularly in 1) promotion of basic research of cancer biology and cancer treatment, 2) promotion of translational research and 3) collecting fundamental pathological information for cancer diagnosis and treatment.

13. Yoshida J, Ishii G, Hishida T, Aokage K, Tsuboi M, Ito H, Yokose T, Nakayama H, Yamada K, Nagai K. Limited resection trial for pulmonary ground-glass opacity nodules: case selection based on high-resolution computed tomography-interim results. *Jpn J Clin Oncol*, 45:677-681, 2015
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DIVISION OF TRANSLATIONAL RESEARCH (KASHIWA CAMPUS)

Katsuya Tsuchihara, Sachiyo Mimaki, Hideki Makinoshima, Shingo Matsumoto, Wataru Okamoto, Ayako Suzuki, Atsushi Yagishita, Rumi Fujioka, Hiroko Kumakura, Megumi Iwakura, Koutatsu Matsushima, Masahiro Takita, Motoki Kasahara, Sayuri Todoroki, Tomohiro Sakamoto, Hiroyasu Esumi, Satoshi Owada, Tatsunosuke Ikemura, Satoshi Tada, Takanori Kawashima, Kenta Murata, Chikako Nakai

Introduction

This Division closely collaborates with intramural and extramural basic and clinical researchers to develop novel anti-cancer therapeutics as well as to prove their concepts. The Division has been developing genome biomarker diagnostics based on next generation DNA sequencing technologies, exploring rational molecular targets for anti-cancer therapies, and elucidating molecular mechanisms of oncogenesis, tumor progression and therapeutic responses. The Division also managed a data center that handles clinical and genome information of advanced lung and gastrointestinal cancer cases that were enrolled in a nationwide cancer genome screening program, SCRUM-Japan.

Routine activities

Weekly conferences for the whole division and individual research groups are held. A monthly tele-conference is held with the Group of Translational Research at Tsukiji Campus.

Research activities

- 1) Developing a multiplex mutation detection kit for KRAS and NRAS genes for selecting anti-EGFR antibody treatment for advanced colorectal cancer. The kit was approved and reimbursed in Japan in April 2015.
- 2) Developing a prototype of a multiplex gene alteration detection kit for choosing appropriate drugs for advanced lung cancer.
- 3) Establishing a datacenter and an interactive database program for SCRUM-Japan (Figures 1 and 2).

- 4) Identifying that EGFR inhibitors affect glycolysis of lung adenocarcinoma cells via the PI3K pathway and induced anti-tumor effect.

Clinical trials

- 1) Screening Project for Individualized Medicine in Japan (SCRUM-Japan): Data center
- 2) Biomarker Research for Anti-EGFR Monoclonal Antibodies by Comprehensive Cancer Genomics (BREAC Study): Secretariat, data center, genome analysis

Education

This Division accepted and trained the following trainees: Graduate students from the University of Tokyo (four), Tokyo Medical and Dental University (one), Keio University (one) and Juntendo University (one), staff physician of National Cancer Center Hospital East (one) and Tottori University (one), senior resident (one) and junior resident (two), visiting scientists (six)

Future prospects

Integrating the multi-omics analysis and precise clinical information is necessary to develop novel anti-cancer therapeutics. Education of specialists with a background of medical oncology, biology and bioinformatics is most important.

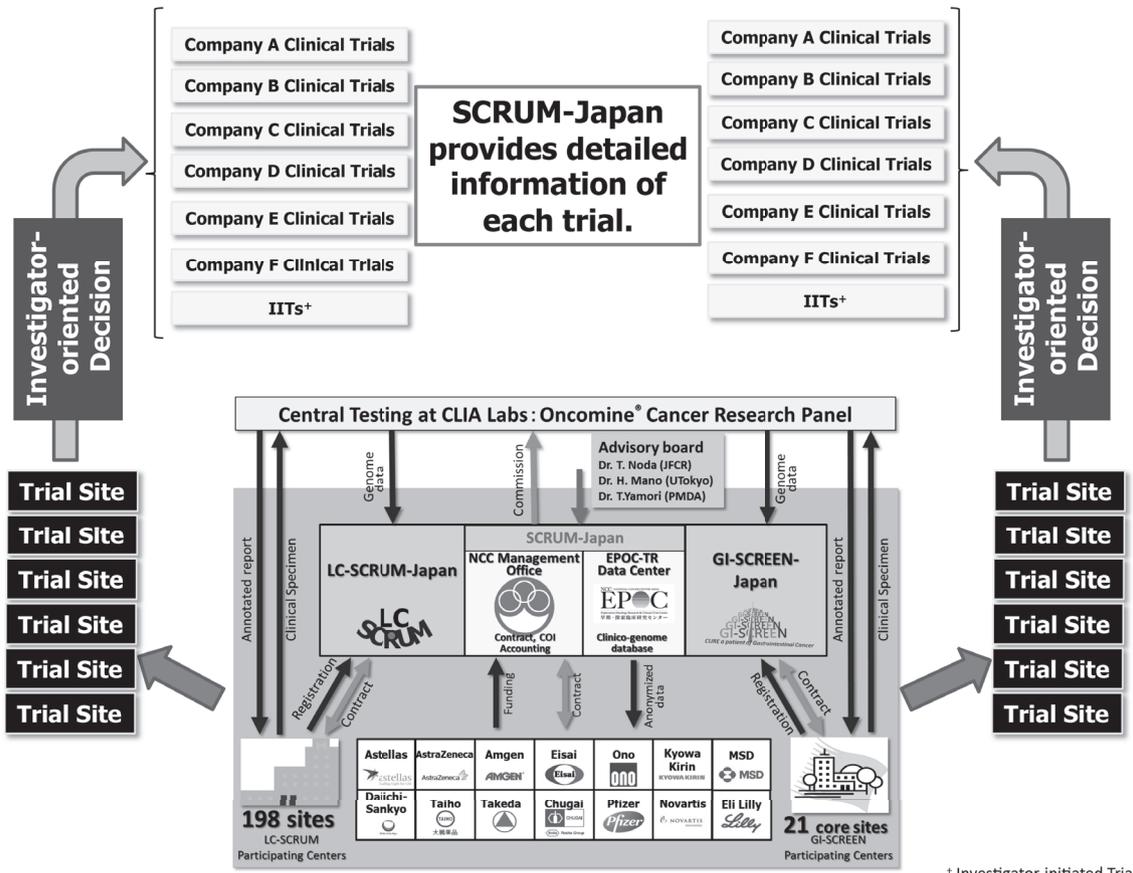


Figure 1. Nationwide cancer genome screening program, SCRUM-Japan

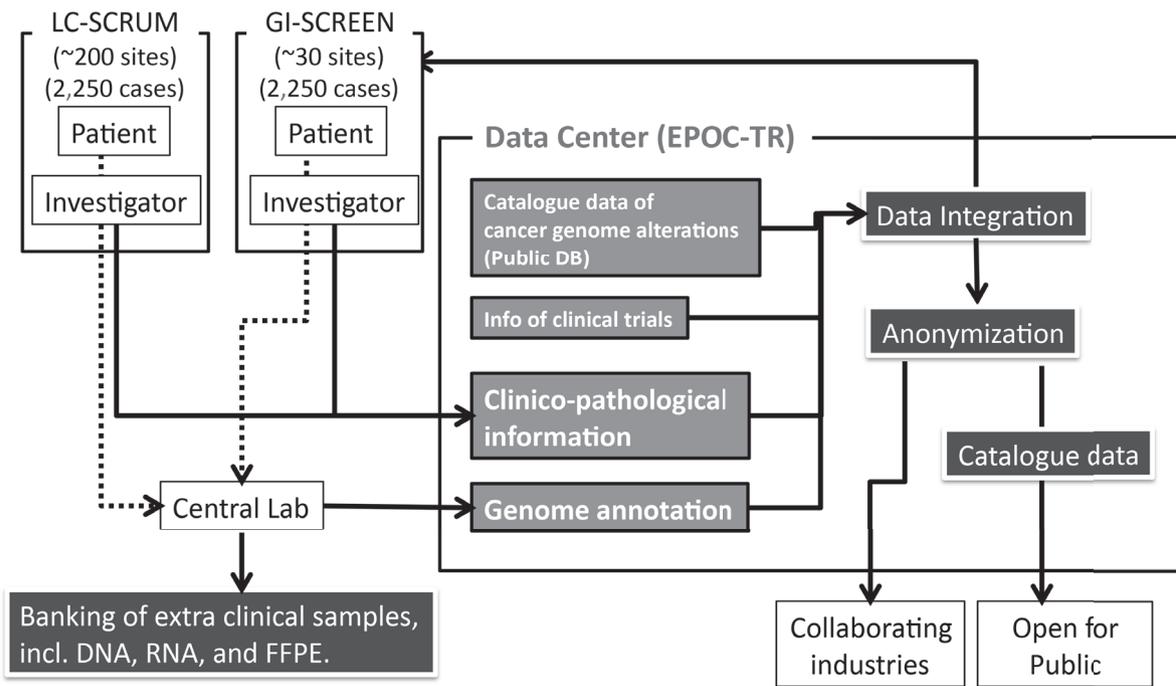


Figure 2. Flow of the clinical and genomic information in SCRUM-Japan

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Journal

1. Matsumura Y, Umemura S, Ishii G, Tsuta K, Matsumoto S, Aokage K, Hishida T, Yoshida J, Ohe Y, Suzuki H, Ochiai A, Goto K, Nagai K, Tsuchihara K. Expression profiling of receptor tyrosine kinases in high-grade neuroendocrine carcinoma of the lung: a comparative analysis with adenocarcinoma and squamous cell carcinoma. *J Cancer Res Clin Oncol*, 141:2159-2170, 2015
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4. Taniguchi H, Yamazaki K, Yoshino T, Muro K, Yatabe Y, Watanabe T, Ebi H, Ochiai A, Baba E, Tsuchihara K, Japanese Society of Medical Oncology. Japanese Society of Medical Oncology Clinical Guidelines: RAS (KRAS/NRAS) mutation testing in colorectal cancer patients. *Cancer Sci*, 106:324-327, 2015
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6. Umemura S, Tsuchihara K, Goto K. Genomic profiling of small-cell lung cancer: the era of targeted therapies. *Jpn J Clin Oncol*, 45:513-519, 2015
7. Kohno T, Nakaoku T, Tsuta K, Tsuchihara K, Matsumoto S, Yoh K, Goto K. Beyond *ALK-RET*, *ROS1* and other oncogene fusions in lung cancer. *Transl Lung Cancer Res*, 4:156-164, 2015
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DIVISION OF TRANSLATIONAL RESEARCH (TSUKIJI CAMPUS)

Takashi Kohno, Hitoshi Ichikawa, Hiroki Sasaki, Takashi Kubo

Introduction

This Division facilitates early phase clinical trials by conducting translational research (TR) focusing on the development of therapeutic and in vitro diagnostic seeds and the discovery of biomarkers.

Research activities

Establishment of NGS-based genomic testing system for precision cancer medicine

We developed a next-generation sequencing (NGS)-based in-house genomic testing system in which an original cancer gene panel (NCC oncopanel) was used to guide cancer treatments, and are continuously improving this system to construct an accurate and clinically useful in vitro diagnostics (IVD) system. In 2015, we renewed our original gene panel (NCC oncopanel v3) and confirmed its performance in a prospective feasibility study, which tested patients considering entry into an early phase clinical trial in a sequencing laboratory located in the Research Institute. Fifty-four patients were successfully examined, and actionable genetic alterations were identified in 24 patients (Figure). In addition, we set up the SCI-Lab, a laboratory for clinical sequencing with international standard quality assurance, in the Department of Clinical Laboratories of the Hospital through the technology transfer of our genomic testing system.

Preclinical studies using newly established cell lines of common cancers in Asia

In collaboration with the Division of Genetics, we have newly established 59 diffuse-type gastric cancer (GC)-derived cell lines (NSC-1~49 series) from the cancer ascites of 34 patients. Now, we possess 94 GC cell lines including 80 diffuse-type (new 59 and existing 21) and 14 intestinal-type, and

also have 52 esophageal squamous cell carcinoma (ESCC) cell lines. In 2015, we successfully established six pancreatic and one ovarian cancer cell lines. We are conducting omics analyses for gene expression and copy number variation, and hot spot- and genome wide-gene alteration in these cell lines. Moreover, for an in vivo preclinical study, their tumorigenicity and histopathological characteristics of PDXs, such as fibroblast rich-, hypovascular-, and dormant-state, were evaluated. Through collaboration with five pharmaceutical companies, in vitro and in vivo preclinical studies are being conducted to translate “therapeutic and diagnostic seeds” to the cancer clinic.

Clinical trials

TOP-GEAR: Trial of Onco-Panel for Gene-profiling to Estimate both Adverse events and Response by cancer treatment (UMIN000011141)

Education

Graduate students, post-doctoral fellows, and chief residents in the National Cancer Center (NCC) were educated through the “on-the-job training” in several translational research projects.

Future prospects

The feasibility and clinical utility of our clinical sequencing system with international standard quality assurance will be shown. Early-phase clinical trials will further progress through utilization of original cancer cell lines.

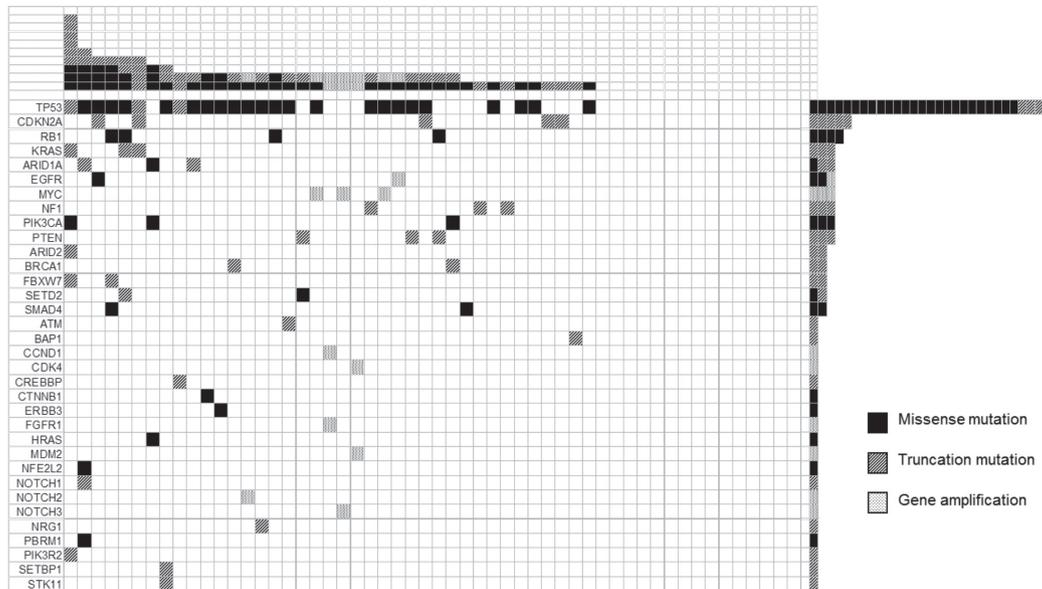


Figure 1. Gene alterations detected by clinical sequencing using NCC oncopanel ver. 3

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- Saeki N, Ono H, Yanagihara K, Aoyagi K, Sasaki H, Sakamoto H, Yoshida T. rs2294008T, a risk allele for gastric and gallbladder cancers, suppresses the PSCA promoter by recruiting the transcription factor YY1. *Genes Cells*, 20:382-391, 2015
- Yamanoi K, Arai E, Tian Y, Takahashi Y, Miyata S, Sasaki H, Chiwaki F, Ichikawa H, Sakamoto H, Kushima R, Katai H, Yoshida T, Sakamoto M, Kanai Y. Epigenetic clustering of gastric carcinomas based on DNA methylation profiles at the precancerous stage: its correlation with tumor aggressiveness and patient outcome. *Carcinogenesis*, 36:509-520, 2015
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- Higuchi Y, Kojima M, Ishii G, Aoyagi K, Sasaki H, Ochiai A. Gastrointestinal Fibroblasts Have Specialized, Diverse Transcriptional Phenotypes: A Comprehensive Gene Expression Analysis of Human Fibroblasts. *PLoS One*, 10:e0129241, 2015
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- Kohno T, Nakaoku T, Tsuta K, Tsuchihara K, Matsumoto S, Yoh K, Goto K. Beyond *ALK-RET*, *ROS1* and other oncogene fusions in lung cancer. *Transl Lung Cancer Res*, 4:156-164, 2015
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DIVISION OF CANCER IMMUNOLOGY

Hiroyoshi Nishikawa, Daisuke Sugiyama, Chika Sakai, Yasuko Tada, Miyuki Nakai, Tomoka Takaku, Sayuri Yoshimatsu, Yoshiko Takeuchi, Yuki Fujioka, Danbee Ha, Motoya Mie, Masahiro Tokunaga, Shigeyuki Mori, Sho Isoyama, Hiroki Fukutomi

Introduction

The Division of Cancer Immunology aims at identifying novel strategies that can tip the balance to augmenting anti-tumor immune responses by focusing on anti-tumor immune responses and their suppressive mechanisms in a tumor microenvironment. Regulatory T (Treg) cells, actively engaged in the maintenance of immunological self-tolerance and homeostasis, are present in tumor tissues with higher frequencies compared with the periphery and inhibit the development of effective anti-tumor immune responses. We are now investigating the detailed mechanisms of Treg-cell infiltration/proliferation in tumor tissues to control them for a novel target of cancer immunotherapy.

Research activities

- 1) We have established a sample collection system of cancer tissues and peripheral blood from cancer patients such as gastrointestinal and lung cancers in the National Cancer Center Hospital East. Tumor infiltrating lymphocytes and peripheral blood lymphocytes are prepared and stocked in a cell bank with a barcode system. This system provides a chance to analyze kinetics of immune responses pre- and post-therapy including immunotherapy. Furthermore, somatic mutations and gene expression were also examined together to define the cellular immune response to neo antigens derived from somatic mutations and shared antigens derived from aberrantly or highly expressing self-antigens (Figure 1).
- 2) In collaboration with Osaka University, we addressed the role of FOXP3⁺ T cells in colorectal cancers. While abundant Treg-cell infiltration

into tumors is significantly associated with poor clinical outcomes in various types of cancer, the role of Treg cells is controversial in colorectal cancers, in which FOXP3⁺ T-cell infiltration indicated better prognosis in some studies. FOXP3⁺ T cells infiltrating into colorectal cancers were divided into subpopulations including FOXP3⁺ suppressive Treg cells and non-suppressive inflammatory FOXP3⁺ T cells, and showed that colorectal cancers were classified into two types, one with predominant infiltration of immune-suppressive FOXP3-high Treg cells and the other with inflammatory non-suppressive FOXP3-low T cells in addition to FOXP3-high Treg cells. The two types showed opposite prognosis: the former type is poor, the latter better. In addition, the possible contribution of tissue cytokines (IL-12, TGF- β and TNF- α) and colonic microbiota (*Fusobacterium nucleatum*) to the development of the two different types was detected. Therefore, in addition to depletion of FOXP3^{hi} Treg cells from tumor tissues to augment tumor immunity, strategies to locally increase FOXP3^{lo} non-Treg cells, for example, by the use of specific microbes could be tumor-suppressive and -preventive.

Education

Post-doctoral fellows and graduate school students from Osaka University and Akita University are trained in our Division.

Future prospects

Samples from peripheral blood and tumor tissues have been collected more rapidly than expected. In addition to immune assays, we also analyze environmental factors such as

microbiota in colon cancers. Base on this, we will comprehensively investigate immune cells such as CD4⁺, CD8⁺ T cells and macrophages, cancer cells

and environmental factors to clarify the molecular mechanisms that control immune balances in a tumor microenvironment.

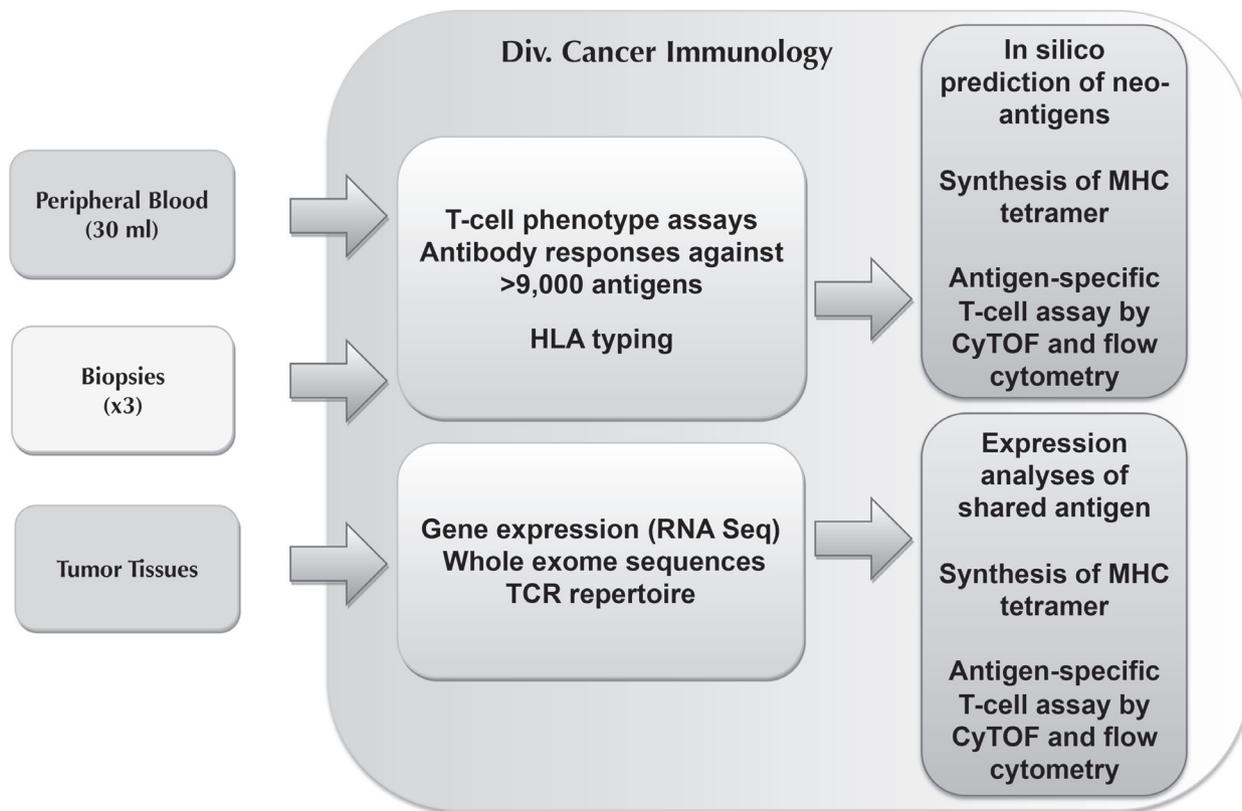


Figure 1. Immunological assay in the NCC

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1. Nishikawa H. Overview: New Modality for Cancer Treatment. *Oncology*, 891:33-35, 2015
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Akinobu Hamada, Mitsuhiro Hayashi, Hiroaki Aikawa, Miyuki Momma

Introduction

The Division of Clinical Pharmacology and Translational Research Group is focused on the development of a pharmacokinetics/pharmacodynamics (PK/PD) analyzing system. The system provides drug exposure in blood and tissues by using high-sensitivity liquid chromatography tandem mass spectrometry (LC-MS/MS) and spatial drug distribution on tissue by using mass spectrometry imaging without labeling reagents. We are also focused on the development of an immunomonitoring system detecting patient's ADCC activity.

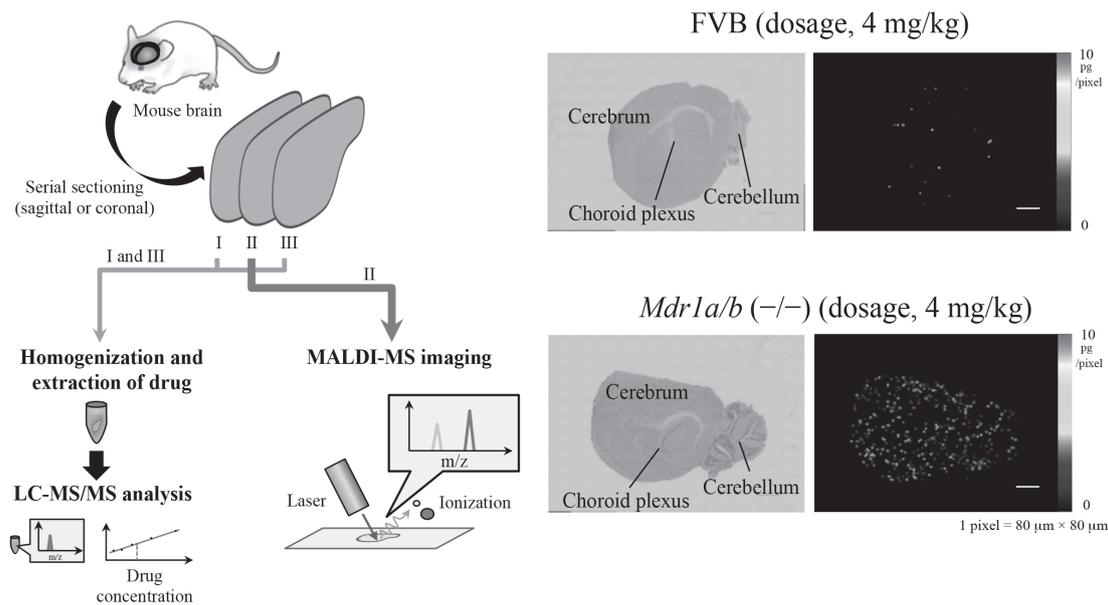
Research activities

We established a quantitative mass spectrometry imaging system that provides both quantitative information and spatial distribution of

target drugs. We used this system to visualize the amount and the distribution of anti-cancer drugs in several mouse models. To assess the efficacy and the behavior of target drugs in tumor tissue, we are now establishing not only a cell-derived xenograft mouse model but also a patient-derived xenograft model. Moreover, we established an immunomonitoring system that can detect ADCC activity from patient's PBMC. Both research projects were submitted as papers to scientific journals.

Future prospects

The combination of PK/PD analysis, mass spectrometry imaging, measurement of ADCC activity and establishment of a PDX model can provide us with more accurate information about patients. These systems will help to actualize personalized medicine in the future.



p糖タンパク質(Mdr1)の基質薬剤の脳内組織移行性は、ノックアウトマウスで上昇

Figure 1. MALDI-MSI imaging analysis showed that the intra-brain transitivity of the drug was elevated on Mdr1(-/-) mouse brain.

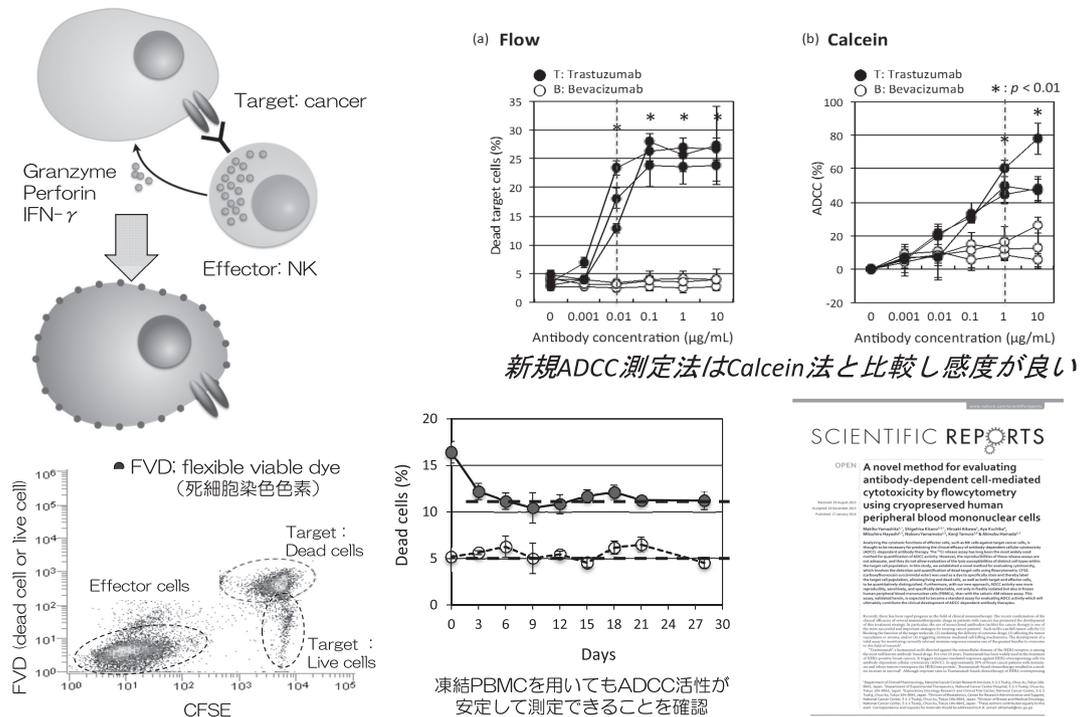


Figure 2. We developed a highly sensitive method for quantifying the ADCC activity of patient's blood.

List of papers published in 2015

Journal

- Fujiwara Y, Kobayashi S, Nagano H, Kanai M, Hatano E, Toyoda M, Ajiki T, Takashima Y, Yoshimura K, Hamada A, Minami H, Ioka T. Pharmacokinetic Study of Adjuvant Gemcitabine Therapy for Biliary Tract Cancer following Major Hepatectomy (KHBO1101). *PLoS One*, 10:e0143072, 2015
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- Otani S, Hamada A, Sasaki J, Wada M, Yamamoto M, Ryuge S, Takakura A, Fukui T, Yokoba M, Mitsufuji H, Toyooka I, Maki S, Kimura M, Hayashi N, Ishihara M, Kasajima M, Hiyoshi Y, Katono K, Asakuma M, Igawa S, Kubota M, Katagiri M, Saito H, Masuda N. Phase I and pharmacokinetic study of erlotinib administered in combination with amrubicin in patients with previously treated, advanced non-small cell lung cancer. *Am J Clin Oncol*, 38:405-410, 2015
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- Yoshitake Y, Fukuma D, Yuno A, Hirayama M, Nakayama H, Tanaka T, Nagata M, Takamune Y, Kawahara K, Nakagawa Y, Yoshida R, Hirotsue A, Ogi H, Hiraki A, Jono H, Hamada A, Yoshida K, Nishimura Y, Nakamura Y, Shinohara M. Phase II clinical trial of multiple peptide vaccination for advanced head and neck cancer patients revealed induction of immune responses and improved OS. *Clin Cancer Res*, 21:312-321, 2015

DIVISION OF DEVELOPMENTAL THERAPEUTICS

Yasuhiro Matsumura, Masahiro Yasunaga, Yoshikatsu Koga

Introduction

Our Division has been involved in basic research on drug delivery systems (DDS) and antibody therapeutics including an anticancer agent incorporating a micelle system, monoclonal antibody development (mAb), and antibody drug conjugate. We also investigate the mechanism of cancer-induced blood coagulation and are developing a new cancer diagnosis based on the cancer-specific mAb. In addition to the research work, we are operating the Japan Clinical Oncology Group Tumor Repository.

Routine activities

- Examination of clinical trials as an IRB member
- Operation of the JCOG Tumor Repository
- Management of personal information protection in the National Cancer Center (NCC) East Hospital

Research activities

1) DDS in Cancer Chemotherapy

Tumor-targeted delivery of therapeutic agents is a longstanding pharmacological goal to improve the treatment selectivity and therapeutic index. Most scientists have sought to use 'active' receptor-mediated tumor-targeting systems. However, the 'passive' targeting afforded by the "Enhanced Permeability and Retention (EPR) effect" provides a versatile and non-saturable approach for tumor-selective delivery. Polymeric micelles are ideally suited to exploit the EPR effect, and have been used for the delivery of a range of anticancer drugs in preclinical and clinical studies.

We showed the stronger antitumor effect and lower toxicity of the combination of the epirubicin-incorporating polymeric micelle and DACHP (oxaliplatin parent complex)-incorporating

polymeric micelle in a human gastric cancer model than that of epirubicin and oxaliplatin.

2) Cancer Stromal Targeting Therapy

In spite of the recent success of antibody drug conjugate (ADC) therapy in patients with hypervascular and special tumors recognized by a particular mAb, there are several issues to be solved for ADC to be counted as a universal therapy for any types of cancer. Especially, most human solid tumors possess abundant stroma that hinders the distribution of ADC. To overcome these drawbacks, we developed a unique strategy that the cancer-stromal targeting (CAST) therapy by cytotoxic immunoconjugate bound to the collagen 4, tissue factor (TF), or fibrin network in the tumor stroma from which the payload is released gradually and distributed throughout the tumor, resulting in the arrest of tumor growth due to induced damage to tumor cells and tumor vessels. We successfully developed a mAb (102-10 clone) that reacted only with human fibrin, not with human fibrinogen and cross-reacted with mouse fibrin but not with mouse fibrinogen. The specificity of our 102-10 differs from existing anti-fibrin mAbs. Namely, 102-10 reacts only with a fibrin clot, but not with fibrinogen, soluble fibrin, or D-dimer. The anti-fibrin antibody therefore did not make an immune complex in the bloodstream and circulated in the blood for a long time. We then prepared the antibody drug conjugate (ADC) that is MMAE conjugated anti-fibrin mAb. The ADC may selectively extravasate from leaky tumor vessels, bind to the fibrin network in the stroma and create a scaffold from which effective sustained release of the free MMAE occurs. This free MMAE may easily reach the cancer cells by diffusion through the stroma barrier. Another benefit is that MMAE released from the ADC may also attack the vascular endothelial cells.

3) Infrastructure for the mAb development

We have established an infrastructure for antibody development including antigen production, animal immunization, hybridoma production, antibody expansion and purification, SPR characterization, and ELISA development. Simultaneously, we have found various cell surface molecules specific to colorectal cancer and succeeded in developing one of those molecules.

4) Noninvasive Diagnostic Test for Colorectal Cancer

Regarding colorectal cancer (CRC), we investigated the applicability of the fecal miRNA test (FmiRT) to fecal samples used for a previous fecal occult blood test (FOBT) stored under various conditions.

Education

1) Doctoral student

Graduate School of Frontier Science, The University of Tokyo: four students

Juntendo University Graduate School of Medicine: two students

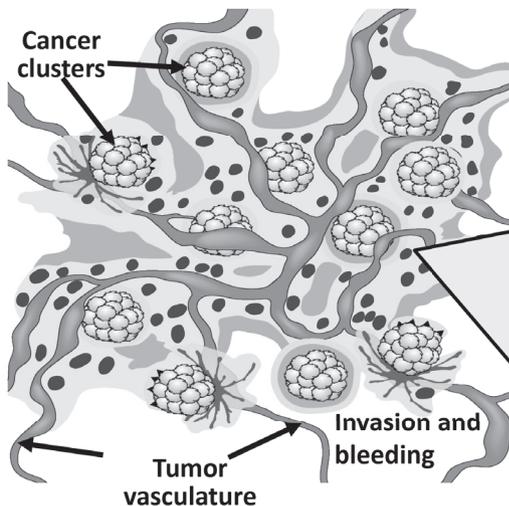
Department of Gastroenterology and Hepatology, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba: one student

Department of Neurosurgery, Kumamoto University Graduate School of Medical Science: one student

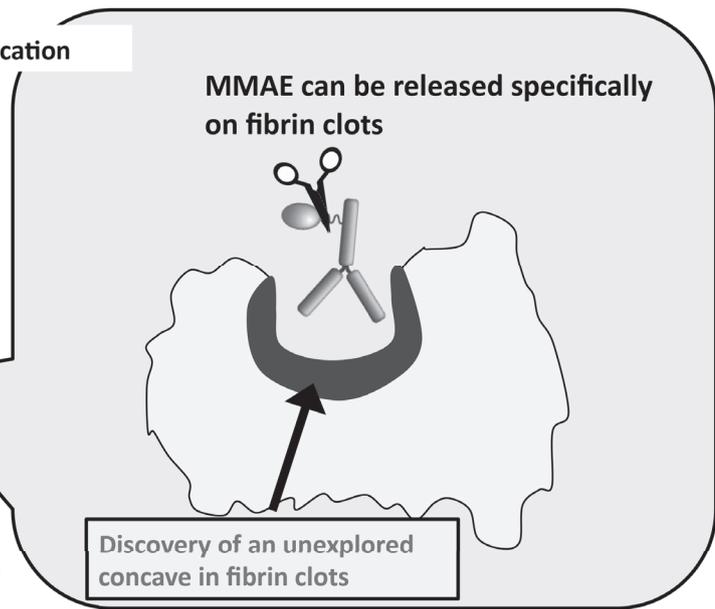
2) Master course student

Graduate School of Frontier Science, The University of Tokyo: two students

The “malignant cycle of blood coagulation” generates Versatile cancer stroma



Magnification



Fuchigami H et al. in preparation

Figure 1. CAST therapy using anti-insoluble fibrin antibody - MMAE conjugate

List of papers published in 2015

Journal

1. Ahn J, Miura Y, Yamada N, Chida T, Liu X, Kim A, Sato R, Tsumura R, Koga Y, Yasunaga M, Nishiyama N, Matsumura Y, Cabral H, Kataoka K. Antibody fragment-conjugated polymeric micelles incorporating platinum drugs for targeted therapy of pancreatic cancer. *Biomaterials*, 39:23-30, 2015
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DIVISION OF CANCER IMMUNOTHERAPY (KASHIWA CAMPUS)

Tetsuya Nakatsura, Yasushi Uemura, Toshiaki Yoshikawa, Keigo Saito, Manami Shimomura, Rong Zhang, Nobuhiro Tsuchiya, Yoshitaka Tada, Tatsuaki Iwama, Shoichi Mizuno, Yumi Tokumitsu, Kayoko Shoda, Yukiko Kozaki, Norihiro Fujinami, Shiori Sugai, Megumi Ozaki

Introduction

Our Division aims to investigate evidenced-based cancer immunotherapy, repeating basic research and translational research. This Division is focused on developing not only more effective immunotherapies but also an immunological method for suppression of recurrence or for cancer prevention.

Research activities

Three-dimensional (3D) cell culture is beneficial for physiological studies of tumor cells, due to its potential to deliver a high quantity of cell culture information that is representative of the cancer microenvironment and predictive of drug responses *in vivo*. Currently, gel-associated or matrix-associated 3D cell culture is comprised of intricate procedures that often result in experimental complexity. Therefore, we developed an innovative anti-cancer drug sensitivity screening technique for 3D cell culture on NanoCulture Plates (NCP) by employing the imaging device BioStation CT. Here, we showed that the human breast cancer cell lines BT474 and T47D form multicellular spheroids on NCP plates and compared their sensitivity to the anti-cancer drugs trastuzumab and paclitaxel using the BioStation CT. The anticancer drugs reduced spheroid migration velocity and suppressed spheroid fusion. In addition, primary cells derived from the human breast cancer tissues B58 and B61 grown on NCP plates also exhibited similar drug sensitivity. These results were in good agreement with the conventional assay method using ATP quantification. We confirmed the antitumor effects of the drugs on cells seeded in 96-well plates using the BioStation CT imaging technique. We expect this method to be useful in research for new antitumor

agents and for drug sensitivity tests in individually tailored cancer treatments (3).

Novel treatment modalities are required urgently in patients with Hepatocellular carcinoma (HCC). A vaccine that induces cytotoxic T lymphocytes (CTLs) is an ideal strategy for cancer, and glypican-3 (GPC3) is a potential option for HCC. Blocking the programmed death-1 (PD-1)/PD-L1 pathway is a rational strategy to overcome tumor escape and tolerance toward CTLs. In the present study, we investigated whether anti-PD-1 blocking antibodies (α PD-1 Ab) enhanced the number of vaccine-induced peptide-specific CTLs in peripheral blood mononuclear cells (PBMCs) following the administration of GPC3 peptide vaccine to both patients and in a mouse model. The inhibitory receptor PD-1 was highly expressed in *ex vivo* GPC3-specific CTLs isolated from the PBMCs of vaccinated HCC patients. *In vitro*, interferon- γ induced PD-L1 expression in liver cancer cell lines. In addition, PD-1 blockade increased the number of GPC3-specific CTLs, which degranulate against liver cancer cell lines. *In vivo* experiments using tumor-bearing mouse models showed that the combination therapy of peptide vaccine and α PD-1 Ab suppressed tumor growth synergistically. PD-1 blockade increased the number of peptide-specific tumor-infiltrating T cells (TILs) and decreased the expression of inhibitory receptors on TILs. This study demonstrated that PD-1/PD-L1 blockade augmented the antitumor effects of a peptide vaccine by increasing the immune response of vaccine-induced CTLs, and provided a foundation for the clinical development of a combination therapy using a GPC3 peptide vaccine and α PD-1 Ab (7).

The use of dendritic cells (DC) to prime tumor-associated antigen-specific T-cell responses provides a promising approach to cancer

immunotherapy. Embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC) can differentiate into functional DCs, thus providing an unlimited source of DCs. However, the previously established methods of generating practical volumes of DCs from pluripotent stem cells (PSC) require a large number of PSCs at the start of the differentiation culture. In this study, we generated mouse proliferating myeloid cells (pMC) as a source of antigen-presenting cells (APC) using lentivirus-mediated transduction of the c-Myc gene into mouse PSC-derived myeloid cells. The pMCs could propagate almost indefinitely in a cytokine-dependent manner, while retaining their potential to differentiate into functional APCs. After treatment with IL4 plus GM-CSF, the pMCs showed impaired proliferation and differentiated into immature DC-like cells (pMC-DC) expressing low levels of major histocompatibility complex (MHC)-I, MHC-II, CD40, CD80, and CD86. In addition, exposure to maturation stimuli induced

the production of TNF α and IL12p70, and enhanced the expression of MHC-II, CD40, and CD86, which is thus suggestive of typical DC maturation. Similar to bone marrow-derived DCs, they stimulated a primary mixed lymphocyte reaction. Furthermore, the *in vivo* transfer of pMC-DCs pulsed with H-2K(b)-restricted OVA257-264 peptide primed OVA-specific cytotoxic T cells and elicited protection in mice against challenge with OVA-expressing melanoma. Overall, myeloid cells exhibiting cytokine-dependent proliferation and DC-like differentiation may be used to address issues associated with the preparation of DCs (8).

Clinical trials

We are performing a phase I study of HSP105 peptide vaccine for patients with esophageal cancer and colorectal cancer.

List of papers published in 2015

Journal

1. Tsuchiya N, Sawada Y, Endo I, Uemura Y, Nakatsura T. Potentiality of immunotherapy against hepatocellular carcinoma. *World J Gastroenterol*, 21:10314-10326, 2015
2. Tsuchiya N, Sawada Y, Endo I, Saito K, Uemura Y, Nakatsura T. Biomarkers for the early diagnosis of hepatocellular carcinoma. *World J Gastroenterol*, 21:10573-10583, 2015
3. Sakamoto R, Rahman MM, Shimomura M, Itoh M, Nakatsura T. Time-lapse imaging assay using the BioStation CT: a sensitive drug-screening method for three-dimensional cell culture. *Cancer Sci*, 106:757-765, 2015
4. Imamura Y, Mukohara T, Shimono Y, Funakoshi Y, Chayahara N, Toyoda M, Kiyota N, Takao S, Kono S, Nakatsura T, Minami H. Comparison of 2D- and 3D-culture models as drug-testing platforms in breast cancer. *Oncol Rep*, 33:1837-1843, 2015
5. Ofuji K, Tada Y, Yoshikawa T, Shimomura M, Yoshimura M, Saito K, Nakamoto Y, Nakatsura T. A peptide antigen derived from EGFR T790M is immunogenic in non-small cell lung cancer. *Int J Oncol*, 46:497-504, 2015
6. Kinoshita Y, Tanaka S, Souzaki R, Miyoshi K, Kohashi K, Oda Y, Nakatsura T, Taguchi T. Glypican 3 expression in pediatric malignant solid tumors. *Eur J Pediatr Surg*, 25:138-144, 2015
7. Sawada Y, Yoshikawa T, Shimomura M, Iwama T, Endo I, Nakatsura T. Programmed death-1 blockade enhances the antitumor effects of peptide vaccine-induced peptide-specific cytotoxic T lymphocytes. *Int J Oncol*, 46:28-36, 2015
8. Zhang R, Liu TY, Senju S, Haruta M, Hirose N, Suzuki M, Tatsumi M, Ueda N, Maki H, Nakatsuka R, Matsuoka Y, Sasaki Y, Tsuzuki S, Nakanishi H, Araki R, Abe M, Akatsuka Y, Sakamoto Y, Sonoda Y, Nishimura Y, Kuzushima K, Uemura Y. Generation of mouse pluripotent stem cell-derived proliferating myeloid cells as an unlimited source of functional antigen-presenting cells. *Cancer Immunol Res*, 3:668-677, 2015
9. Nakatsuka R, Matsuoka Y, Uemura Y, Sumide K, Iwaki R, Takahashi M, Fujioka T, Sasaki Y, Sonoda Y. Mouse dental pulp stem cells support human umbilical cord blood-derived hematopoietic stem/progenitor cells *in vitro*. *Cell Transplant*, 24:97-113, 2015

Book

1. Sawada Y, Yoshikawa T, Ofuji K, Sakai M, Nakatsura T. Cancer vaccines: current status and future perspectives. In: Song J (ed), Cancer immunotherapy: mechanisms of cancer immunity, engineering immune-based therapies and developing clinical trials - book series: Frontiers in Cancer Immunology Volume 1, pp 236-258, 2015
2. Yoshikawa T, Sawada Y, Sakai M, Ofuji K, Nakatsura T. Development of glypican-3-targeted cancer immunotherapy. In: Seya T, Matsumoto M, Udaka K, Sato N (eds), Inflammation and immunity in cancer, Japan, Springer Japan, pp 133-143, 2015

DIVISION OF CANCER IMMUNOTHERAPY (TSUKIJI CAMPUS)

Kiyoshi Yoshimura, Shigehisa Kitano, Tetsuhiko Asao, Ayumu Ito, Yonju Kim, Moeko Inoue, Masanori Fuse, Rie Ishibashi, Miki Kojima

Introduction

The Division of Cancer Immunotherapy aims to develop novel cancer immunotherapies as well as an immune monitoring system for finding biomarkers to predict the efficacy or side effects resulting from the application in clinical trials.

Routine activities

Maintenance of laboratory on 12F of the NCC Hospital and biotherapy core facility on 6F of the NCC institute: The maintenance includes an annual checkup and repair of research instruments, the deep freezer, the freezer, the tank for liquid nitrogen and the refrigerator.

Research activities

- Development of cancer immunotherapy via chimeric antigen receptor T cell (CAR-T) therapy for targeting Molecule L against disseminated gastric cancer
- Development of CAR-T therapy for Molecule N against advanced pancreatic cancer
- Development of CAR-T therapy for Molecule G against lung cancer
- Development of CAR-T therapy for acute myeloid lymphoma
- Development of immunotherapy for solid cancers by genetically activated and invasive T cells to maximize the effect of immune checkpoint inhibitors. Elucidation of mechanism of T cell infiltration to find predictive marker for immune checkpoint inhibitors
- Pre-clinical basic research for the first-in-human (FIH) clinical trial using novel CAR-T therapy
- Research on fundamental system for cancer immune cellular therapy in clinical practice

- Development of cancer immunotherapy against malignant pleural mesothelioma using antibodies for cancer-specific antigen and CAR-T
- Establishment of novel recognition system against cancer stem cell-like cells utilizing DNA or RNA aptamer
- Phase II clinical trial for adjuvant therapy against hepatocellular carcinoma using peptide vaccine (completed)
- Doctor-led clinical trial of multiple peptides mixed vaccine targeting pediatric cancer (completed)
- Pre-clinical research for FIH clinical trial of anti-CD4 antibody therapy
- Basic research on FIH clinical trial for induced pluripotent stem cell-based T cell therapy
- Development of predictive diagnostic method for recurrent hepatocellular carcinoma using blood samples
- Study of fundamental system for new immunotherapy in clinical practice (completed)

Findings

- 1) Molecule L expressed on the cell surface membrane expressed in gastric cancer and cancer stem cell-like cells is identified. Cytotoxic activation of CAR-T cells against the Molecule L is also confirmed.
- 2) Molecule N expressed on the cell surface membrane expressed in pancreatic cancer and cancer stem cell-like cells is identified. The Molecule N has the possibility to influence tumor micro environment based on the proliferation tumor cells and chemokine production by the downstream of signal transduction of Molecule N. In addition, it is possibly related to a mechanism of infiltration of T cells into solid cancer.
- 3) Molecule Y is expressed on T cell which is

infiltrated into solid cancers and influences T cell activation. The Molecule Y is under study because it seems to have a direct influence on the T cell infiltration unlike regular activation of T cell which produces interferon gamma.

- 4) Basic development of modified CAR-T cells forming activated and invasive T cells is in progress. The modified T cells will infiltrate into solid cancers and increase their number inside the cancer cell.
- 5) Immuno-monitoring for anti GD2 antibody therapy in combination with IL-2 and CSF against refractory neuroblastoma phase I has been completed and phase II is under preparation.
- 6) Clinical application of FITC-CAR-T therapy which was proposed by Dr. Tamada from Yamaguchi University is in progress. Our target is to apply the therapy against malignant pleural mesothelioma in two years.
- 7) Cell processing for CD19-CAR-T therapy (phase I) was executed. The operation of the therapy was set up based on the result of the investigation on cell processing. Investigation was done by US and Australian institutions.

Clinical trials

- Cell processing after leukapheresis, preservation and immunological analysis for CD19-CAR-T

List of papers published in 2015

Journal

1. Maeda Y, Yoshimura K, Matsui H, Shindo Y, Tamesa T, Tokumitsu Y, Hashimoto N, Tokuhisa Y, Sakamoto K, Sakai K, Suehiro Y, Hinoda Y, Tamada K, Yoshino S, Hazama S, Oka M. Dendritic cells transfected with heat-shock protein 70 messenger RNA for patients with hepatitis C virus-related hepatocellular carcinoma: a phase 1 dose escalation clinical trial. *Cancer Immunol Immunother*, 64:1047-1056, 2015
2. Ishiguro S, Yoshimura K, Tsunedomi R, Oka M, Takao S, Inui M, Kawabata A, Wall T, Magafa V, Cordopatis P, Tzakos AG, Tamura M. Involvement of angiotensin II type 2 receptor (AT2R) signaling in human pancreatic ductal adenocarcinoma (PDAC): a novel AT2R agonist effectively attenuates growth of PDAC grafts in mice. *Cancer Biol Ther*, 16:307-316, 2015
3. Tokumitsu Y, Yoshino S, Iida M, Yoshimura K, Ueno T, Hazama S, Oka M. Intraoperative dissemination during gastrectomy for gastric cancer associated with serosal invasion. *Surg Today*, 45:746-751, 2015
4. Shindo Y, Yoshimura K, Kuramasu A, Watanabe Y, Ito H, Kon-do T, Oga A, Ito H, Yoshino S, Hazama S, Tamada K, Yagita H, Oka M. Combination immunotherapy with 4-1BB activation and PD-1 blockade enhances antitumor efficacy in a mouse model of subcutaneous tumor. *Anticancer Res*, 35:129-136, 2015

therapy

- Immune-monitoring phase I for anti GD2 antibody therapy in combination with IL-2 and CSF against refractory neuroblastoma

Education

- Training a doctor on a Ph.D. course
- Training a resident physician from respiratory medicine
- Working in close coordination with other branches at the NCC hospital and having junior doctors develop a deeper understanding of immunotherapy.

Future prospects

With NCC staff support, our research has been moving ahead after the initial setting up of our laboratory in May 2015 despite the fact that we went through a rough time in the first few months due to medical device problems, failures during take over and establishment of new projects. We will continue to act as an intermediary between basic research and clinical applications, aiming to develop novel immunotherapies. We are planning to publish papers and apply for patents in 2016.

DIVISION OF PSYCHO-ONCOLOGY

Asao Ogawa, Hiroya Kinoshita, Ken Shimizu

Introduction

The aim of the Division is to develop mind-centered interventions to restore, maintain, and improve the quality of life of patients and their families throughout cancer treatment, and for end-of-life care. The Division has focused on developing effective interventions for delirium, dementia, and depression in cancer patients as well as on determining the mechanism underlying the relationship between cancer and the mind through a combination of neuropsychiatric, psychosocial, and behavioral sciences.

Research activities

1) Development of the Japanese Version of the Edmonton Symptom Assessment System - Revised

A revised version of the Edmonton Symptom Assessment System (ESAS-r) is a self-report symptom measurement tool, which includes nine common symptom-related items of advanced cancer: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath. We administered the tool to validate and investigate optimal cutoff points for the Japanese version of the ESAS-r in 292 Japanese adult patients with cancer. As for results of the study, the Japanese version of the ESAS-r is a reliable (intraclass correlation coefficient: 0.90) and valid (Cronbach's alpha: 0.87) tool for measuring symptoms, and can

accurately represent the severity of many symptoms in Japanese adult patients with cancer (Yokomichi N, et al. *J Pain Symptom Manage.* 2015; Yamaguchi T, et al. *J Pain Symptom Manage.* 2015).

2) Effect of continuous deep sedation on survival in patients with advanced cancer (J-Proval): a propensity score-weighted analysis of a prospective cohort study.

We aimed to examine whether CDS shortens patient survival using the propensity score-weighting method, and to explore the effect of artificial hydration during CDS on survival. After propensity-score weighting, median survival was 22 days (95% CI 21-24) and 26 days (24-27), respectively (median difference -1 day [95% CI -6 to 4]; HR 1.01 [95% CI 0.87-1.17]; log-rank $p=0.91$). Age (pinteraction=0.67), sex (pinteraction=0.26), performance status (pinteraction=0.90), and volume of artificial hydration (pinteraction=0.14) did not have an effect modification on the association between sedation and survival, although care setting did have a significant effect modification (pinteraction=0.021). CDS does not seem to be associated with a measurable shortening of life in patients with advanced cancer cared for by specialized palliative care services, and could be considered a viable option for palliative care in this setting (Maeda I, et al. *Lancet Oncol.* 2016).

List of papers published in 2015

Journal

1. Baba M, Maeda I, Morita T, Inoue S, Ikenaga M, Matsumoto Y, Sekine R, Yamaguchi T, Hirohashi T, Tajima T, Tatara R, Watanabe H, Otani H, Takigawa C, Matsuda Y, Nagaoka H, Mori M, Tei Y, Hiramoto S, Suga A, Kinoshita H. Survival prediction for advanced cancer patients in the real world: A comparison of the Palliative Prognostic Score, Delirium-Palliative Prognostic Score, Palliative Prognostic Index and modified Prognosis in Palliative Care Study predictor model. *Eur J Cancer*, 51:1618-1629, 2015
2. Hamano J, Morita T, Inoue S, Ikenaga M, Matsumoto Y, Sekine R, Yamaguchi T, Hirohashi T, Tajima T, Tatara R, Watanabe H, Otani H, Takigawa C, Matsuda Y, Nagaoka H, Mori M, Yamamoto N, Shimizu M, Sasara T, Kinoshita H. Surprise Questions for Survival Prediction in Patients With Advanced Cancer: A Multicenter Prospective Cohort Study. *Oncologist*, 20:839-844, 2015
3. Hamano J, Morita T, Ozawa T, Shishido H, Kawahara M, Aoki S, Demizu A, Goshima M, Goto K, Gyoda Y, Hashimoto K, Otomo S, Sekimoto M, Shibata T, Sugimoto Y, Matsunaga M, Takeda Y, Nagayama J, Kinoshita H. Validation of the Simplified Palliative Prognostic Index Using a Single Item From the Communication Capacity Scale. *J Pain Symptom Manage*, 50:542-547.e4, 2015
4. Maeda I, Morita T, Kinoshita H. Reply to H. Nakayama et al. *J Clin Oncol*, 33:2228-2229, 2015
5. Wada S, Shimizu K, Inoguchi H, Shimoda H, Yoshiuchi K, Akechi T, Uchida M, Ogawa A, Fujisawa D, Inoue S, Uchitomi Y, Matsushima E. The Association Between Depressive Symptoms and Age in Cancer Patients: A Multicenter Cross-Sectional Study. *J Pain Symptom Manage*, 50:768-777, 2015
6. Kizawa Y, Morita T, Miyashita M, Shinjo T, Yamagishi A, Suzuki S, Kinoshita H, Shirahige Y, Yamaguchi T, Eguchi K. Improvements in Physicians' Knowledge, Difficulties, and Self-Reported Practice After a Regional Palliative Care Program. *J Pain Symptom Manage*, 50:232-240, 2015
7. Miura T, Matsumoto Y, Hama T, Amano K, Tei Y, Kikuchi A, Suga A, Hisanaga T, Ishihara T, Abe M, Kaneishi K, Kawagoe S, Kuriyama T, Maeda T, Mori I, Nakajima N, Nishi T, Sakurai H, Morita T, Kinoshita H. Glasgow prognostic score predicts prognosis for cancer patients in palliative settings: a subanalysis of the Japan-prognostic assessment tools validation (J-ProVal) study. *Support Care Cancer*, 23:3149-3156, 2015
8. Umezawa S, Fujimori M, Matsushima E, Kinoshita H, Uchitomi Y. Preferences of advanced cancer patients for communication on anticancer treatment cessation and the transition to palliative care. *Cancer*, 121:4240-4249, 2015
9. Igarashi T, Abe K, Miura T, Tagami K, Motonaga S, Ichida Y, Hasuo H, Matsumoto Y, Saito S, Kinoshita H. Oxycodone frequently induced nausea and vomiting in oxycodone-naïve patients with hepatic dysfunction. *J Palliat Med*, 18:399, 2015
10. Mori M, Shimizu C, Ogawa A, Okusaka T, Yoshida S, Morita T. A National Survey to Systematically Identify Factors Associated With Oncologists' Attitudes Toward End-of-Life Discussions: What Determines Timing of End-of-Life Discussions? *Oncologist*, 20:1304-1311, 2015
11. Shimizu K, Nakaya N, Saito-Nakaya K, Akechi T, Ogawa A, Fujisawa D, Sone T, Yoshiuchi K, Goto K, Iwasaki M, Tsugane S, Uchitomi Y. Personality traits and coping styles explain anxiety in lung cancer patients to a greater extent than other factors. *Jpn J Clin Oncol*, 45:456-463, 2015
12. Umezawa S, Fujisawa D, Fujimori M, Ogawa A, Matsushima E, Miyashita M. Prevalence, associated factors and source of support concerning supportive care needs among Japanese cancer survivors. *Psychooncology*, 24:635-642, 2015
13. Yokomichi N, Morita T, Nitto A, Takahashi N, Miyamoto S, Nishie H, Matsuoka J, Sakurai H, Ishihara T, Mori M, Tarumi Y, Ogawa A. Validation of the Japanese Version of the Edmonton Symptom Assessment System-Revised. *J Pain Symptom Manage*, 50:718-723, 2015
14. Kinoshita H, Maeda I, Morita T, Miyashita M, Yamagishi A, Shirahige Y, Takebayashi T, Yamaguchi T, Igarashi A, Eguchi K. Place of death and the differences in patient quality of death and dying and caregiver burden. *J Clin Oncol*, 33:357-363, 2015

Book

1. Ogawa A. Long-term cognitive function. In: Bruera E, Higginson IJ, von Gunten CF, Morita T (eds), *Textbook of Palliative Medicine and Supportive Care*, Second Edition, USA, CRC Press, pp 1269-1275, 2015

DIVISION OF RADIATION ONCOLOGY AND PARTICLE THERAPY

Tetsuo Akimoto, Sadatomo Zenda, Hidenobu Tachibana, Ryosuke Kohno, Kenji Hotta, Hiromi Baba

Introduction

The aim of research in the Division of Radiation Oncology and Particle Therapy at the National Cancer Center Hospital East is to study and develop innovative treatment techniques and pilot a clinical trial for proton beam therapy (PBT). Medical physicists mainly perform development and verification of the systems for beam irradiation, a dose calculation system, dose measurement and imaging of PBT. Radiation oncologists mainly perform studies on the clinical trials, efficacy and side-effects of PBT.

Routine activities

At present, the staff of the Radiation Oncology and Particle Therapy Division consists of seven consultant physicians (radiation oncologists), six radiation technologists, four medical physicists, one nurse, and one clerk. We have more than 300 new patients for PBT every year, and quality assurances of PBT are performed by medical physicists and radiation technologists, and the conference on verification of treatment planning is held every morning in addition to a weekly work conference regarding research activities. PBT are routinely based on three-dimensional radiation therapy planning and PBT using RT-dedicated multi-detector-row helical computed tomography (CT) scanning in order to confirm a precise radiation dose to the targeted tumors. Respiratory-gating has been applied especially in radiotherapeutic management for patients with lung, esophagus and liver cancers. The section is responsible for PBT that is composed of seven operating staff members and one technician for fabricating the compensator and aperture; they are sent from manufacturing companies and work in collaboration with the other staff members of the Division. PBT consists of two treatment rooms, both of which are routinely

used for rotational gantry treatment. The Division ensures quality assurance and regular maintenance of the PBT machines for precise dose delivery and safe treatment.

Research activities

- 1) PBT as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study.
- 2) Phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer.
- 3) Phase I/II study of dose escalated PBT combined with chemotherapy for esophageal cancer.
- 4) Establishment of feasibility and effectiveness of line scanning for localized prostate cancer.
- 5) Proton dose distribution measurements using a MOSFET detector with a simple dose-weighted correction method for LET effects.
- 6) Radiobiological evaluation of cellular response to PBT.
- 7) Radiobiological evaluation of combined effect of chemotherapeutic agents on enhancement of PBT.
- 8) Standardization of methods of PBT and quality assurance of PBT among Japanese proton beam facilities.
- 9) Establishment of infrastructure for multi-institutional study of PBT for various cancers.
- 10) Technical development of intensity modulated proton beam therapy (IMPT).

Clinical trials

The following in-house and multi-institutional clinical trials are under way.

- 1) Phase II study of PBT for malignant melanoma of nasal cavity.
- 2) Phase II study of PBT combined with chemotherapy for inoperable non-small cell lung cancer.

- 3) Phase I/II study of dose escalated study of PBT combined with chemotherapy for esophageal cancer
- 4) Phase I/II study of line scanning for localized prostate cancer

Education

We established an education and training system for residents and junior radiation oncologists through clinical conferences and lectures on radiation oncology, physics and radiation biology. In addition, a training course regarding quality

assurance of radiation therapy including proton beam therapy has been regularly held for medical physicists and radiological technologists.

Future prospects

We are now aiming at the establishment of the system that can provide high-quality and safe proton beam therapy. In addition, we would like to promote research and development of innovative technologies regarding proton beam therapy, radiation biology and medical physics.

Table 1. Number of patients treated with PBT during 2011-2015

| | 2011 | 2012 | 2013 | 2014 | 2015 |
|------------------------------|------|------|------|------|------|
| New patients | 200 | 245 | 378 | 331 | 310 |
| Head and neck cancers | 49 | 45 | 35 | 33 | 38 |
| Lung and mediastinal cancers | 24 | 76 | 101 | 82 | 80 |
| Hepatocellular carcinoma | 27 | 35 | 38 | 21 | 23 |
| Prostate cancer | 93 | 79 | 143 | 111 | 85 |
| Others | 7 | 17 | 45 | 54 | 84 |

Table: The changes in the number of patients treated with PBT

List of papers published in 2015

Journal

1. Tahara M, Kiyota N, Mizusawa J, Nakamura K, Hayashi R, Akimoto T, Hasegawa Y, Iwae S, Monden N, Matsuura K, Fujii H, Onozawa Y, Homma A, Kubota A, Fukuda H, Fujii M. Phase II trial of chemoradiotherapy with S-1 plus cisplatin for unresectable locally advanced head and neck cancer (JCOG0706). *Cancer Sci*, 106:726-733, 2015
2. Hotta K, Kohno R, Nagafuchi K, Yamaguchi H, Tansho R, Takada Y, Akimoto T. Evaluation of monitor unit calculation based on measurement and calculation with a simplified Monte Carlo method for passive beam delivery system in proton beam therapy. *J Appl Clin Med Phys*, 16:228-238, 2015
3. Mizowaki T, Aoki M, Nakamura K, Yorozu A, Kokubo M, Karasawa K, Kozuka T, Nakajima N, Sasai K, Akimoto T. Current status and outcomes of patients developing PSA recurrence after prostatectomy who were treated with salvage radiotherapy: a JROSG surveillance study. *J Radiat Res*, 56:750-756, 2015
4. Hashimoto Y, Akimoto T, Iizuka J, Tanabe K, Mitsuhashi N. Correlation between the changes in the EPIC QOL scores and the dose-volume histogram parameters in high-dose-rate brachytherapy combined with hypofractionated external beam radiation therapy for prostate cancer. *Jpn J Clin Oncol*, 45:81-87, 2015
5. Motegi A, Kawashima M, Arahira S, Zenda S, Toshima M, Onozawa M, Hayashi R, Akimoto T. Accelerated radiotherapy for T1 to T2 glottic cancer. *Head Neck*, 37:579-584, 2015
6. Zenda S, Ishi S, Akimoto T, Arahira S, Motegi A, Tahara M, Hayashi R, Asanuma C. DeCoP, a Dermatitis Control Program using a moderately absorbent surgical pad for head and neck cancer patients receiving radiotherapy: a retrospective analysis. *Jpn J Clin Oncol*, 45:433-438, 2015
7. Hatanaka S, Miyabe Y, Tohyama N, Kumazaki Y, Kurooka M, Okamoto H, Tachibana H, Kito S, Wakita A, Ohotomo Y, Ikagawa H, Ishikura S, Nozaki M, Kagami Y, Hiraoka M, Nishio T. Dose calculation accuracies in whole breast radiotherapy treatment planning: a multi-institutional study. *Radiol Phys Technol*, 8:200-208, 2015
8. Zenda S, Kawashima M, Arahira S, Kohno R, Nishio T, Tahara M, Hayashi R, Akimoto T. Late toxicity of proton beam therapy for patients with the nasal cavity, para-nasal sinuses, or involving the skull base malignancy: importance of long-term follow-up. *Int J Clin Oncol*, 20:447-454, 2015

DIVISION OF FUNCTIONAL IMAGING

Hirofumi Fujii, Izumi O. Umeda, Masayuki Yamaguchi, Mitsuyoshi Yoshimoto

Introduction

The Division of Functional Imaging actively investigates three kinds of imaging modalities, namely, radionuclide imaging, optical imaging and magnetic resonance (MR) imaging, to establish therapeutic strategies for minimally invasive and personalized cancer treatments. For radionuclide and optical imaging, some experimental studies were performed to develop unique applications of imaging probes and the usefulness of new methods was evaluated by *in vivo* imaging. For MR imaging, some experimental and clinical studies were done using two kinds of scanners: a 9.4 T scanner dedicated to small animal imaging and a 3.0 T whole-body scanner.

Research activities

In the field of nuclear medicine, we studied the prediction of the therapeutic efficacy of liposomal anti-cancer agents, such as Doxil[®], by using SPECT imaging with radiolabeled liposomes. We found a good correlation between tumor accumulation of radiolabeled liposomes and the therapeutic efficacy of Doxil. This result suggested that radiolabeled liposomes would be useful to predict the sensitivity of liposomal drugs to the patients, and this method will contribute to the development of personalized medicine.

Radiolabeled liposomes are also promising for tumor theranostics because of their high affinity to tumors. However, conventional liposomes also accumulate in normal tissues such as liver and spleen. This has hindered their clinical application. We have already developed a certain system that accelerated the clearance from normal tissues using a unique chelating ligand, EC (ethylenedicysteine). However, our concept did not work on mouse xenograft models bearing human cancer. We decreased the liposomal dosage according to the

hepatic clearance rate of the mouse and modified liposomes with PEG. As a result, we could overcome this problem due to the difference of mouse strain and we made progress in clinical application of this concept.

In boron neutron capture therapy (BNCT), 4-borono-L-phenylalanine (BPA) is a representative ¹⁰B carrier and PET using ¹⁸F-FBPA, which is an analogue of BPA, has been performed to estimate BPA uptake in tumors. We compared the transport mechanism of ¹⁸F-FBPA with that of ¹⁴C-BPA in *in vitro* studies. In a cell uptake experiment, the uptake of ¹⁸F-FBPA and ¹⁴C-BPA was drastically inhibited by 2-aminobicyclo-(2.2.1)-heptane-2-carboxylic acid (BCH), indicating that these are transported through a system L transporter. Western blotting revealed that A-253 and FaDu that showed the high FBPA uptake highly express L-type amino acid transporter 1. In addition, ¹⁸F-FBPA uptake significantly correlated with ¹⁴C-BPA uptake. We investigated the correlation between ¹⁸F-FBPA uptake and BPA uptake in tumor-bearing mice models. A biodistribution study and microPET study indicated that the tumor uptake of ¹⁸F-FBPA correlated with a boron concentration derived from BPA. These results suggest that ¹⁸F-FBPA PET is useful to estimate the sensitivity to BNCT using BPA.

In the field of magnetic resonance (MR) imaging, superparamagnetic iron oxide (SPIO)-enhanced MR imaging was investigated to precisely visualize the margins of treated areas of hepatic tumors after radiofrequency ablation (RFA) as well as radiation therapies. Our experimental studies using rats revealed that SPIO particles remained for a long time in damaged liver tissues due to RFA or radiotherapy, and visualized the damaged liver tissues as dark areas in contrast to tumors as bright areas on MR images. Therefore, it was suggested that SPIO-enhanced MR imaging was utilized to delineate the margin of RFA- or radio-

treated areas. In addition, our recent experiments have demonstrated that the visualization of the margins of irradiated liver tissue helps to evaluate the response of liver cancer lesions to radiotherapy. Collectively, we contend that this imaging technique helps clinicians to evaluate the risk of recurrence and enhance the curability of liver tumors.

Clinical trials

We carried out a prospective cohort study to investigate metabolite levels in the brain after cancer chemotherapy in 68 Japanese breast cancer patients by using MR spectroscopy (MRS). This was a cooperative study with the Division of Psycho-Oncology, National Cancer Center. A 3.0-tesla MR scanner and MRS methods called PRESS and MEGA-PRESS detected various brain metabolites including glutamate and γ -aminobutyric acid (GABA), which are principal neurotransmitters. Importantly, these MRS methods allowed longitudinal observation of brain metabolite levels

during the prospective study (average duration, 54 weeks; standard deviation, 19 weeks). Thus we contend that MR spectroscopy by using a 3.0-tesla MR scanner is a valuable approach to longitudinally monitor brain metabolite levels in chemotherapy-treated breast cancer patients. This approach will hopefully provide important information with regard to chemotherapy-related cognitive impairment (so called "chemo-brain") in breast cancer survivors.

Education

Some graduate school students took part in our studies and received doctor or master degrees in the field of medicine and related sciences.

Future prospects

We will develop our research projects to translate our research products into clinical practice.

List of papers published in 2015

Journal

1. Yoshimoto M, Kurihara H, Fujii H. Theragnostic imaging using radiolabeled antibodies and tyrosine kinase inhibitors. *ScientificWorldJournal*, 2015:842101, 2015
2. Nagai M, Yamaguchi M, Mori K, Furuta T, Ashino H, Kurosawa H, Kasahara H, Minami M, Fujii H. Magnetic resonance-based visualization of thermal ablative margins around hepatic tumors by means of systemic ferucarbotran administration before radiofrequency ablation: animal study to reveal the connection between excess iron deposition and T2*-weighted hypointensity in ablative margins. *Invest Radiol*, 50:376-383, 2015
3. Okamoto M, Naka K, Kitagawa Y, Ishiwata K, Yoshimoto M, Shimizu I, Toyohara J. Synthesis and evaluation of 7 α -(3-[(18)F] fluoropropyl) estradiol. *Nucl Med Biol*, 42:590-597, 2015
4. Fujii H, Iimoto T, Tsuzuki T, Iizumi S, Someya S, Hamamichi S, Kessler MM. Collaboration of local governments and experts responding to the increase of the environmental radiation level secondary to the nuclear accident: a unique activity to relieve residents' anxiety. *Radiat Prot Dosimetry*, 167:370-375, 2015
5. Iimoto T, Nunokawa J, Fujii H, Takashima R, Hashimoto M, Fukuhara T, Yajima T, Matsuzawa H, Kurosawa K, Yanagawa Y, Someya S. Collaboration of local government and experts responding to increase in environmental radiation level due to the nuclear disaster: focusing on their activities and latest radiological discussion. *Radiat Prot Dosimetry*, 167:358-364, 2015

DIVISION OF SCIENCE AND TECHNOLOGY FOR ENDOSCOPY

Kazuhiro Kaneko, Tomonori Yano, Mari Takahashi, Atsushi Yagishita

Introduction

Approximately 50 years have passed since the gastrofiberscope came into existence, and diagnostic techniques have progressed rapidly. Now, endoscopy is widely used for screening, diagnosis, and treatment of early cancer in aerodigestive tracts including the pharynx, esophagus, stomach, and colorectum. With conventional endoscopy, observations are made using white light to illuminate the mucosal surface with special attention paid to the appearance of reddish and irregular portions compared to adjacent areas. Thus, detection of suspicious early cancerous lesions has been largely based on macroscopic characteristics of the lesions.

One of the characteristics of early cancer is the growth of blood vessels (neovascularity). Using two narrow wave bands of light (blue: 390-445nm; green: 530-550nm) that can be absorbed by circulating hemoglobin, Narrow band imaging (NBI) endoscopy may provide better images of the capillaries in the mucosal surface.

Another characteristic of a tumor is hypoxia. As a tumor grows, it rapidly outgrows its blood supply, leaving portions of the tumor with regions where the oxygen concentration is significantly lower than in healthy tissues. Thus, there have been attempts to visualize spatial distribution of tumor hypoxia, such as fluorescent labeling techniques or hemoglobin absorption-based techniques. However, these methods are limited because of low spatiotemporal resolution. We developed an imaging technology that can derive oxygen saturation (StO₂) images from small numbers of wavelength measurements. Thus, next-generation novel endoscopy will be required to make visible specific functions in cancerous tissues. To advance the technology, laser light and near-infrared light will be necessary.

Routine activities

The present research activities mainly focus on the development of new instruments for endoscopic diagnosis and new endoscopic treatment modalities. In the present situation, because questions still need to be raised in development research regarding endoscopy, our Division collaborates with the Endoscopy Division. Therefore, endoscopic diagnosis is routinely performed for cancer patients and endoscopic treatment, such as EMR or ESD, is performed in patients with early GI tract cancers. We give lectures to resident doctors regarding individual projects. Furthermore, meetings are constantly conducted with faculties including of technology and science students of the university.

Research activities

Research studies have been conducted in various fields: endoscopic diagnosis and treatment, and prevention of cancer in the GI tract and head and neck. In addition, the present research is to develop new devices or procedures in innovative less-invasive laparoscopic surgery for gastrointestinal malignancies. These projects are conducted as prospective clinical studies and preclinical studies in collaboration with not only commercial companies but also the faculties of Technology and Science of the university.

Developing research into novel endoscopy systems is being performed. Hypoxia imaging is detected for neoplastic lesions of the head and neck and alimentary tracts, with two types of visualized images: a pseudocolor StO₂ image and a StO₂ overlay image. Another project is a new bioimaging system using near-infrared light with a wavelength of over 1,000 nm with various spectrums. This system is capable of penetrating through the gastrointestinal wall and obtaining images. Furthermore, a preclinical study of molecular

imaging endoscopy using small molecules, peptides and antibodies was planned this year. With a low-temperature atmospheric pressure plasma system, endoscopic hemostasis and inactivation of bacteria are being investigated. A novel diagnosis system using photosensitizing agents, such as hypericin, has been constructed. A novel tattooing system under endoscopy has been developed. Now, a patent is being sought for this system. Ongoing projects are to develop needle graspers, needle ultrasonic coagulators in the surgical field. A clinical trial regarding confocal laser endocytoscopy using fluorescein is planned. This type of endocytoscopy is classified into a new category.

Clinical trials

A first-in-human clinical trial of hypoxia imaging was incorporated into the endoscopic diagnosis of early and advanced cancers of the esophagus, stomach, and colorectum. We conducted a proof-of-concept trial for 40 patients with neoplastic lesions in the esophagus including the pharynx, stomach and colorectum. In this first-in-human trial (UMIN 000004983), two types of StO₂ images were used. One was a pseudocolor StO₂ image that showed StO₂ levels as different hues, and the other was a StO₂ overlay image that overlapped StO₂ levels in blue on a white light illumination image to detect background mucosa. In a system of near-infrared light with nanoparticles, nanoparticles of rare earth act as fluorescent agents. Nanoparticles attached probe excite due to emission of near-infrared light, when probes attach to the surface of cancer cells. Now, molecular imaging endoscopy for the use of this system with InGaAs CCD has been developed in collaboration with the Technology Department of the University. Preclinical studies, such as a low-temperature atmospheric pressure plasma system, and photodynamic diagnosis of hypericin, are performed using animal models. Furthermore, a clinical trial for biodegradable (BD) stent implantation for benign esophageal stricture after curative treatment and a clinical trial for photodynamic diagnosis using 5ALA are ongoing. A treatment of a new concept for a precursor or early cancer of the duodenum was planned in collaboration with Norway University of Science and Technology.

Education

The aim is the cultivation of human resources who specialize in endoscopic diagnosis and treatment for alimentary tract cancer. Staff supervise individual residents. The importance of positiveness is highlighted in periodic case conferences and joint conferences among internal medicine, surgery and radiology. Staff supervise in congress presentations and writing manuscripts after deciding upon individual themes, and a lot of discussion is undertaken in department conferences. For residents interested in development research, the opportunity to study is supported after graduation. Personal exchanges were performed with PMDA.

Future prospects

Existing endoscopic diagnosis for neoplasia of the alimentary tract is performed on the basis of the morphological features of tumors. Molecular imaging endoscopy is a novel system to visualize cancer using a specific laser source under phosphor combined with cancer-specific agents. We can obtain new imaging, since functions or the metabolic state in cancer cells is visualized. In additional modalities, there are photodynamic diagnosis, endomicroscopy, and hypoxia imaging endoscopy. We endeavor to perform first-in-human clinical trials. These modalities will be expected as next-generation endoscopy, and we try innovative approaches to produce all-new endoscopy in collaboration with academia and companies.

List of papers published in 2015

Journal

1. Osera S, Ikematsu H, Odagaki T, Oono Y, Yano T, Kobayashi A, Ito M, Saito N, Kaneko K. Efficacy and safety of endoscopic radial incision and cutting for benign severe anastomotic stricture after surgery for lower rectal cancer (with video). *Gastrointest Endosc*, 81:770-773, 2015
2. Zako T, Yoshimoto M, Hyodo H, Kishimoto H, Ito M, Kaneko K, Soga K, Maeda M. Cancer-targeted near infrared imaging using rare earth ion-doped ceramic nanoparticles. *Biomater Sci*, 3:59-64, 2015
3. Satake H, Yano T, Yoda Y, Fujii S, Zenda S, Tomioka T, Shinozaki T, Miyazaki M, Kaneko K, Hayashi R. Feasibility of salvage endoscopic resection for patients with locoregional failure after definitive radiotherapy for pharyngeal cancer. *Endosc Int Open*, 3:E274-E280, 2015
4. Zako T, Ito M, Hyodo H, Yoshimoto M, Watanabe M, Takemura H, Kishimoto H, Kaneko K, Soga K, Maeda M. Extra-luminal detection of assumed colonic tumor site by near-infrared laparoscopy. *Surg Endosc*, 2015
5. Ikematsu H, Matsuda T, Osera S, Imajoh M, Kadota T, Morimoto H, Sakamoto T, Oono Y, Kaneko K, Saito Y. Usefulness of narrow-band imaging with dual-focus magnification for differential diagnosis of small colorectal polyps. *Surg Endosc*, 29:844-850, 2015
6. Kanesaka T, Uedo N, Yao K, Ezoe Y, Doyama H, Oda I, Kaneko K, Kawahara Y, Yokoi C, Sugiura Y, Ishikawa H, Kato M, Takeuchi Y, Muto M, Saito Y. A significant feature of microvessels in magnifying narrow-band imaging for diagnosis of early gastric cancer. *Endosc Int Open*, 3:E590-E596, 2015
7. Mochizuki S, Uedo N, Oda I, Kaneko K, Yamamoto Y, Yamashina T, Suzuki H, Kodashima S, Yano T, Yamamichi N, Goto O, Shimamoto T, Fujishiro M, Koike K, SAFE Trial Study Group. Scheduled second-look endoscopy is not recommended after endoscopic submucosal dissection for gastric neoplasms (the SAFE trial): a multicentre prospective randomised controlled non-inferiority trial. *Gut*, 64:397-405, 2015
8. Satake H, Yano T, Muto M, Minashi K, Yoda Y, Kojima T, Oono Y, Ikematsu H, Aoyama I, Morita S, Miyamoto S, Fujii S, Yoshizawa A, Ochiai A, Hayashi R, Kaneko K. Clinical outcome after endoscopic resection for superficial pharyngeal squamous cell carcinoma invading the subepithelial layer. *Endoscopy*, 47:11-18, 2015
9. Osera S, Yano T, Odagaki T, Oono Y, Ikematsu H, Ohtsu A, Kaneko K. Peritonitis related to percutaneous endoscopic gastrostomy using the direct method for cancer patients. *Surg Endosc*, 29:2941-2946, 2015

DIVISION OF SURGICAL TECHNOLOGY

Masaaki Ito, Takahiro Kinoshita

Activities/Research activities

Our research activity in the Department of Surgical Innovation started in 2013. The main purpose of this Department is to develop surgical devices that are truly necessary, to deliver them to clinical fields, and to prove their efficacy and safety through clinical trials.

The three main elements of our innovation are creating devices reflecting true needs in the medical field, practicing with the devices in clinical trials and connecting our innovations to a wider world.

We have collaborated between clinical surgeons and engineers in the NEXT Innovating Group. We have continued to clarify problem points in previously developed Japanese medical devices

and focused on innovation plans and formed partnerships with various companies.

Contents of innovation

Establishment of NEXT Conference

We started discussions to make innovative surgical devices in the NEXT Conference, which was jointly held by professionals consisting of surgeons and coordinators of surgical innovation, intellectual property and pharmaceutical affairs. Specific devices started to be created through discussion in the NEXT Conference.

Innovation schemes were divided into two groups according to the risk level: Level I and Level II.

The devices made were as follows:

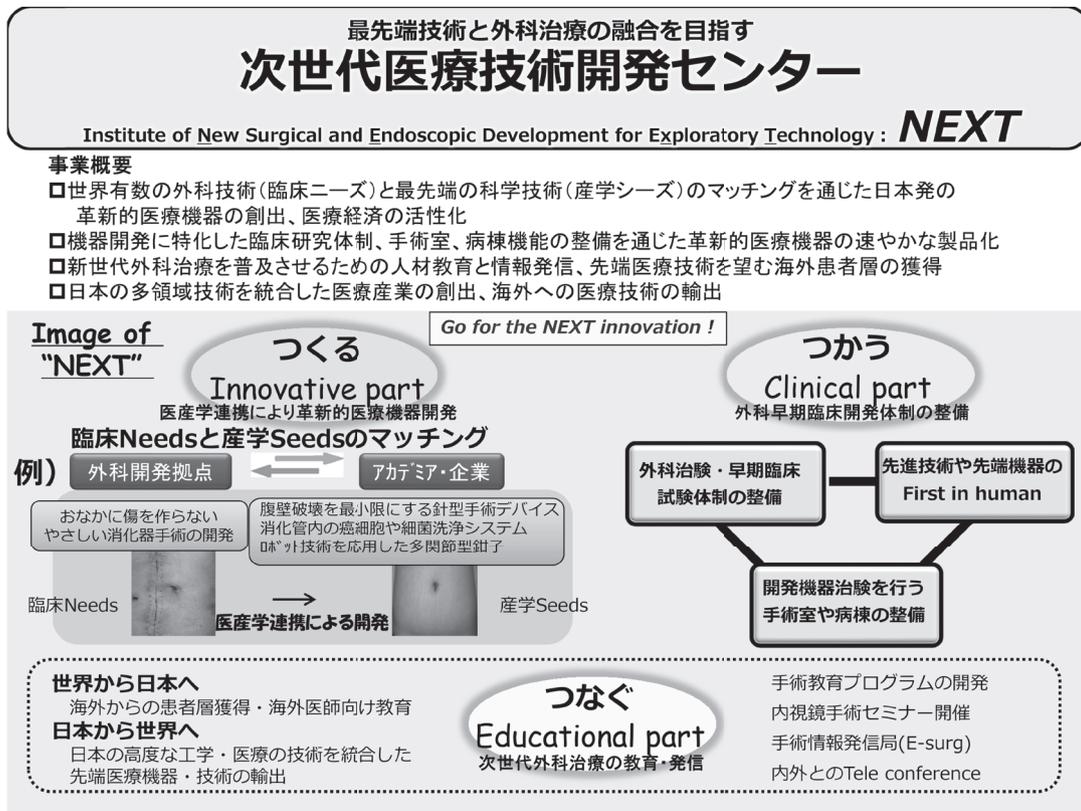


Figure 1.

Level I Devices

- 1) Device assisting standing position during long-time surgery
- 2) Suture thread for training
- 3) Endoscopic simulator

Level II Devices

- 1) Surgical robot undertaking endoscopy
- 2) Anal drain reducing anastomotic pressure
- 3) New puncture therapy

Surgical robotic system innovated by the National Cancer Center (NCC)-certified venture company, A-Traction

A-Traction Company was established in August 2015 to innovate new surgical robotic systems.

This venture company received a major investment from Medventure Partners Company and was certified as a collaborative company with the National Cancer Center.

Create supportive infrastructure for surgical innovation

We are aiming to establish a clinical trials infrastructure for surgical innovation in the National Cancer Center Hospital East. Two surgical clinical trials were completed this year and reinforced the infrastructures through these trials.

List of papers published in 2015

Journal

1. Shiomi A, Ito M, Maeda K, Kinugasa Y, Ota M, Yamaue H, Shiozawa M, Horie H, Kuriu Y, Saito N. Effects of a diverting stoma on symptomatic anastomotic leakage after low anterior resection for rectal cancer: a propensity score matching analysis of 1,014 consecutive patients. *J Am Coll Surg*, 220:186-194, 2015
2. Kawai T, Shin M, Nishizawa Y, Horise Y, Nishikawa A, Nakamura T. Mobile locally operated detachable end-effector manipulator for endoscopic surgery. *Int J Comput Assist Radiol Surg*, 10:161-169, 2015
3. Ohue M, Hamaguchi T, Ito Y, Sakai D, Noura S, Kinugasa Y, Fujita S, Shimada Y, Saito N, Moriya Y. A phase I trial of preoperative S-1 in combination with oxaliplatin and pelvic radiation for lower rectal cancer with T4 and lateral pelvic lymph node metastasis. *Int J Clin Oncol*, 20:338-344, 2015
4. Kobayashi S, Ito M, Yamamoto S, Kinugasa Y, Kotake M, Saida Y, Kobatake T, Yamanaka T, Saito N, Moriya Y. Randomized clinical trial of skin closure by subcuticular suture or skin stapling after elective colorectal cancer surgery. *Br J Surg*, 102:495-500, 2015
5. Yokota M, Kojima M, Higuchi Y, Nishizawa Y, Kobayashi A, Ito M, Saito N, Ochiai A. Spread of tumor microenvironment contributes to colonic obstruction through subperitoneal fibroblast activation in colon cancer. *Cancer Sci*, 106:466-474, 2015
6. Yokota M, Kobayashi A, Nomura S, Nishizawa Y, Ito M, Nagai K, Saito N. Patterns and treatment of recurrence following pulmonary resection for colorectal metastases. *World J Surg*, 39:1758-1766, 2015
7. Kondo A, Nishizawa Y, Akamoto S, Fujiwara M, Okano K, Suzuki Y. Internal inguinal hernia on the transplant side after kidney transplantation: a case report. *Surg Case Rep*, 1:108, 2015

Clinical trials concerning robotic surgery for gastric cancer and rectal cancer are on-going.

Activity of regional cooperation group for surgical innovation, C-Square

Last year, we established a regional cooperation group for surgical innovation with a framework that consisted of Chiba Prefecture, Chiba Industry Advancement Center, Chiba University and the National Cancer Center Hospital. The aim of the activities of C-Square is to realize surgical innovation based on clinical needs through use of regional industrial technology. Development of certain new surgical devices began through two symposiums held in C-square.

Education

We held regular in-house seminars to teach about surgical innovations for the development of human resources.

Future prospect

We are going to establish a clinical support team for early-phase surgical innovations and aim to make a road-map for surgical innovation.

SECTION OF EXPERIMENTAL ANIMALS

Yoshikatsu Koga, Kimie Iijima, Taeko Aruga, Aki Kawaida

Introduction

The basic and translational research undertaken in the Exploratory Oncology Research & Clinical Trial Center (EPOC) is aimed toward future clinical use. To develop anti-cancer drugs based on a novel concept or a novel imaging technology, animal experiments are necessary. The Section of Experimental Animals supports the animal experiments conducted in EPOC.

Routine activities

- Health management of the experimental animals and maintenance of the animal laboratories.
 - Animal-breeding rooms: specific pathogen-free

(SPF) rooms (eight rooms for mice and one room for rats), conventional rooms (one room for mice, one room for rats, hamsters, and rabbits, and one room for pigs), and P2 animal laboratory.

- Approval of animal experiments and gene recombinant experiments in accordance with regulations.
 - In 2015, 58 studies involving animal experiments and 35 studies with gene recombinant experiments were approved by the Committee of Experimental Animals and Gene Recombination.

List of papers published in 2015

Journal

1. Ahn J, Miura Y, Yamada N, Chida T, Liu X, Kim A, Sato R, Tsumura R, Koga Y, Yasunaga M, Nishiyama N, Matsumura Y, Cabral H, Kataoka K. Antibody fragment-conjugated polymeric micelles incorporating platinum drugs for targeted therapy of pancreatic cancer. *Biomaterials*, 39:23-30, 2015
2. Koga Y, Manabe S, Aihara Y, Sato R, Tsumura R, Iwafuji H, Furuya F, Fuchigami H, Fujiwara Y, Hisada Y, Yamamoto Y, Yasunaga M, Matsumura Y. Antitumor effect of antitissue factor antibody-MMAE conjugate in human pancreatic tumor xenografts. *Int J Cancer*, 137:1457-1466, 2015
3. Yamamoto Y, Hyodo I, Koga Y, Tsumura R, Sato R, Obonai T, Fuchigami H, Furuya F, Yasunaga M, Harada M, Kato Y, Ohtsu A, Matsumura Y. Enhanced antitumor effect of anti-tissue factor antibody-conjugated epirubicin-incorporating micelles in xenograft models. *Cancer Sci*, 106:627-634, 2015
4. Tsumura R, Sato R, Furuya F, Koga Y, Yamamoto Y, Fujiwara Y, Yasunaga M, Matsumura Y. Feasibility study of the Fab fragment of a monoclonal antibody against tissue factor as a diagnostic tool. *Int J Oncol*, 47:2107-2114, 2015