Exploratory Oncology
Research & Clinical Trial Center

Preface

In 2011, our National Cancer Center was selected as one of the five designated centers for early/exploratory clinical trial. With a 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 in 2012, which focus on early/exploratory clinical trial and translational research (TR). The NCC-EPOC has been actually activated in April 2013 consisting of a phase I unit in each campus, 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. For innovative oncology drug developments from Japan, three missions are hung up in the NCC-EPOC: to conduct first-in-human (FIH) trials, investigator-initiated trials (IIT) with unapproved agents, and TRs during early clinical studies. The activity in each unit in 2013 is described as below.

1) Phase I unit: The Experimental Therapeutics Department consisting of several medical oncologists with backgrounds from each organ department was newly organized in both hospitals in order to conduct all comer type FIH/phase I studies. Regular weekly teleconference is held to collaborate the two groups in each hospital. In 2013, 6 sponsor-initiated FIH trials have already been conducted in total at both hospitals. The number of the phase I studies in the NCC is ranked as the largest academic center in Asia. There were several international phase I studies including FIH study.

2) IIT support unit: The central support/data center for IIT has been established with a total of 37 members including project manager, monitor, data manager, biostatistician, medical writer, and auditors. Since launched in 2012, the NCC-EPOC has initiated 14 registrational IITs in accordance with ICH-GCP (so-called "ishi-syudo chiken") with an unapproved agent. Eight of the 18 studies has already completed its accrual in collaboration with several major cancer centers. These IITs are categorized into three group: 4 developmental studies with new academia seeds, 7 exploratory studies unapproved agents developed by industry, and 4 studies as expanded access program for unapproved agents. As for the academic seeds development, 11 seeds are being designated for clinical implications including three seeds already under clinical trials. Alliance contract between the NCC and the National Institute of Biomedical Innovation has been formally achieved for establishing a nation-wide oncology seeds collection network. Intellectual property in the NCC is being integrated for efficient new seeds/drugs development.

3) TR unit: New procedure of companion diagnosis for RET fusion gene, which was originally discovered in the NCC-Research Institute, was established and transferred to a laboratory company, which became a basis of the nation-wide genome screening network (LC-SCRUM). Several pharmaceutical companies, who conducted similar new agent development studies for tiny population with driver gene alterations, joined this network under contract with NCC. A similar screening system for some driver gene has also started in colorectal cancers using original developed screening panel, followed by an organization of nation-wide genome screening academia-industry consortium (SCRUM-JAPAN) using a cutting-edge pan-cancer NGS panel. A total of 13 pharmaceutical companies are collaborating with the consortium for 4,500 patients with lung and gastrointestinal cancer genome screening in association with new agent studies. This study will contribute to make a public data base of genome profiling and a distribution of precision medicine in Japan. In the immunotherapy division, an IIT with an originally developed cancer vaccine has already been studied and a new immune-modulating agent is being developed in collaboration with investigators in the University of Tokyo. Another project of new immune cell therapy with FITC-CART is also under preclinical investigations. A biotech company focusing on the development of new CAR-T therapy was launched in February 2015, which is the first venture company in NCC.

The goal of the NCC-EPOC is to establish a top innovative academic research organization in the world based on close alliances between academia-industry-government.

Atsushi Ohtsu, M.D., Ph.D.
Director, Exploratory Oncology Research & Clinical Trial Center

Organization

President:
Tomomitsu Hotta

Director:
Atsushi Ohtsu

Phase I Group

Department of Experimental Therapeutics

Chief (Kashiwa): Toshihiko Doi
Chief (Tsukiji): Noboru Yamamoto

Clinical Trial Management Office

Chief (Kashiwa): Koichi Goto
Chief (Tsukiji): Noboru Yamamoto

Translational Research Group

Division of Translational Research

Chief (Kashiwa): Katsuya Tsuchihara
Chief (Tsukiji): Takashi Kohno

Division of Cancer Immunotherapy

Chief (Kashiwa): Tetsuya Nakatsura
Chief (Tsukiji): Kiyoshi Yoshimura

Activities of the Divisions

Department of Experimental Therapeutics

[Kashiwa] Toshihiko Doi, Yoichi Naito, Kohei Shitara, Hideaki Takahashi, Kiyotaka Yoh, Tomoko Yamazaki Takahiro Kogawa
[Tsukiji] Noboru Yamamoto, Kenji Tamura, Yutaka Fujiwara, Shunsuke Kondo, Satoru Iwasa, Shigehisa Kitano, Yuko Tanabe, Akihiko Shimomura

Introduction

The NCC-EPOC Phase I Group has been organized to promote the early drug development especially the first in human (FIH) trial in 2012. The Phase I group consisted of two sub-units (NCCE-Kashiwa & NCC-Tsukiji) which are organized by each hospital. The goal of the NCC-EPOC Phase I Group is to perform initial clinical evaluation of promising new anti-cancer compounds emerging from the laboratory. Our Phase 1 unit is the largest program in Japan, indeed in Asia, and we contribute to the development of new cancer drugs through early phase trials.

In April 2013, the Department of Experimental Therapeutics has been launched to strongly promote the EPOC missions as previously described. The members of the Department of Experimental Therapeutics consisted of the specialists of their oncology fields (shown as a staff list).

Routine activities

The Department plays an important role of the new anti-cancer drug development in our center as well as in Japan. The top priority is to conduct the FIH trials, and we also perform the Phase I trials for solid tumors (i.e., all comers). Recently, we join the global Phase I trial to accelerate the new drug development in Japan. Web- or tel.-conferences are held with the EU and US sites, and we are discussing about the patient enrollment as well as the further developmental strategy. Routine web-conference are also held between Kashiwa and Tsukiji campus every Friday morning, and we are sharing information about adverse event, patient enrollment and are referring the candidate each other to accelerate enrollment.

Research activities

The elucidation of the proof of concept is essential in the new anti-cancer drug development especially in early phase, we conduct several translational researches in collaboration with the research institute adjoins. In each campus, the comprehensive genomic analyses, those are named as ABC-study and TOP-GEAR-study in Kashiwa and Tsukiji, respectively, are ongoing to facilitate the patient enrollment for the new molecular targeted drugs under investigation.

Clinical trials

In 2014, 39 Phase I trials have been conducted in both campus (Table 1).

Table 1. Phase I trials in the Dept. of Experimental Therapeutics in 2014

No.	Site	Target	FIH	Target	Enrollment in 2013	Status
1	Kashiwa+Tsukiji	CDDP micelles		Solid tumors	5	Closed
2	Kashiwa+Tsukiji	CDK4/6		Solid tumors	5	Closed
3	Kashiwa+Tsukiji	PD-L1		Solid tumors	16	Closed
4	Kashiwa+Tsukiji	FGFR	○	Solid tumors	12	Closed
5	Kashiwa+Tsukiji	FGFR	○	Solid tumors	10	Ongoing
6	Kashiwa+Tsukiji	PD-1		Solid tumors	23	Ongoing
7	Tsukiji	PIM	○	Solid tumors	2	Closed
8	Tsukiji	PI3K		Solid tumors	2	Closed
9	Tsukiji	PARP		Solid tumors	3	Closed
10	Tsukiji	PI3K		Solid tumors	9	Closed
11	Tsukiji	CDK4/6		Solid tumors	11	Closed
12	Tsukiji	Hedgehog		Solid tumors	7	Closed
13	Tsukiji	tubulin		Solid tumors	3	Closed
14	Tsukiji	B7-H3	○	Solid tumors	3	Ongoing
15	Tsukiji	FGFR	○	Solid tumors	2	Ongoing
16	Tsukiji	PD-L1		Solid tumors	10	Ongoing
17	Tsukiji	HSP90	○	Solid tumors	9	Ongoing
18	Tsukiji	CTLA-4		Solid tumors	6	Ongoing
19	Kashiwa	c-Met		Solid tumors	0	Closed
20	Kashiwa	targeting hypoxia		Solid tumors	5	Closed
21	Kashiwa	anti-cancer-stem cell		Solid tumors	7	Ongoing
22	Kashiwa	PTK2		Solid tumors	4	Ongoing
23	Kashiwa	FGFR		Solid tumors	4	Ongoing
24	Kashiwa	epirubicin micelles		Solid tumors	9	Ongoing
25	Kashiwa	EGFR		Solid tumors	13	Ongoing
26	Kashiwa	c-Met		Solid tumors	17	Ongoing
27	Kashiwa	*****		Solid tumors	17	Ongoing
28	Kashiwa	TEM-1		Solid tumors	6	Ongoing
29	Kashiwa	PI3K		Solid tumors	1	Ongoing
30	Kashiwa	MEK		Solid tumors	2	Ongoing
31	Kashiwa	c-Met		Solid tumors	5	Ongoing
32	Kashiwa	c-Met		Solid tumors	3	Ongoing
33	Kashiwa	MEK		Solid tumors	2	Closed
34	Kashiwa	EGFL7		Solid tumors	-	Withdrawal
35	Kashiwa	****		Solid tumors	7	Ongoing
36	Kashiwa	FGFR	○	Solid tumors	4	Ongoing
37	Kashiwa	IGFIR		Solid tumors	5	Ongoing
38	Kashiwa	****		Solid tumors	0	Ongoing
39	Kashiwa	****		Solid tumors	0	Ongoing

FIH: first in human trial

List of papers published in 2014

Journal

Phase I Group (Tsukiji)

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Phase I Group (Kashiwa)

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Division of Translational Research (Kashiwa)

Katsuya Tsuchihara, Sachiyo Mimaki, Hideki Makinoshima, Shingo Matsumoto, Wataru Okamoto, Atsushi Yagishita, Akiko Nagatsuma, Takayuki Yoshino, Atsushi Watanabe, Kazuyoshi Yanagihara, Yuka Nakamura, Atsushi Ochiai, Takeshi Kuwata, Yasuhiro Matsumura

Introduction

Basic and translational researchers at the National Cancer Center (NCC) Kashiwa Campus are involved in this division, the aim of which is to develop novel anti-cancer therapeutics as well as to prove their concepts. The Division also closely collaborates with intramural and extramural clinical research teams to develop a precision medicine of cancer treatment.

Routine activities

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

Research activities

1. Implication of genome biomarkers for cancer therapy
   ABC study, a pilot study in which feasibility and effectiveness of trans-organ multiplex genomic biomarker testing were investigated, has done. More than 250 cases with various solid tumors were analyzed and comprehensive clinical reports were returned to the physicians. Following the success of the study, we plan a nation-wide multi-center genome screening program for advanced lung and gastro-intestinal cancers. We named the program, "SCRUM-Japan" and it will be launched in 2015.
2. Genome-wide identification of the driver gene alterations of small cell lung cancer (SCLC) has done. About 40% of the patients harbored activating alterations of PI3K/AKT pathway molecules and these alterations could be targets for PI3K/MTOR inhibitors. An investigator-initiated trial to prove the efficacy of a PI3K/MTOR inhibitor for SCLC patients with alterations of PI3K/AKT pathway molecules is planned.
3. Comprehensive genome, epigenome and transcriptome analyses of lung adenocarcinoma cell lines performed by next-generation sequencing were finished. This dataset is consisted with multi-omics data of 26 cell lines, and 13 of 26 cell lines were established from Japanese patients' samples which have not been well characterized. All the data are compiled into a database which is open for public (http://dbtss/hgc/jp/) and it is expected to be used for exploring new therapeutic targets and biomarkers.
4. EGFR inhibition for EGFR-mutated lung adenocarcinoma is one the most successful molecular targeted therapies. We identified that EGFR inhibitors suppress lung adenocarcinoma cell-specific activation of aerobic glycolysis via the inhibition of kinase activities of EGFR. These findings highlight the importance of metabolic regulation of cancer cells to achieve therapeutic efficacy in molecular-targeted therapies.

Clinical trials

1. Analyses of Biopsy Samples for Cancer Genomics (ABC Study): Study representative and secretariat
2. Biomarker Research for Anti-EGFR Monoclonal Antibodies by Comprehensive Cancer Genomics (BREAC Study): Secretariat

Education

This division accepted and trained the following trainees;

Graduate students from the University of Tokyo (4), Tokyo Medical and Dental University (1), Keio University (1) and Juntendo University (1), Staff physician (2), senior resident (1), junior resident (3), Visiting scientists (6)

Future prospects

We aim to establish cancer precision medicine using cutting-edge technologies identifying useful molecular biomarkers. As well as exploring and implicating biological findings which stratify each cancer patient, it is important to provide infrastructures to securely and robustly use biomarkers for daily clinical use.

List of papers published in 2014

Journal

1. Umemura S, Mimaki S, Makinoshima H, Tada S, Ishii G, Ohmatsu H, Niho S, Yoh K, Matsumoto S, Takahashi A, Morise M, Nakamura Y, Ochiai A, Nagai K, Iwakawa R, Kohno T, Yokota J, Ohe Y, Esumi H, Tsuchihara K, Goto K. Therapeutic priority of the PI3K/AKT/mTOR pathway in small cell lung cancers as revealed by a comprehensive genomic analysis. J Thorac Oncol, 9:1324-1331, 2014
2. Makinoshima H, Takita M, Matsumoto S, Yagishita A, Owada S, Esumi H, Tsuchihara K. Epidermal growth factor receptor (EGFR) signaling regulates global metabolic pathways in EGFR-mutated lung adenocarcinoma. J Biol Chem, 289:20813-20823, 2014
3. Suzuki A, Makinoshima H, Wakaguri H, Esumi H, Sugano S, Kohno T, Tsuchihara K, Suzuki Y. Aberrant transcriptional regulations in cancers: genome, transcriptome and epigenome analysis of lung adenocarcinoma cell lines. Nucleic Acids Res, 42:13557-13572, 2014
4. Nasuno T, Mimaki S, Okamoto M, Esumi H, Tsuchihara K. Effect of a poly(ADP-ribose) polymerase-1 inhibitor against esophageal squamous cell carcinoma cell lines. Cancer Sci, 105:202-210, 2014

Division of Translational Research (Tsukiji)

Takashi Kohno, Hitoshi Ichikawa, Akinobu Hamada, Shuichi Shinma, Natsuko Hama, Yuka Kitamura, Yusuke Yoshioka, Tatsuhiro Shibata, Hiroki Sasaki

Introduction

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

Research activities

Clinical sequencing for early phase clinical trials

A next generation sequencer-based clinical sequencing, which enables us to identify genetic alterations, including gene fusions in 90 cancer-related genes, were applied to analyze 130 cases of advanced cancers in the TOPICS-1 (Trial of Onco-Panel for Introduction into Clinical Study-Phase 1) study (Figure 1). The actionable gene aberrations were defined in Expert Panel meetings to subject patients to phase I clinical trials to address "proof-of-concept" of the relationship between gene aberrations and therapeutic effects. Gene aberrations with therapeutic implications were found in about a half of cases, and <10% of patients were enrolled into phase I clinical trials according to "match" between genetic alterations and drug targets.

Novel Pharmacodynamic analysis for the development of new anticancer agents

Drug exposure and distribution in several tissues impact pharmacology, toxicology, and efficacy in drug development. MALDI (matrix-assisted laser desorption ionization) Mass Imaging system enables us to evaluate concentrations and spatial distributions of anticancer agents and metabolites within target tumor tissues. Procedures of processing of tumor tissues, analysis, and data processing have been set for the analysis of patient samples.

Preclinical Studies Using Newly Established Gastric Cancer Cell Lines

Tens of cell lines of gastric cancer of Japanese patients were obtained by culturing tumor samples, since such cell lines had not been available up to the present. Omics analysis, such as expression profiling and NGS-based mutation screening, were conducted to obtain basic information on these cell lines. In vitro and in vivo preclinical studies of molecular-targeted drugs are being conducted by collaborative studies with pharmaceutical industries to deriver new therapeutic agents to early phase clinical trial projects in EPOC.

Education

Graduate students, post-doctoral fellows, and chief residents in NCC were educated through the "on the job training" in several translational research projects.

Future prospects

Feasibility of clinical sequencing in academic institutions has been shown by our study. The next step is to establish quality assurance and accuracy to apply to cancer clinic in NCC. Early phase clinical trials will further progress through utilization of Mass Imaging as well as original cancer cell lines.

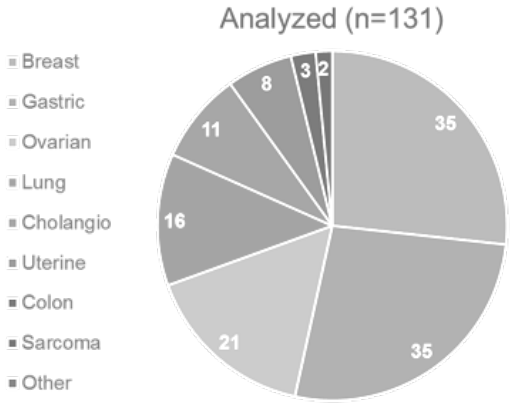

Figure 1. Subjects enrolled into the TOPICS-1 study

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Journal

1. Hirakawa A, Yonemori K, Kuwatsuka Y, Kodaira M, Yamamoto H, Yunokawa M, Hamada A, Shimizu C, Tamura K, Gemma A, Fujiwara Y. A descriptive analysis of postchemotherapy development of interstitial lung disease using spontaneous reporting data in Japan. Curr Drug Saf, 9:220-226, 2014
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11. Oue N, Anami K, Schetter AJ, Moehler M, Okayama H, Khan MA, Bowman ED, Mueller A, Schad A, Shimomura M, Hinoi T, Aoyagi K, Sasaki H, Okajima M, Ohdan H, Galle PR, Yasui W, Harris CC. High miR-21 expression from FFPE tissues is associated with poor survival and response to adjuvant chemotherapy in colon cancer. Int J Cancer, 134:1926-1934, 2014
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Division of Cancer Immunotherapy

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

Introduction

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

Research activities

Specific cellular immunotherapy for cancer requires efficient generation and expansion of cytotoxic T lymphocytes (CTLs) that recognize tumor-associated antigens. However, it is difficult to isolate and expand functionally active T-cells *ex vivo*. We investigated the efficacy of a new method to induce expansion of antigen-specific CTLs for adoptive immunotherapy. We used tumor-associated antigen glypican-3 (GPC3)-derived peptide and cytomegalovirus (CMV)-derived peptide as antigens. Treatment of human peripheral blood mononuclear cells (PBMCs) with zoledronate is a method that enables large-scale γδ T-cell expansion. To induce expansion of γδ T cells and antigen-specific CTLs, the PBMCs of healthy volunteers or patients vaccinated with GPC3 peptide were cultured with both peptide and zoledronate for 14 days. The expansion of γδ T cells and peptide-specific CTLs from a few PBMCs using zoledronate yields cell numbers sufficient for adoptive transfer. The rate of increase of GPC3 specific CTLs was approximately 24- to 170,000-fold. This study indicates that simultaneous expansion of γδ T cells and peptide-specific CTLs using zoledronate is useful for adoptive immunotherapy (1).

Lung cancer is the leading cause of cancer related deaths worldwide. Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib and erlotinib, have demonstrated marked clinical activity against non-small cell lung cancer (NSCLC) harboring activating epidermal growth factor receptor (EGFR) mutations. However, in most cases, patients develop acquired resistance to EGFR TKI therapy. The threonine to methionine change at codon 790 of EGFR (EGFR T790M) mutation is the most common acquired resistance mutation, and is present in ~50% cases of TKI resistance. New treatment strategies for NSCLC patients harboring the EGFR T790M mutation are required. We evaluated the immunogenicity of an antigen derived from EGFR with the T790M mutation. Using BIMAS we selected several EGFR T790M derived peptides bound to human leukocyte antigen (HLA)-A*02:01. T790M-A peptide (789-797) (IMQLMPFGC)-specific CTLs were induced from PBMCs of HLA-A2+ healthy donors. An established T790M-A-specific CTL line showed reactivity against the NCSLC cell line, H1975-A2 (HLA-A2+, T790M+), but not H1975 (HLA-A2-, T790M+), and the corresponding wild-type peptide (ITQLMPFGC)-pulsed T2 cells using an interferon-γ (IFN-γ) enzyme-linked immuno spot (ELISPOT) assay. This CTL line also demonstrated peptide-specific cytotoxicity against H1975-A2 cells. This finding suggests that the EGFR T790M mutation-derived antigen could be a new target for cancer immunotherapy (2).

We previously reported that heat shock protein 105 (HSP105) is overexpressed in a variety of human cancers, including colorectal, pancreatic and esophageal cancer and has proven to be a novel biomarker for the immunohistochemical detection of these cancers. We used HLA-transgenic mice (Tgm) and the PBMCs of colorectal cancer patients to identify HLA-A2 and HLA-A24-restricted HSP105 epitopes, as a means of expanding the application of HSP105-based immunotherapy to HLA-A2- or HLA-A24-positive cancer patients. In addition, we investigated by *ex vivo* IFN-γ ELISPOT assay whether the HSP105-derived peptide of cytotoxic T cells (CTLs) exists in PBMCs of pre-surgical colorectal cancer

patients. We found that four peptides, HSP105 A2-7 (RLMNDMTAV), HSP105 A2-12 (KLMSSNSTDL), HSP105 A24-1 (NYGIYKQDL) and HSP105 A24-7 (EYVYEFRDKL), are potential HLA-A2 or HLA-A24-restricted CTL HSP105-derived epitopes (3).

GPC3 is expressed by>40% of ovarian clear cell carcinoma (CCC) and is a promising immunotherapeutic target. Therefore, we conducted a phase II trial to evaluate the clinical outcome of ovarian CCC patients treated with a GPC3-derived peptide vaccine. The GPC3 peptide was administered at a dose of 3 mg per body. Patients received an intradermal injection of the GPC3 peptide emulsified with incomplete Freund's adjuvant. Vaccinations were performed biweekly from the first until the 6th injection and were then repeated at 6-week intervals after the 7th injection. Treatment continued until disease progression. We herein present two patients with chemotherapy-refractory ovarian CCC who achieved a significant clinical response in an ongoing trial of a GPC3 peptide vaccine. Case 1, a 42-year-old patient with advanced recurrent ovarian CCC with liver and retroperitoneal lymph node metastases, received the HLA-A24-restricted GPC3 peptide vaccine. Contrast-enhanced CT at week 10 revealed a partial response (PR) using RECIST criteria. Case 2 was a 67-year-old female with multiple lymph node metastases. She was injected with the HLA-A2-restricted GPC3 peptide vaccine. According to RECIST, PR was achieved at week 37 (4).

Clinical trials

We completed Phase II study of GPC3 peptide vaccine as adjuvant treatment for HCC after surgical resection or RFA and Phase I study of peptide cocktail vaccine for patients with refractory pediatric sarcoma. We are performing a phase II study with a GPC3 peptide vaccine in ovarian CCC patients and a phase I study with a GPC3 peptide vaccine in Pediatric cancer patients.

List of papers published in 2014

Journal

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