The 2nd International Cancer Research Symposium of Training Plan for Oncology Professionals

February 2 (Sat), 3 (Sun), 2019
Sheraton Miyako Hotel Osaka “Yamato-no-Ma”
6-1-55, Uehommachi, Tennoji-ku, Osaka 543-0001, JAPAN
http://www.miyakohotels.ne.jp/osaka/english/

Hosted by 7-University Joint Project of Training Plan for Oncology Professionals
Mini Lecture 2
Session 2 Radiation Oncology
Combination of radiation therapy and immunotherapy: A New trend for a tumor?

Mini Lecture 3
Session 3 Gastrointestinal Oncology
Immunotherapy for cancers, current concepts and future directions

Mini Lecture 1
Session 1 Cancer Immunotherapy: Harnessing our immune system to fight against cancer

Luncheon Seminar 1
Session 1 Cancer Precision Medicine; where we are and should go?

Evening Seminar
Poster Session-1
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Strategies for the Treatment of EGFR Mutation Positive Patient
D A Y  2

CONTENTS  February 3 (Sun), 2019  Yamato-no-Ma

Poster Session-2  9:00 – 10:00

Poster-1  Chair: Shosaku Nomura, M.D.,Ph.D. (Kansai Medical University)
Toru Otori, Ph.D. (Faculty of Pharmacy, Kindai University)  Kohei Ofune (Kansai Medical University)
Yuko Nakayama (Kobe University Graduate School of Medicine)  Yuta Yamanaka, M.D. (Kansai Medical University)
Yoshiko Azuma, M.D. (Kansai Medical University)  Yukie Tsubokura, M.D. (Kansai Medical University)

Poster-2  Chairpersons: Masanori Toyoda, M.D.,Ph.D. (Kobe University Graduate School of Medicine)
Hajime Monzen, Ph.D. (Kindai University Faculty of Medicine)
Yuki Hashimoto (Kansai Medical University)  Motohide Kaneda (Graduate School of Science and Engineering Research, Kindai University)
Akihito Kitao, M.D. (Kobe University Graduate School of Medicine)  Tomohiro Sagawa (Graduate School of Medicine, Osaka University)
Masayoshi Inoue, M.D. (Higashiosaka City Medical Center)

Mini Lecture 4  10:10 – 10:40

Chair: Toyoaki Hida, M.D.,Ph.D. (Chief, Dept. of Thoracic Oncology, Aichi Cancer Center)
Seiji Yano, M.D.,Ph.D. (Professor, Division of Medical Oncology, Cancer Research Institute, Kanazawa University)

Recent topics of ALK/BRAF altered lung cancer

Session 5  Thoracic Oncology 2  10:40 – 11:25

Chairpersons: Tomoya Kawaguchi, M.D.,Ph.D. (Graduate School of Medicine, Osaka City University)
 Nobuyuki Yamamoto, M.D.,Ph.D. (Wakayama Medical University)
 Sehhoon Park, M.D. (Samsung Medical Center)  Satomi Watanabe, M.D.,Ph.D. (Kindai University Faculty of Medicine)
 Tadaaki Yamada, M.D.,Ph.D. (Kyoto Prefectural University of Medicine)

Luncheon Seminar 2  11:35 – 12:25

Chair: Takayasu Kurata, M.D.,Ph.D. (Professor, First Department of Internal Medicine) (Professor, Department of Thoracic Oncology, Kansai Medical University Hospital)

Nelusha Amaladas (Principal Research Associate, Cancer Immunobiology Department, Eli Lily and Company)

Pemetrexed enhances anti-tumor efficacy of PD-1 pathway blockade by promoting intra-tumor immune response via immunogenic tumor cell death and T cell-intrinsic mechanisms

Mini Lecture 5  12:35 – 13:05

Chair: Yosuke Togashi, M.D.,Ph.D. (National Cancer Center Japan)
Shuta TOMIDA, Ph.D. (Associate Professor, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University)

Application of Clinical Sequencing for Cancer Genomic Medicine

Session 6  Immunotherapy  13:05 – 13:50

Chairpersons: Kenji Chamoto, Ph.D. (Kyoto University Graduate School of Medicine)
Hidetoshi Hayashi, M.D.,Ph.D. (Kindai University Faculty of Medicine)
Chun-Yu Liu, M.D.,Ph.D. (Division of Transfusion Medicine, Department of Medicine, and Comprehensive Breath Health Center, Taipei Veterans General Hospital, Taipei, Taiwan School of Medicine, National Yang-Ming University, Taipei, Taiwan)
Koji Haratani, M.D.,Ph.D. (Kindai University Faculty of Medicine)  Shigeki Yagyu, M.D.,Ph.D. (Kyoto Prefectural University of Medicine)

Closing Ceremony  13:50 – 14:00

Closing Remark
Masayuki Hino, M.D., Ph.D. (Graduate School of Medicine, Osaka City University)
Greeting from the Director of On behalf of "7-university Joint Project
Upon the Opening of The 2nd International Cancer Research Symposium of
Training Plan for Oncology Professionals:

On behalf of "7-university Joint Project: Advanced Creative Plan for Cancer Education Base
including Genome Science and Medical Care according to life stage of cancer patients", it is my
great pleasure to announce you that the 2nd International Cancer Research Symposium will be
held on February 2 and 3, 2019 in Osaka, Japan. This educational symposium contains lectures
from the experts and presentations of original data from young investigators. In addition to
Genome science and immuno-oncology, the most exciting topics in oncology field at the
moment, the cutting-edge topics will be discussed in the organ specific sections. We hope we
will continue to develop a good scientific relation, transcending national boundaries, through a
meaningful exchange of opinions, and stimulating talks.

The 2nd International Cancer Research Symposium gathers 40 young investigators from Korea,
Taiwan, China and Japan. Most of Japanese doctors are currently being trained in 7-university
Joint Project (or its graduates), investigators not only from 7-university but also Kyoto University,
Kyoto Pharmaceutical University, Osaka University, Nara Medical University, Wakayama Medical
University and some young yet outstanding investigators from Asian countries. We hope many
of you will join this International Symposium and it will enrich your knowledge base and serve
your advancement in the field of cancer treatment.

We cordially welcome you to this 2nd International Cancer Research Symposium of Training Plan
for Oncology Professionals.

Kazuhiko Nakagawa, M.D.,Ph.D.
Professor, Department of Medical Oncology,
Kindai University Faculty of Medicine
Messages from the Executive Secretariats of The 2nd International Cancer Research Symposium of Training Plan for Oncology Professionals:

It is our great pleasure to invite you to the 2nd International Cancer Research Symposium of Training Plan for Oncology Professionals, taking place in Osaka, Japan on Feb 2-3, 2019.

The essential aim of this symposium to facilitate the mutual interaction among the young investigators from Korea, Taiwan, China, and Japan, and learn from each other. Young investigators who are actively involved in basic and clinical research will present their original data coming from their field of specialization including medical oncology, hematology, radiation oncology, surgery, and nursing at either oral or poster session.

For this symposium, we invite the experts from Japan and overseas, who are very active in their special fields. They will give us cutting-edged information in the area and visions for the future. You will be updated by each lecture/seminar and will become familiar to what the young investigators here are currently working on through this symposium.

We hope you to have hot discussions for each presentation. Don’t be shy or too worry if you are not good at communicating in English. We are here to assist you!

Also, please do not forget to enjoy your stay in Osaka, known as “City of Food”.

Best regards,

Hisato Kawakami, M.D.,Ph.D.
Tsutomu Iwasa, M.D.,Ph.D.
Takeshi Yoshida, M.D.,Ph.D.

Executive secretariats of The 2nd International Cancer Research Symposium of Training Plan for Oncology Professionals Department of Medical Oncology, Kindai University Faculty of Medicine

Hisato Kawakami, M.D.,Ph.D.
Associate Professor (Lecturer)
Department of Medical Oncology,
Kindai University Faculty of Medicine
Osaka, Japan

Tsutomu Iwasa, M.D.,Ph.D.
Assistant Professor (Lecturer)
Department of Medical Oncology,
Kindai University Faculty of Medicine
Osaka, Japan

Takeshi Yoshida, M.D.,Ph.D.
Assistant Professor (Lecturer)
Department of Medical Oncology,
Kindai University Faculty of Medicine
Osaka, Japan
Keynote Lecture

Chair

Kazuhiko Nakagawa, M.D., Ph.D.
Professor, Department of Medical Oncology, Kindai University Faculty of Medicine

Cancer Precision Medicine; where we are and should go?

Yusuke Nakamura, M.D., Ph.D.
Director of Cancer Precision Medicine Research Center, Japanese Foundation for Cancer Research

Education
1977 Graduate of Osaka University School of Medicine, M.D. Degree
1984 Ph. D. Degree, Molecular Genetics of Osaka University

Academic Appointment
1977-1981 Second Department of Surgery, Osaka University School of Medicine
1981-1984 Research fellow, Institute for Molecular and Cellular Biology, Osaka University
1984-1988 Research Associate, Howard Hughes Medical Institute, University of Utah
1987-1989 Research Assistant Professor, Department of Human Genetics, University of Utah
1989-1993 Senior Associate, Howard Hughes Medical Institute, University of Utah
1989-1994 Head of Biochemistry Department, Cancer Institute, Tokyo
1994-2012 Professor, Laboratory of Molecular Medicine, Institute of Medical Science
The University of Tokyo
1996-1999 Professor, Department of Clinical Genetics, Osaka University School of Medicine
1995-2000 Head, Division of Genome Analysis, Cancer Institute, Tokyo
1995-2011 Director, Human Genome Center, Institute of Medical Science
The University of Tokyo
2005-2010 Director, RIKEN Center for Genomic Medicine
2011 Special Advisor to the Japanese Cabinet
Secretary General, Office of Medical Innovation, Cabinet Secretariat, Government of Japan
2012-2018 Professor, Department of Medicine, Section of Hematology/Oncology
Professor, Department of Surgery
Deputy Director, Center for Personalized Therapeutics
The University of Chicago
2018-present Project Director for SIP (Strategic Innovation and Promotion Program) “AI Hospital Systems” assigned by the Japanese Prime Minister
Director of Cancer Precision Medicine Research Center, Japanese Foundation for Cancer Research (Tokyo)
The 2nd International Cancer Research Symposium of
Training Plan for Oncology Professionals
February 2 (Sat), 2019 Yamato-no-Ma

Oral Session

Session 1  Genome Science  11:05‒11:50
Luncheon Seminar 1  12:05‒12:55
Mini Lecture 1  13:00‒13:30
Session 2  Radiation Oncology  13:30‒14:15
Mini Lecture 2  14:25‒14:55
Session 3  Gastrointestinal Oncology  14:55‒15:40
Mini Lecture 3  15:45‒16:15
Session 4  Thoracic Oncology 1  16:15‒16:45

Poster Session-1

Poster 1-1/Poster 1-2  16:55‒18:05

Chairpersons

Session 1  Genome Science
Kazuto Nishio, M.D.,Ph.D. (Kindai University Faculty of Medicine)
Masayuki Takeda, M.D.,Ph.D. (Kindai University Faculty of Medicine)

Session 2  Radiation Oncology
Ryohei Sasaki, M.D.,Ph.D. (Kobe University Graduate School of Medicine)
Yasumasa Nishimura, M.D.,Ph.D. (Kindai University Faculty of Medicine)

Session 3  Gastrointestinal Oncology
Takao Tamura, M.D.,Ph.D. (Kindai University Faculty of Medicine)
Hisato Kawakami, M.D.,Ph.D. (Kindai University Faculty of Medicine)

Session 4  Thoracic Oncology 1
Kazuya Fukuoka, M.D., Ph.D. (Kindai University Faculty of Medicine)
Hiroyasu Kaneda, M.D., Ph.D. (Graduate School of Medicine, Osaka City University)

Poster Session-1
Toshio Shimizu, M.D.,Ph.D. (National Cancer Center Hospital)
Kozo Kuribayashi, M.D., Ph.D. (Hyogo College of Medicine)
Shizue Suzuki, Ph.D., RN. (Kobe City College of Nursing)
Genome Science

Han-Byoel Lee, M.D. (Department of Surgery, Seoul National University Hospital)

Abstract

Development of an NGS-based multigene assay to predict recurrence risk in hormone receptor-positive, HER2-negative, node-negative breast cancer

Han-Byoel Lee 1, Kyung Eun Kim 1, Young Wook Ju 1, Ji-Gwang Jung 1, Han-Suk Ryu 2, Sae Byul Lee 3, Hee Jin Lee 4, Min-Su Kim 5, Sunyoung Kwon 5, Jinkyung Kim 6, Jong Won Lee 3, Sun Kim 5, Sungroh Yoon 5, Aerree Kim 6, Wonshik Han 1

1 Department of Surgery, Seoul National University Hospital, Seoul, Korea; 2 Department of Pathology, Seoul National University Hospital; 3 Department of Surgery, Asan Medical Center; 4 Department of Pathology, Asan Medical Center; 5 Seoul National University College of Engineering; 6 Department of Pathology, Korea University Guro Hospital

Multigene assays provide prognostic information in hormone receptor (HR)-positive breast cancer. Compared to RT-PCR or microarray used in currently available assays, an NGS-based RNA-sequencing allows for a more precise expression analysis with a broader coverage in a larger number of genes at lower costs. The purpose of this study was to develop and validate an NGS-based multigene prognostic assay to predict distant recurrence risk in HR-positive, HER2-negative, node-negative breast cancer. After selecting genes that are well correlated with the 21-gene assay recurrence score from public RNA datasets, targeted RNA-sequencing was performed and expression data was developed. Using independent expression datasets, we developed and verified an algorithm that predicts RS. We then validated the prognostic ability of the prognostic score derived from the algorithm using samples with long-term follow-up data. The prognostic value is greatest when using the prognostic score cut-off value of 20, and consistent for 283 patients with age <50 (5yr MFS 98.4 ± 0.9% vs 79.2 ± 4.2%; HR 5.763; 95% CI 2.869-11.575).

We developed an NGS-based multigene assay that accurately predicts distant recurrence risk in HR-positive, HER2-negative, node-negative breast cancer. The prognostic ability is consistent for younger patients under age 50. This assay may be an alternative to commercially available assays.
Clonality and loss of heterozygosity are associated with prognosis and molecular subtype in high grade serous ovarian cancer

Hisamitsu Takaya¹, Hidekatsu Nakai¹, Kosuke Murakami¹, Kazuko Sakai², Kazuto Nishio², Noriomi Matsumura¹

¹ Department of Obstetrics and Gynecology, Kindai University Faculty of Medicine
² Department of Genome Biology, Kindai University Faculty of Medicine

High grade serous ovarian cancer (HGSOC) comprises four gene expression subtypes, of which the Mesenchymal type has the worst prognosis. High degree of loss of heterozygosity (LOH) indicates homologous recombination deficiency, a characteristic associated with sensitivity to platinum and PARP inhibitors. This study aimed to clarify genetic features of HGSOC by using The Cancer Genome Atlas data (n=573). Clonality Index (Cl), indicating intratumor heterogeneity, was determined as we previously reported. We found high Cl (≥ 3) cases exhibited short progression-free survival (PFS) (p=0.016), whereas high LOH score was associated with prolonged PFS and overall survival (OS) (p=0.020, 8.25x10^-5, respectively). The Cl and the LOH scores were significantly different among the four gene expression subtypes (p<0.0001, respectively), of which the highest Cl and the lowest LOH scores were observed in the Mesenchymal subtype. In conclusion, this study revealed the relationship between gene expression subtype and genetic alteration in HGSOC, suggesting the poor prognosis of the Mesenchymal subtype is caused by increased intratumor heterogeneity and decreased platinum sensitivity.
Detection of AXL-expressing circulating tumor cells (CTCs) using an automated microcavity array (MCA) system

Shunsuke Teraoka, Yasuhiro Koh, Mio Ikeda, Jun Oyanagi, Kuninobu Kanai, Atsushi Hayata, Nahomi Tokudome, Hiroaki Akamatsu, Yuichi Ozawa, Keiichiro Akamatsu, Masayuki Higuchi, Masanori Nakanishi, Hiroki Ueda, Nobuyuki Yamamoto

Objectives: Noninvasive diagnostics including circulating tumor DNA and CTCs has been extensively developed over the last decade and we have previously reported that CTCs can be utilized for evaluating molecular features of non-small-cell lung cancer (NSCLC). AXL, a receptor tyrosine kinase is linked to epithelial-to-mesenchymal transition (EMT) leading to cancer progression and regarded as a potential therapeutic target. Here, we established the detection of AXL expression on CTCs.

Materials and Methods: Preclinical experiments were performed by spiking NSCLC cell lines H1299, PC9, and HCC827 and a breast cancer cell line MDA-MB231 with varying levels of CK and AXL expression. The cells were spiked into 3 ml of peripheral whole blood sample from healthy donors. Then, the cancer cells were enriched using MCA system, and detected by staining for CD45, DAPI, cytokeratin (CK) or vimentin (VM) with the addition of AXL. For clinical evaluation, 3ml of peripheral whole blood was collected from advanced NSCLC patients for the detection.

Results: DAPI-positive, CK or VM-positive, and CD45-negative cells were defined as CTCs. Among CK-positive cancer cells AXL expression was detected in 5 and 17% of high CK-expressing HCC827 and PC9 cells, respectively. AXL was also detected in 52 and 75% of low CK-expressing H1299 and MDA-MB231 cells, respectively. On the other hand, among VM-positive cancer cells AXL expression was detected in 72 and 88% of VM-expressing MDA-MB231 and H1299 cells, respectively where was 1 and 7% of PC9 and HCC827 cells with low VM expression. Sixteen advanced NSCLC were enrolled for clinical evaluation and results from thirteen were available for data analysis. The characteristics of the patients were as follows: median age 68 years (range, 49-84); male 85%; stage III/IV, 31/69%; Adenocarcinoma/ Squamous carcinoma/ other, 54/38/8%. For detecting CTCs, both CK and VM in 6 patients, only CK in 6 patients, and only VM in 1 patient were evaluated, respectively. AXL-expressing CK-positive CTCs were detected in 25% of patients (median, 0; range, 0-1). On the other hand, AXL-expressing VM-positive CTCs were detected in 86% of patients (median, 2; range, 0-6), suggesting the trend of AXL-positive cells undergoing EMT.

Conclusion: We established the detection method for AXL-expressing CTCs by MCA system. Our data suggest that incorporating VM staining is necessary to detect the AXL expression on CTCs precisely and further clinical evaluation is warranted.
Luncheon Seminar 1

Chair
Nariaki Matsuura, M.D., Ph.D.
President, Osaka International Cancer Institute

Cancer Immunotherapy:
Harnessing our immune system to fight against cancer

Kazuhiro Kakimi, M.D., Ph.D.
The University of Tokyo Hospital Department of Immunotherapeutics

Education
1988 M.D. Kyoto University
1995 Ph.D. Kyoto University

Career
1988-1989 Resident, Department of Internal Medicine, Kyoto University Hospital, Japan
1989-1991 Clinical fellow, Department of Internal Medicine, Ako Municipal Hospital, Japan
1995-1996 Assistant Professor, Department of Bioregulation, School of Medicine, Mie University
1996-2002 Research Associate, Department of Molecular and Experimental Medicine, The Scripps Research Institute, USA
2002-2004 Assistant Professor, Department of Internal Medicine, Tokyo Medical University
2004-2014 Project Associate Professor, Department of Immunotherapeutics, The University of Tokyo Hospital
2014-present Project Professor, Department of Immunotherapeutics, The University of Tokyo Hospital
2017-present Unit leader, Cancer Immunology Data Multi-level Integration Unit, Medical Science Innovation Hub Program, RIKEN
Combination of radiation therapy and immunotherapy: A New trend for a tumor?
Radiation Oncology

Mingwei Ma, M.D. (Department of Radiation Oncology, Peking University First Hospital)

Education
- Sept 2012-Sept 2015: Peking University First Hospital, Beijing, China
- Sept 2007-Sept 2012: Hebei Medical University, Hebei, China.

Work Experience
- June 2018-present: Peking University First Hospital
- Sept 2012-June 2018: Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

Awards/Honors
- Best Popularity Award in 2016 annual meeting of radiation oncology in Beijing
- Guanghua Scholarship of Peking University in 2015

Academic/Professional Memberships and Other Professional Activities
- Participated in China PEACE Collaborative project taken by Chinese Academy of Medical Science, Fujui Hospital
- Carried out research on application of real-time Clarity® Autoscan ultrasonic guidance on treatment of prostate cancer up to now.

Abstract

A Reliable Nomogram is identified to predict the Probabilities of Having Indications for Adjuvant Prostatic Radiotherapy

Ming-wei Ma 1, Xian-shu Gao 1, Mu Xie 1, Bo Zhao 1, Dian Wang 2

1 Department of Radiation Oncology, Peking University First Hospital, No.7 Xishiku Street, Beijing, China, 100034
2 Department of Radiation Oncology, Rush University Medical Center (RUMC), 500 S. Paulina, Chicago, IL 60612
E-mail: dian_wang@rush.edu

Purpose/Objective(s): The purpose of this study is to examine our cohort of RP patients and to develop the above nomogram through the correlation of pretreatment PSA, clinical T stage and biopsy Gleason Score with adverse features such as extraprostatic extension, positive margin(s), and Gleason Score 8-10 that are commonly indicated for adjuvant radiotherapy.

Materials/Methods: We analyzed 1440 RP patients between August, 2000 and August, 2015 at our hospital. Patients who had a history of neoadjuvant hormonal therapy, or transurethral resection of the prostate (TURP) were excluded from this analysis. A total of 627 patients were eligible for analysis. Average age was 66 years. All patients had a preoperative PSA level, biopsy Gleason Score, pelvic MRI and clinical T stage (TNM 2009 classification). Preoperative PSA level clinical T stage (T2a/b, T2c, T3a, T3b), and biopsy Gleason score (5 to 6, 3+4 = 7, 4 + 3 = 7, 8 to 10) were recorded as preoperative predictors. These predictors were used in multivariable logistic regression analysis based nomograms to estimate the probabilities of extraprostatic extension, positive margin(s) after RP, respectively. Analyses were performed with open-source statistical software R (version 3.2.1).

Results: Preoperatively, 41% of patients had a PSA level between 10 and 20 ng/mL, 80% had T2, and 50% had biopsy Gleason score 7; postoperatively, 47% had extraprostatic extension disease, 36% had positive margin, and 22% had Gleason Score 8-10. Nomograms were developed for the predicted probabilities of having the indications of adjuvant radiation therapy (pathologically extraprostatic extension disease or positive margin(s)). The calibration curve for probabilities showed good agreement between prediction by nomogram and actual observation. The C-index of the nomograms for predicting for extraprostatic extension disease, or positive margin(s) were 0.707, 0.659, respectively. The risk of having one of the indications of adjuvant radiation therapy increased with increases in predictors.

Conclusion: Using clinic-pathological information, we produced nomograms that accurately predict the probabilities for adjuvant radiation therapy after RP, which may help individualize initial treatment options.
Dosimetrically effective fast neutrons for boron neutron capture therapy (BNCT) of malignant melanoma

Yusuke Sakai\(^1\), Harumi Narumoto\(^2\), Ryoichi Seki\(^3\), Masaaki Takashina\(^4\), Masahiko Koizumi\(^1\), Hiroshi Toki\(^3\), and Mitsuhiro Fukuda\(^3\)

\(^1\) Department of Medical Physics and Engineering, Graduate School of Medicine, Osaka University, Suita, Japan
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Thermal neutrons are known to be effective for BNCT of malignant melanoma. We investigate to determine whether fast neutrons of above 10 keV can be dosimetrically effective for BNCT of malignant melanoma, by the use of bolus.

PHITS is used for simulation using various neutron beam energies from the thermal energy to 30 keV. The neutron beams of 10 cm diameter incident perpendicularly to the front of phantom of a cylindrical shape. The diameter of the cylinder is 20 cm and the depth 10 cm. The cylinder configuration is as follows: The frontal part of the cylinder is composed of a skin-equivalent material from the surface to 0.4 cm depth, and the rest of the cylinder is composed of a muscle-equivalent material from 0.4 cm to 10 cm depth. A part of the skin-equivalent material is a melanoma, which forms a round-disk shape of diameter 6 cm and is distributed from the surface to the depth 0.4 cm with the disk center at the beam central axis. A water bolus is placed directly on the front of the cylinder, covering all front. The thickness of the bolus is varied from 0.5 to 3.0 cm. The sets of neutron energies of 1 keV with the bolus of 2.0 cm thickness, 10 keV with 2.5 cm, and 20 keV with 3.0 cm, respectively, are found to be dosimetrically effective. In comparison to thermal neutrons, these sets or their combinations are equally dosimetrically effective for BNCT of malignant melanoma by the use of thick bolus. We also find that they would be superior to the thermal neutrons to malignant melanoma invasive below skin. Fast neutrons above 10 keV are found to be dosimetrically effective by the use of thick bolus, for BNCT of malignant melanoma and especially of malignant melanoma invasive below skin.
CyberKnife® treatment for prostate cancer: Is it possible to determine the optimal collimator combination using a plan quality objective function?

Maria Varnava 1, Iori Sumida 1, Hirokazu Mizuno 1, Hiroya Shiomi 1,2, Osamu Suzuki 3, Yasuo Yoshioka 4, Kazuhiko Ogawa 1

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E-mail: mvarnava@radonc.med.osaka-u.ac.jp
2 Miyakojima IGRT Clinic, Miyakojima-ku, Osaka, Japan
3 Department of Carbon Ion Radiotherapy, Osaka University Graduate School of Medicine, Suita, Osaka, Japan
4 Department of Radiation Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Tokyo, Japan

Stereotactic body radiation therapy with CyberKnife® for prostate cancer has long treatment times, which may affect the accuracy of the treatment because the length of treatment time affects patient discomfort and hence setup errors during a treatment session. The aim of this study was to use a new plan quality objective function, including time, to investigate whether it is possible to determine the optimal collimator combination that would provide treatment plans with the shortest possible time and clinically acceptable dose distributions. For each one of 11 prostate cancer patients, 20 plans were created based on all combinations between one small (φ10–25 mm) and one large (φ35–60 mm) Iris™ collimator size. The objective function was used as a penalty to evaluate the quality of all 220 treatment plans. The penalty considered the level of achievement of the dosimetric and treatment time planning goals, the probability of complications occurring to the organs at risk, and the probability of tumor control.Plans with a low penalty were considered superior. Two methods were used to find the optimal combination: (a) generation of heat maps for the mean penalty and standard deviation of the penalty of the plans from each combination, and (b) investigation of the highest-frequency small and large collimator sizes in groups of superior plans.

The heat maps revealed optimal combinations of 25/35 (small/large size), 25/40, 25/50, and 25/60 mm. The highest-frequency small and large collimator sizes found in superior-plan groups were 25 and 50 mm, respectively. These results suggest 25/50 mm to be the optimal combination, which produced plans that balanced short treatment times and acceptable distributions.

The proposed objective function allows for sufficient quantification of the plan quality and has the potential for determining optimal collimator combinations in CyberKnife® treatment for prostate cancer.
Mini Lecture 2

Chair
Hironobu Minami, M.D.,Ph.D.
Professor, Department of Medical Oncology and Hematology, Kobe University Hospital, & Kobe University Graduate School of Medicine

ImmunoTherapy for cancers, current concepts and future directions

Eiji Oki, M.D., Ph.D.
Associate Professor, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University

EDUCATION
(Degrees/ Diplomas/ Licensures and Certifications)
1999 Ph.D. Kyushu University, Graduate School
1993 M.D. Kyushu University, Faculty of Medicine

PROFESSIONAL TRAINING and EMPLOYMENT
(Present Academic Appointment)
2015-present Associate Professor, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University
2014-2015 Associate Professor, Department of Surgery and Molecular Targeting Therapy, Graduate School of Medical Sciences, Kyushu University
2011-2014 Assistant Professor, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University
1999-2017 Department of Surgery, National Beppu Medical Center
2008-2010 Department of Gastroenterological Surgery, National Kyushu Cancer Center
2003-2008 Assistant Professor, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University
2001-2003 Department of Surgery, Munakata Medical Association Hospital
1999-2001 Research fellow, Department of Adult Oncology, Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA, USA
1995-1999 Research fellow, Graduate School of Medical Science, Kyushu University
1994-1995 Intern, Department of Surgery, Saga Prefectural Hospital KOSEIKAN
1993-1994 Intern, Department of Surgery II, Kyushu University Hospital

PROFESSIONAL AFFILIATIONS AND ACTIVITIES and BOARD CERTIFICATION
- Japanese Society of Medical Oncology (Board Certified Medical Oncologist)
- Japan Surgical Society (Board Certified Surgeon)
- The Japanese Society of Gastroenterological Surgery (Board Certified Gastroenterologist)
- Japan Society for Endoscopic Surgery (Board Certified Endoscopic Surgeon)
- Japan Society of Clinical Oncology
- Japanese Gastric Cancer Association
- Fellow of American College of Surgeon (ACS)
- American society of clinical oncology (ASCO)

HONORS AND AWARDS
2002 International Symposium on Cancer Research and Therapy Subsidy Award
2007 Japan Esophageal Society, Best paper award
2016 Fukuoka Medical Society award
2017 Japanese Society of Gastroenterological Carcinogenesis Ohara award
**Abstract**

*Mutational characteristics and prognosis of Fusobacterium nucleatum-high colorectal cancer patients.*

Dae-Won Lee¹, Sae-Won Han¹, Jun-Kyu Kang², Jeong Mo Bae³, Hwang-Phill Kim², Jae-Kyung Won³, Seung-Yong Jeong⁴, Kyu Joo Park⁴, Gyeong Hoon Kang³, and Tae-You Kim¹

¹ Department of Internal Medicine, ² Pathology, ³ Surgery Seoul National University Hospital, Seoul, Korea; ² Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; E-mail: silver2sky@hanmail.net

There is a close link between *Fusobacterium nucleatum* and colorectal cancer (CRC) development. This study aimed to evaluate the relationship between *F. nucleatum*, pathway mutation, and patient prognosis in CRC. The study population consisted of two separate cohorts (adjuvant cohort and palliative cohort). The adjuvant cohort (N=128) consist of CRC patients who received curative surgery followed by adjuvant chemotherapy. Palliative cohort (N=118) included patients with metastatic CRC. *F. nucleatum* amount in the tumor tissue and adjacent normal tissue were measured by qPCR. Patients were grouped into binary according to *F. nucleatum* amount (high and low). Targeted next-generation sequencing of 40 genes included in the five critical pathways (WNT, P53, RTK-RAS, PI3K, and TGF-β) was performed in the adjuvant cohort. Patients with MSI-H and CIMP-H had higher amount of *F. nucleatum* in tumor tissue. *F. nucleatum*-high patients had higher rates of transition mutation and C to T (G to A) nucleotide change regardless of MSI status. In addition, mutation rate of AMER1 and ATM gene, and TGF-β pathway was higher in *F. nucleatum*-high patients. *F. nucleatum*-high was associated with poor overall survival (OS) in the palliative cohort. Multivariate analysis revealed *F. nucleatum*-high as an independent negative prognostic factor for OS [HR 1.69 (95% CI 1.04-2.75), p=0.034]. However, *F. nucleatum* amount was not associated with recurrence in the adjuvant cohort. In conclusion, *F. nucleatum*-high was associated with poor survival in metastatic CRC. In addition, we identified mutational characteristics of CRC according to *F. nucleatum* amount.
Gastrointestinal Oncology

Naoki Takegawa, M.D., Ph.D. (Kindai University Faculty of Medicine)

Education
April 2002-March 2008  Fukui University
April 2014-March 2017  Kindai Graduate University

Work Experience
April 2008-March 2010  Resident at Konan Hospital
April 2010-March 2012  Kobe Century Memorial Hospital
April 2012-March 2014  Hyogo cancer center
April 2014-present  Kindai University

Academic/Professional Memberships and Other Professional Activities
• The Japanese Society of Medical Oncology
• The Japanese Society of Internal Medicine
• The Japanese Society of Gastroenterology
• The Japan Gastroenterological Endoscopy Society

Abstract

The antitumor efficacy of DS-8201a is dependent on the expression levels of HER2 in KRAS mutated colorectal cancer cells

Naoki Takegawa 1, Hisato Kawakami 1 *, Junji Tsurutani 1, Kimio Yonesaka 1, Koji Haratani 1, Yoshikane Nonagase 1, Osamu Maenishi 2, and Kazuhiko Nakagawa 1

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DS-8201a is a novel antibody-drug conjugate (ADC) composed of an anti-HER2 antibody and a novel potent topoisomerase I inhibitor exatecan derivative. A phase 1 dose-expansion study of DS-8201a for HER2 expressing colorectal cancer (CRC) demonstrated promising anti-tumor effects. In this study, we evaluated the efficacy of DS-8201a in CRC cell lines that express various levels of HER2 protein but lacking HER2 amplification. In vitro growth inhibition assay, DS-8201a decreased the number of viable cells in a manner dependent on HER2 expression, whereas the other therapies targeting HER2 signaling did not. In co-culture models of HER2-expressing cells and HER2 negative cells, the cell death was observed not only in HCT116-H2H cells, but also in HER2 negative HCT116-Mock cells, suggesting a potential bystander killing effect of DS-8201a. These findings were further confirmed in vivo model. Our results may offer a new treatment option against CRC according to the expression levels of HER2 protein.
Gastrointestinal Oncology

Tomohisa Okuno, M.D. (Osaka City University Graduate School of Medicine)

Education
2010 Medical doctor, Kawasaki medical School, 577 Matsushima Kurashiki city
Okayama Japan

Degree
M.D in Kawasaki University of medicine

Work Experience
2010-2013, 2016-present Department of Surgical Oncology, Osaka City University
Graduate School of Medicine
2013-2016 Department of Surgery, Osaka Ekisaikai Hospital

Awards/Honors
• First prize award; The 55th Annual meeting of Japan society of clinical oncology
• Best poster award; The 27th Meeting of the Japanese association for Metastasis Research

Academic/Professional Memberships and Other Professional Activities
• Board Certified Surgeon
• Board Certified Gastroenterologist of the Japanese Society of Gastroenterology
• General Clinical Oncologist (by JBCT)
• American Association for Cancer Research Associate member
• A member of Japan Surgical Society, Japanese Gastric cancer Association, Japanese Cancer
Association, Japanese Society of Oncology, Japanese Society of Gastroenterological Surgery

Abstract

Extracellular vesicles from scirrhous gastric cancer induce mesothelial-mesenchymal
transition of peritoneal mesothelial cells

Tomohisa Okuno 1,2,3, Masakazu Yashiro 1,2,3, Shuhei Kushiyama 1,2,3, Sadaaki Nishimura 1,2,3, Shingo Togano 1,2,3, Kenji Kuroda 1,2,3, Tatsuro Tamura 1, Takahiro Toyokawa 1, Hiroaki Tanaka 1, Kazuya Muguruma 1, Kosei Hirakawa 1, Masaichi Ohira 1

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Background: Gastric cancer is a major cause of cancer death, particularly on the basis of peritoneal metastasis. Human scirrhous gastric carcinoma (SGC) is characterized by rapid cancer cell infiltration and proliferation accompanied by extensive stromal fibrosis. We previously reported that SGC cells ("seed") might change the peritoneum to favorable environment, so-called pre-metastatic niche ("soil"). Cancer 77:1668-75, 1996. Recently, it has been clarified that extracellular vesicles (EVs) play an important role for cell-cell interactions. In this study, we investigated the effect of EVs from SGC cells on the pre-metastatic niche formation of the peritoneum.

Methods: Four SGC cell line, 2 gastric cancer cell line and PM cells were used. PKH26-labeled EVs derived from SGC were intravenously injected into nude mice and examined by a fluorescence microscope. The morphology and gene expression of PM cells was investigated in the addiction of EVs by microscope and RT-PCR. Clinical significance of CD9 and CD63 evaluated on human gastric cancer specimens.

Results: PKH26-labeled EVs were frequently found in the peritoneum, stomach and liver. PM cells uptake EVs of gastric cancer cells and change morphology from cobblestone shape to spindle shape in vitro. mRNA expression level of MMPs and mesenchymal markers, such as N-cadherin in PM cells was increased following the addiction of EVs. The high expression of CD9 and CD63 was significantly correlated with distant metastasis.

Conclusion: EVs from gastric cancer cells might induce a pre-metastatic niche at peritoneum by the morphologic and genetic changes of mesothelial cells.
Mini Lecture 3

Chair
Tetsuya Mitsudomi, M.D., Ph.D.
Professor, Department of Surgery, Kindai University Faculty of Medicine

Strategies for the Treatment of EGFR Mutation Positive Patient

Ken Uchibori, M.D., Ph.D.
Deputy Medical director, Division of Thoracic Medical Oncology,
Cancer Institute Hospital of JFCR

Education
1999-2005 M.D., Tokyo Medical and Dental University, School of medicine.
2014-2018 Ph.D., Tokyo Medical and Dental University, graduate school of medical and dental science, doctoral program.

Work history
2017-present Deputy Medical director, Division of Thoracic Medical Oncology, Cancer Institute Hospital of JFCR,
2014-2017 Clinical fellow, Department of Respiratory Medicine, Tokyo Medical and Dental University
2012-2014 Medical Director, Department of Thoracic Oncology, Hyogo Cancer Center
2011-2012 Assistant professor, Department of Respiratory Medicine, Tokyo Medical and Dental University
2008-2011 Staff doctor, Department of Respiratory Medicine, Yokosuka Kyosai Hospital
Concurrent genetic alterations predict the progression to target therapy in EGFR-mutated advanced non-small cell lung cancer

Youjin Kim, MD, 1,2 Boram Lee, MD, 3, 4 Joon Ho Shim, MD, 3, 4 Se-Hoon Lee, MD, PhD, 3, 4, *Woong-Yang Park, MD, PhD, 3, 4 Yoon-La Choi, MD, PhD, 3, 4 Jong-Mu Sun, MD, PhD, 3, 4 Jin Seok Ahn, MD, PhD, 4 Myung-Ju Ahn, MD, PhD, 4 Keunchil Park, MD, PhD, 4

1 Division of Hematology-Oncology, Departments of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
2 Department of Health Sciences and Technology, Samsung Advanced Institute of Health Science and Technology, Sungkyunkwan University, Seoul, Korea.
3 Samsung Genome Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.
4 Department of Pathology and Translational Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.
* These authors contributed equally to this study

Introduction: EGFR-mutant non-small cell lung cancer (NSCLC) displays diverse outcomes to tyrosine kinase inhibitor (TKI) treatment. Since co-occurring genomic alterations might describe different biological subsets of patients with this cancer, exploring co-occurring genomic alterations that impact patient’s outcome using a comprehensive gene panel is potentially important.

Methods: This retrospective cohort study was conducted with the panel-sequencing data acquired from January 2014 to May 2017, and clinical outcome data collected until February 2018. This study includes all eligible patients who possess panel-sequencing data prior to treatment with 1st/2nd-generation EGFR-TKIs (cohort 1) or 3rd-generation EGFR-TKIs following initial EGFR-TKI failure (cohort 2).

Results: Seventy-five patients (mean [SD] age, 58.5 [11.0] years; 68.0% women) were included in cohort 1, and 82 patients (mean [SD] age, 57.3 [9.1] years; 67.1% women) were included in cohort 2. In cohort 1, alterations in TP53 were independently associated with worse PFS (hazard ratio [HR], 2.02; [95% CI, 1.04–3.93]; p = 0.038) in multivariate analysis. In cohort 2, TP53 mutation was associated with significantly worse PFS (8.9 versus 12.8 months; p = 0.029). RB1 mutation was significantly associated with worse (median PFS, 1.9 versus 11.7 months; p < 0.001). PTEN mutation was associated with significantly worse PFS (2.6 versus 10.3 months; p = 0.001). MDM2 amplification was associated with worse PFS (6.6 versus 10.4 months; p = 0.025). In cohort 2, multivariate analysis revealed that alterations in TP53 (HR, 2.23; 95% CI, 1.16–4.29; p = 0.01), RB1 (HR, 5.62; 95% CI, 1.96–16.13; p = 0.001), PTEN (HR, 5.84; 95% CI, 1.56–21.85; p = 0.009), and MDM2 (HR, 2.46; 95% CI, 1.02–5.94; p = 0.046) were independently associated with worse PFS.

Conclusions: Co-occurring genomic alterations detected by panel sequencing are associated with the clinical outcomes of EGFR-TKI treatment in NSCLC.
Abstract

Osimertinib Resistance Mechanisms in EGFR T790M-positive lung cancer

Ryoji Kato 1, Hidetoshi Hayashi 1, Kimio Yonesaka 1, Koji Haratani 1, Takayuki Takahama 1, Hitomi Sakai 1, Tsutomu Iwasa 1, Kaoru Tanaka 1, Takeshi Yoshida 1, Masayuki Takeda 1, Hiroyasu Kaneda 4, Shigeki Shimizu 2, Kazuko Sakai 3, Akihiko Ito 2, Kazuto Nishio 3 and Kazuhiro Nakagawa 1

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2 Department of Pathology and 3 Department of Genome Biology, Kindai University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan
4 Department of Clinical Oncology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka, Osaka, 545-8585, Japan

Background: Few studies have evaluated the predictive value and resistance mechanisms to osimertinib using plasma cell-free deoxyribonucleic acid (cfDNA) in T790M-mutant non-small-cell lung cancer (NSCLC) patients.

Methods: We retrospectively analyzed patients with advanced NSCLC treated with osimertinib at Kindai University Hospital between August 2014 and January 2018. Additionally, we performed Cancer Personalized Profiling by deep sequencing (CAPP-Seq) cfDNA analysis to study resistance mechanisms to osimertinib.

Results: We identified 50 patients, with T790M mutation positive of tumor in 38 patients (76%), plasma in 11 patients (22%), and both tumor and plasma in one patient (1%). Among these 50 patients, the median progression free survival was 8.1 months and the response rate was 65%. Plasma cfDNA was obtained from 32 samples, with 4 samples before osimertinib, 7 samples during osimertinib, and 21 samples after progression.

Conclusions: The efficacy of osimertinib was similar to previous reports. We will present our work on plasma cfDNA, soluble heregulin level in serum and resistance mechanisms to osimertinib.
**Poster 1**

**P1-1**

**HER2 genomic amplification in circulating tumor DNA and estrogen receptor positivity predict primary resistance to trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer.**

**Education**

April 2003-March 2009  Faculty of Medicine, Yokohama City University

**Work Experience**

2016-present  Department of Medical Oncology, Kindai University Hospital Faculty of Medicine  
2012-2016  Department of Medical Oncology, Nippon Medical School Musashikosugi Hospital  
2009-2012  Kameda Medical Center

**Abstract**

Hitomi Sakai, M.D.

Backgrounds: Trastuzumab emtansine (T-DM1) is approved for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer (ABC), and has high efficacy. However, some patients exhibit primary resistance to T-DM1, and thus methods that can predict resistance in clinical practice are needed. Genomic analysis of circulating tumor DNA (ctDNA) in plasma is a non-invasive and reproducible method. This study aimed to predict primary resistance to T-DM1 by combining genomic analysis of ctDNA and other clinicopathological features of patients with HER2-positive ABC.

Methods: Among 34 patients with HER2-positive ABC had been treated with T-DM1, 16 patients provided written informed consent for ctDNA analysis before T-DM1 administration. HER2 gene copy number and PIK3CA gene mutations were analyzed using plasma ctDNA samples obtained from 16 patients before T-DM1 administration.

Results: Of the 16 cases in which ctDNA was analyzed, 4 cases showing primary resistance and all of them had HER2 amplification negative and ER positive disease. Median time to progression was 318.0 days (95% CI 187-NA) in patients with HER2 amplification negative and ER positive diseases and 56.6 days (95% CI 36-NA) in others (p = 0.0037).

Conclusions: HER2 gene amplification in ctDNA and ER and PR status may predict primary resistance to T-DM1. A liquid biopsy before the initiation of T-DM1 treatment could be a non-invasive way to predict whether a patient would exhibit primary resistance to T-DM1.

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**P1-2**

**Metronomic photodynamic therapy exerts excellent antitumor effects on remote tumor as well as local tumor**

**Education**

April 1986-March 1993  University of the Ryukyus

April 2015-present  Postgraduate student, Graduate School of Medicine, Kyoto University

**Degress**

Bachelor of Medicine

**Work Experience**

June 2002-Sept 2003  Department of Surgery, The University of Hong Kong  
April 2004-Aug 2011  Department of Surgery, Kurashiki Central Hospital  
Sept 2011-Mar 2015  Division of HBP Surgery and Transplantation, Department of Surgery, Kyoto University

**Abstract**

Izumi Kirino 1, 2, Suefumi Aosasa 4, Junji Yamamoto 4, Nariyoshi Shinomiya 1, Shinji Uemoto 1, Yuji Morimoto 2

1 Division o of HBP Surgery and Transplantation, Department of Surgery, Kyoto University, 2 Department of Physiology, 3 Department of Integrated Physiology and Nanomedicine, and 4 Department of Surgery, National Defense Medical College  
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Low-intensity (< 0.1 mW/cm2) yet long-term (> 2-3 days) photodynamic therapy (PDT), termed metronomic PDT (mPDT), is attracting an attention since it effectively induces cell death of cancer cells. As mPDT is required only a very weak light, the light source can be miniaturized and thus fully implantable in human body by using the technology of wireless electric power supply. These advantages suggest that mPDT is applied to deeply located tumors. We recently found that mPDT not only exerts antitumor effect on local tumor but also suppresses the growth of remote tumors. Hence we hypothesized that mPDT activates systemic antitumor immunity through the tumor-specific apoptotic effect, and we conducted several experiments regarding mPDT using a combination of photosensitizer (Photofrin) and implantable light sources. The results showed that slowly progressing apoptosis occurs accompanied by DAMPs expression over the time in mPDT (> 3 days). These findings strongly support our hypothesis and suggest that mPDT has a potential in the systemic treatment of advanced cancers in deeply located organs.
**Poster Session 1**

**P1-3**

**The relationship between anti-tumor activity of γδ T cells and PD-1/PD-L1 axis for γδ T cell immunotherapy**

**Education**

Bachelor of Science in Pharmacy  
April 2012–March 2018  
Kyoto Pharmaceutical University, Kyoto, Japan

**Abstract**

Mako Tomogane, Teruki Shimizu, Masatsugu Miyashita, Yusuke Sano, Daiki Shimizu, Yuki Toda, and Eishi Ashihara

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2 Department of Urology, Kyoto Prefectural University of Medicine, 465, Kajii-cho, Kamigyo-ku, Kyoto City, Kyoto 602-8566, Japan  
3 Department of Urology, Matsushita Memorial Hospital, 5-55, Sotojima-cho, Moriyuchi City, Osaka 570-8540, Japan

T cells are divided into two major populations distinguished by their surface expression of αβ and γδ T cell receptors. αβ T cells recognize non-self peptide fragments restricted by major histocompatibility complex (MHC), whereas γδ T cells display MHC-unrestricted cytotoxicity. γδ T cells recognize isopentenyl pyrophosphate (IPP) produced by cancer cells. Zebrafish long-chain diacylglycerol (ZOL) inhibit farnesyl pyrophosphate (FPP) synthase in the mevalonate pathway. By inhibiting FPP synthase, ZOL treatment accumulates IPP in cancer cells, and γδ T cells exert anti-tumor effect on cancer cells. Programmed cell death-1 (PD-1)/PD ligand1 (PD-L1) axis prevents αβ cell cytotoxicity against cancer cells, and anti-PD-L1 monoclonal antibody (mAb) treatment restores the cytotoxicity. However, the role of this axis in γδ T cell cytotoxicity is not elucidated clearly so far. In this study, we clarified the association between PD-L1-positive cancer cells and γδ T cells for developing γδ T cell immunotherapy. Ex vivo expanded γδ T cells increased up to 450-900 folds and expressed low levels of PD-1. Various levels of PD-L1 were expressed in several cancer cell lines. Anti-PD-L1 mAb treatment enhanced the anti-tumor effect against a part of cancer cells. However, anti-PD-1 mAb treatment didn’t augment the effects against the cell lines. In this study, we exhibited the possibility that PD-1/PD-1 axis may not influence on γδ T cell cytotoxicity. Therefore, the present results suggested that adoptive transfer of ex vivo expanded γδ T cells with the pretreatment of ZOL may serve as an effective cancer immunotherapy.

**P1-4**

**Development of novel molecular targeted agents for Wnt/β-catenin pathway**

**Education**

April 2011–March 2017  
Kyoto Pharmaceutical University (Kyoto, Japan)  
April 2017–present  
Graduate School of Pharmacy, Kyoto Pharmaceutical University (Kyoto, Japan)

**Abstract**

Ryosuke Wakabayashi, Yasunao Hattori, Kazuya Kobayashi, Yuki Toda, Kenichi Akaji, and Eishi Ashihara

1 Department of Clinical and Translational Physiology, Kyoto Pharmaceutical University, 5, Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607-8414, Japan, Email: kd17010@poppy.kyoto-phu.ac.jp  
2 Center for Instrumental Analysis, Kyoto Pharmaceutical University, 1 Shichino-cho, Misasagi, Yamashina-ku, Kyoto 607-8412, Japan  
3 Department of Medicinal Chemistry, Kyoto Pharmaceutical University, 1 Shichino-cho, Misasagi, Yamashina-ku, Kyoto 607-8412, Japan

Wnt/β-catenin pathway plays an important role in developmental processes and cell growth and differentiation. However, aberrant activation of this pathway contributes to carcinogenesis in various types of cancers. Therefore, the Wnt pathway is an attractive target for the treatment of cancer. In order to develop new drugs that inhibit this pathway, we have searched inhibitors of Wnt pathway in our compound libraries using a TCF firefly luciferase-reporter assay. After screening for approximately 250 compounds, we found compounds that inhibit the TCF activities. Compound #37 demonstrated suppression of cell proliferation of various types of cancer cells in a dose-dependent manner. Furthermore, this compound suppressed expression levels of Wnt pathway target genes such as c-myc cyclinD1 survivin. In conclusion, compound #37 suppressed cell growth of various cancer cell lines by inhibiting Wnt/β-catenin signaling. Compound #37 can be a novel agent targeting Wnt/β-catenin signaling. We have been investigating the target molecule in the Wnt/β-catenin pathway and have been exploring structure-activity relationship to develop more suitable compounds.
**Poster 1-5**

**Free Fatty Acids Inhibit Protein Tyrosine Phosphatase 1B and Activate Akt**

**Education**
- April 2012–March 2016: Hyogo College of Medicine, Graduate College of Medicine
- April 2003–March 2009: Hyogo College of Medicine

**Degrees**
- March 2016: Doctor of Philosophy
- April 2009: Doctor of Medicine

**Work Experience**
- April 2016–present: Assistant Professor in Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine
- April 2012–March 2016: Medical staff in Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine
- April 2011–March 2012: Senior resident in Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine
- April 2009–March 2011: Junior resident, Hyogo College of Medicine

**Abstract**
Eisuke Shibata, Toshiyuki Minami, Ryo Takahashi, Takashi Yokoi, Kozo Kuriyayashi, Takashi Kijima

Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan, E-mail: eischen@hyo-med.ac.jp

**Background/Aims:** Accumulating evidence has suggested that free fatty acids (FFAs) interact with protein kinases and protein phosphatases. The present study examined the effect of FFAs on protein phosphatases and Akt.

**Methods:** Activities of protein phosphatase 1 (PP1), protein phosphatase 2A (PP2A), and protein tyrosine phosphatase 1B (PTP1B) were assayed under the cell-free conditions. Phosphorylation of Akt was monitored in MSTD-21H human malignant pleural mesothelioma cells without and with knocking-down phosphatidylinositol 3 kinase (PI3K) or 3-phosphoinositide-dependent protein kinase-1 (PDK1).

**Results:** In the cell-free assay, unsaturated FFAs (uFFAs) such as oleic, linoleic and linolenic acid and saturated FFAs (sFFAs) such as stearic, palmitic, myristic, and behenic acid markedly reduced PTP1B activity, with the potential for uFFAs greater than that of sFFAs. All the investigated sFFAs inhibited PP2A activity, but otherwise no inhibition was obtained with uFFAs. Both uFFAs and sFFAs had no effect on PP1 activity. Oleic acid phosphorylated Akt both on Thr308 and Ser473, while stearic acid phosphorylated Akt on Thr308 alone. The effects of oleic and stearic acid on Akt phosphorylation were abrogated by the PI3K inhibitor wortmannin or the PDK1 inhibitor BX7912 and also by knocking-down PI3K or PDK1.

**Conclusion:** The results of the present study indicate that uFFAs and sFFAs could activate Akt through a pathway along a PI3K/PDK1/Akt axis in association with PTP1B inhibition.

**Poster 1-6**

**First-line chemotherapy with pemetrexed plus cisplatin for malignant peritoneal mesothelioma**

**Education**
- April 2013–October 2017: Hyogo College of Medicine, Graduate College of Medicine
- April 2004–March 2010: Hyogo College of Medicine

**Degrees**
- October 2017: Doctor of Philosophy
- April 2011: Doctor of Medicine

**Work Experience**
- August 2017–present: Assistant Professor in Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine
- April 2014–July 2017: Medical staff in Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine
- December 2013–March 2014: Senior resident in Division of Respiratory Medicine, Takarazuka City Hospital
- April 2013–November 2013: Senior resident in Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine
- April 2011–March 2013: Junior resident, Hyogo College of Medicine

**Abstract**
Eriko Fujimoto, Takashi Kijima, Kozo Kuribayashi, Yoshiki Negi, Shingo Kanemura, Koji Mikami, Hiroshi Doi, Kazuhiro Kitajima & Takashi Nakano

**Background:** Mesothelioma of peritoneal origin has wider variation in treatment outcomes than mesothelioma of pleural origin, likely because peritoneal mesothelioma comprises borderline malignant variants and aggressive malignant peritoneal mesothelioma (MPem). This study retrospectively evaluated the efficacy of first-line systemic pemetrexed and cisplatin chemotherapy in MPem.

**Research design and methods:** Twenty-four patients with Histologically proven MPem were treated with pemetrexed plus cisplatin as a first-line systemic chemotherapy. The response was evaluated radiologically according to standard Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Twenty-two patients underwent 18F-fluorodeoxyglucose positron emission tomography/FDG-PET/ computed tomography (CT) at baseline, and 13 were eligible for metabolic assessment.

**Results:** Two complete responses and 9 partial responses were achieved. Overall response rate and disease control rate were 45.8% and 91.7%, respectively. Median progression-free survival and median overall survival were 11.0 months and 15.8 months, respectively. We- type MPem had significantly longer survival (40.9 months median) than other clinical types (15.5 months) ($P=0.004$). The baseline maximum standardized uptake value in 22 patients was 8.93 (range: 2.5–16.77).

**Conclusions:** Systemic pemetrexed plus cisplatin is active for MPem. Disparity with the outcome of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) needs to receive more emphasis, since peritoneal mesothelioma has a 3-year survival rate of 50%.
Early Stage Clinical Characterization of Malignant Pleural Mesothelioma

Education
April 2013-October 2018
Hyogo College of Medicine, Graduate College of Medicine
April 2005-May 2011
Hyogo College of Medicine

Degrees
October 2018
Doctor of Philosophy
May 2011
Doctor of Medicine

Work Experience
May 2017-present
Assistant Professor in Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine
December 2016-April 2017
Medical staff in Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine
April 2015-November 2016
Medical staff in Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine, Sasayama medical center
April 2014-March 2015
Medical staff in Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine
August 2013-March 2014
Senior resident in Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine
April 2013-July 2013
Senior resident in Division of Respiratory Medicine, Takarazuka City Hospital
April 2011-March 2013
Junior resident, Hyogo College of Medicine

Abstract
Yoshiki Negi 1, Kozo Kuribayashi 1, Toshiyuki Minami 1, Takashi Yokoi 1 and Takashi Kijima 1

1 Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan, E-mail: negi@hyo-med.ac.jp

Background: Although the mortality rate of primary lung cancer has significantly improved with advances in diagnostic techniques, malignant pleural mesothelioma (MPM) still has a very poor prognosis. The median survival time (MST) after diagnosis of MPM is about 1 year. Thus, there is a need to improve the diagnosis and implement treatment interventions at an earlier stage.

Methods: In this study, we retrospectively identified 40 18F-FDG-PET/CT negative MPM cases from 72 cases presented at the Hyogo College of Medicine, Japan, between 2007 and 2015. Overall survival rates of the MPM patients were determined and compared based on pathological features, histology (biphasic or epithelioid types), or treatment provided (trimodal, bimodal or palliative).

Results: The biphasic histological type of early-stage MPM were characterized by poor prognosis (p=0.0006). Additionally, the cytology-negative group (Class III and below) showed significantly shorter survival times (p=0.0290). There was no significant difference in survival between patients who received either surgery option (pleurectomy/decortication or extrapleural pleurectomy), and those who received only chemotherapy (p=0.6991). Interestingly, bimodal therapy (chemotherapy followed by pleurectomy/decortication resulted in a longer survival rate than trimodal therapy (neoadjuvant chemotherapy, extrapleural pleurectomy and hemithoracic radiation). Patients who underwent extrapleural pleurectomy demonstrated a significantly lower median survival (432 days) compared with patients who received pleurectomy or decortication (1383 days, p<0.05).

Conclusions: In early stage PET-negative MPM cases, biphasic histology and Class II and below pleural effusion resulted in a poor prognosis. Surgical treatment using pleurectomy/decortication resulted in higher patient survival outcomes than therapy with extrapleural pneumonectomy.
Poster Session 1

**P1-8**

*The trend of enlightenment for citizens on cancer prevention and the prevention of infectious diseases in Japan: through analysis of newspaper articles*

**Yoshiko Sato, Ph.D.**

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**Abstract**

Yoshiko Sato and Horii Satoshi

1Osaka Prefecture University Graduate School of Nursing, 3-7-30, Habikino, Habikino City, Osaka 583-8555, Japan, E-mail: ysato@nursing.osakafu-u.ac.jp

**Objective:** The purpose of this study is to clarify the trend of enlightenment for citizens concerning cancer prevention and the prevention of infectious diseases in Japan. In this study, enlightenment means acquiring knowledge and deepening understanding on cancer prevention and the prevention of infectious diseases. We used newspaper articles as a source of information for enlightenment.

**Methods:** We used an online article database of Asahi Shimbun which is a representative national newspaper in Japan and searched for articles from 1945 to December 31, 2017, using “cancer prevention” and “prevention of infectious diseases” as keywords; we excluded human resources articles and advertisements. First, we confirmed the annual transition of the retrieved articles. Next, we confirmed the contents of the article and extracted important words related to cancer prevention and the prevention of infectious diseases.

**Results:** The first articles on cancer prevention and the prevention of infectious diseases were published in 1962 and 1975. The number of articles found was 1535 and 497. The peak of the articles on cancer prevention was in 2010, on the prevention of infectious diseases was in 2011. Regarding cancer prevention, many articles concerning the important words “screening,” “vaccine,” “meal/nutrition,” “smoking cessation/smoking,” “infection,” “activity/exercise” and “drinking” were extracted. Regarding the prevention of infectious diseases, many articles on the important words “vaccine,” “disinfection,” “hand wash,” “mask,” “gargle” and “meal/nutrition” were extracted. Among those associated with infection, there were many articles on the prevention of cervical cancer (209), gastric cancer (70), and liver cancer (33).

**Conclusion:** Newspaper articles on cancer prevention and the prevention of infectious diseases reflected social conditions. It was suggested that the role of newspaper articles as a means of enlightenment for the public was insufficient.

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**P1-9**

*Eating Habits & Symptoms disturbing food intake after Gastrectomy in One Year*

**Nana Inoue**

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**Abstract**

Nana Inoue

1Osaka Prefecture University, Faculty of Nursing, 3-7-30, Habikino, Habikino City, Osaka 583-8555, Japan, E-mail: n.inoue@nursing.osakafu-u.ac.jp

**Background:** Patients after gastrectomy suffer from dumping syndrome and gastrointestinal symptoms, and changed eating habits sometimes makes them exhausted. Especially, they have less support to build new eating habits after discharge. At the same time, they lose body weight and physical strength because of difficulties of food intake. Even though, they need support to control food intake and to gain appropriate eating habits in the hospital, they do not have enough supports because of shortening hospitalized period. More aging of the population is escalating, it would be more difficult to adapt into the changed eating habits. Therefore, this study clarifies eating habits and symptoms with food intake after gastrectomy in one year.

**Methods:** Interview was conducted on 7 patients diagnosed stomach cancer with stage Ia, Ib, Iia, IIb, and then have undergone gastrectomy.

**Interview contents:** food intake, eating habits, thought of changed eating habits, gastrointestinal symptoms, and dumping syndrome.

**Results:** From interview contents, categories and subcategories were generated. The interview text was also analyzed with text mining to classify categories to confirm the result.

**Conclusions:** The gathered contents of diet that related to new dietary habits, meal method, thoughts on meals, gastrointestinal symptoms, and dumping syndrome were analyzed by text mining. It will be reported in this symposium.
Self-perceived burden to their families in colorectal cancer patients during treatment and related factors

Miwa Aoki, MSN.

Education
Apr. 2003-Mar. 2007 Faculty of Nursing, University of Kochi
Apr. 2012-Mar. 2014 Division of Health Sciences, Osaka University Graduate School of Medicine

Degrees
Master of Science in Nursing

Work Experience
Jul. 2010-Mar. 2012 Yamanobe Hospital
Apr. 2014-Mar. 2016 Faculty of Nursing, University of Kochi
Aug. 2017- Division of Health Sciences, Osaka University Graduate School of Medicine

Abstract
Miwa Aoki, Harue Arao, Akiko Hatakeyama, Youko Minamiguchi, Yukiko Tatsumi, Yuki Morooka

Background: Japan has a high rate of morbidity for colorectal cancer, which is becoming an important issue. It is thought that colorectal cancer patients experience self-perceived burden to their families (SPB-F) due to the short amount of time they are hospitalized and the treatment given on an outpatient basis.

Purpose: The purpose of this study was to investigate SPB-F experienced in colorectal cancer patients during treatment, and the factors affecting SPB-F.

Methods: Self-administered questionnaire survey was conducted with 362 patients with colorectal cancer receiving treatment in designated cancer hospitals. SPB-F was assessed on a five-point scale (1 = “disagree”; 5 = “strongly agree”). Questionnaire also included sociodemographic, treatment status, and worries of life with medical treatments. T-test and one-way ANOVA were conducted using SPSS ver.25.

Results: The mean age of participants was 67.8 ± 10.3 and 193 (53.7%) were male. The mean SPB-F score was 4.3 ± 1.0. Compared to those 65 or older, there was significantly higher SPB-F score among participants under the age of 65 (p<.01) and those that lived with families, including spouses, more than those that lived alone (p<.01). Participants with recurrent or metastasized cancer had significantly higher SPB-F score than those who had no recurrent or metastasized cancer (p=.00), and participants that had undergone drug treatments had a higher SPB-F score than those that had undergone surgery (p=.00), while PS1-3 participants had higher SPB-F score than PS0 participants (p=.00, p<.05, and p<.01, respectively). In addition, participants worried about ‘diagnosis or treatments’ (p<.05), as well as participants worried about ‘side effects or sequelae’ (p=.00) experienced high SPB-F.

Discussion & Implications: SPB-F of colorectal cancer patients is through to be affected by age, living status, physical functioning status, and treatment-related phenomena such as side effects, and recurrence or metastasis. This suggests the need to confirm patients’ feeling for their families, and for support to reduce their SPB-F.
Poster Session 1

P1-11

Survey on the Information Needs of Patients with Urologic Cancer

**Education**

- Apr. 2001-Mar. 2005: Tokyo Women's Medical University of Nursing
- Apr. 2018-present: Division of Health Sciences, Osaka University Graduate School of Medicine

**Degree**

- Bachelor of Nursing Science

**Work Experience**

- Apr. 2005-Mar. 2013: Tokyo Women's Medical University Hospital
- Apr. 2013-Mar. 2018: University Hospital Kyoto Prefectural University of Medicine

**Abstract**

Yasuyo Sugiura, Harue Arai, Miwa Aoki, Yoko Minamiguchi, Akiko Hatakeyama, Yukiko Tatsumi, Yuki Morooka

Division of Health Sciences, Osaka University Graduate School of Medicine, 1-7, Yamadaoka, Suita, Osaka 565-0871, Japan, E-mail: y-sugiura@sahs.med.osaka-u.ac.jp

**Objectives:** The aims of this study were to investigate the information needs of patients with urologic cancer and to provide suggestions for nursing interventions.

**Methods:** A self-administered questionnaire survey was administered among patients with cancer in 17 designated cancer-care hospitals (response rate = 54.7%, n = 1981). A total of 149 patients with urinary cancer were extracted for analysis. The questionnaire contained items on participant characteristics (age, sex, treatment status, years after diagnosis, and recurrence or metastasis), and 14 information needs were assessed on a five-point scale. The responses to the information needs items were recoded as “strongly agree” = 4 to “disagree” = 0, and the mean scores were calculated and analyzed using t-tests.

**Results:** Men made up 127 (85.2%) of the subjects, and the mean age was 72.9 ± 7.9 (standard deviation [SD]). The primary cancer sites were prostate (60.4%), bladder (22.8%), and kidney (16.8%). The information needs mean scores ± SD were as follows: Patients with prostate cancer scored 3.5 ± 0.7 for “symptoms” and “treatment,” 3.4 ± 0.6 for “side effects,” 3.4 ± 0.7 for “long-term effects,” 3.3 ± 0.7 for “costs,” and 3.2 ± 0.8 for “economic support.” Patients with bladder cancer scored 3.4 ± 0.6 for “treatment,” 3.3 ± 0.8 for “side effects,” and 3.1 ± 1.0 for “symptoms.” Patients with kidney cancer scored 3.9 ± 0.2 for “symptoms” and “treatment,” 3.7 ± 0.7 for “long-term effects,” 3.6 ± 0.8 for “side effects,” 3.3 ± 0.8 for “costs,” and 3.1 ± 0.7 for “treatment” experience of patients of the same generation. Comparing information needs by the presence of recurrence or metastasis, the scores of patients with kidney cancer who had recurrence or metastasis did not differ significantly on any of the information needs items, patients with prostate cancer with recurrence or metastasis had higher scores for “side effects” (p < 0.05), and patients with bladder cancer with recurrence or metastasis had higher scores for “long-term effects” (p < 0.01), compared with the scores of patients with no recurrence or metastasis.

**Conclusion:** Patients with urologic cancer had information needs related to symptoms and treatment. The information needs differed by the primary cancer site and by the presence of recurrence or metastasis. This finding suggests that it is necessary to consider the characteristics of the primary cancer site, recurrence or metastasis status, and cancer stage when providing nursing interventions.

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P1-12

Difficulties and Coping Strategies of Breast Cancer Patients Undergoing Hormonal Therapy

**Education**

- Apr. 1999-Mar. 2001: Saga Medical School, Graduate School of Medical Science
- Apr. 2010-Mar. 2018: Osaka Prefecture University, Graduate School of Nursing Science

**Degree**

- Ph.D in Nursing Science

**Work Experience**

- Apr. 2005-: Osaka Prefecture University Graduate School of Nursing

**Abstract**

Yumi Hayashida and Kyoko Tanaka

Osaka Prefecture University, School of Nursing, 3-7-30, Habikino, Habikino-shi, Osaka, 583-8555, Japan, E-mail: yumihayashida@nursing.osakafu-u.ac.jp

**Objective:** Breast cancer patients undergoing endocrine therapy (hereinafter, “patients”) confront menopausal symptoms and difficulties in interpersonal relationships. Therefore, it is necessary to provide patients with support for physical and psychosocial self-control. The aim of this study was to clarify patients' difficulties and coping strategies, and to obtain suggestions for developing a nursing program to support self-control in patients.

**Methods:** Semi-structured interviews were conducted with eight pre-menopausal and five post-menopausal patients. A qualitative analysis was carried out on each period.

**Results:** The difficulties faced by the patients were divided into 14 categories for pre-menopausal patients and 10 categories for post-menopausal patients. Coping with these difficulties consisted of nine categories for pre-menopausal patients and 15 categories for post-menopausal patients.

**Discussion:** Post-menopausal patients had various coping strategies, followed effective treatments and made use of others and medical institutions. On the other hand, pre-menopausal patients experienced severe menopausal symptoms and strong stress, resulting in trouble in their daily lives. It was difficult for pre-menopausal patients to keep a positive mind and they had concerns and anxiety about recurrence and metastasis. Furthermore, they had difficulties in interpersonal relationships and were in a state of not knowing how to live in their own way. Therefore, it seems necessary for pre-menopausal patients to control menopausal symptoms, manage the emotional aspects of stress, and acquire the ability to share their thoughts in interpersonal relationships.
Optimizing outcomes in EGFR mutation-positive NSCLC Sequencing strategy

Ross Soo, MBBS, Ph.D., FRACP
Senior Consultant, Department of Haematology-Oncology, National University Cancer Institute, Singapore

He received his medical degree from Monash University, and PhD from The University of Western Australia. He underwent specialist training in Melbourne and Sydney and subsequently became a Fellow of the Royal Australasian College of Physicians and the Academy of Medicine, Singapore. He leads the Lung tumor Group at the National University Cancer Institute, Singapore. His research interests are in lung cancer and biomarkers and he has published more than 100 papers.

His professional affiliations include memberships of the European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), the International Association for the Study of Lung Cancer (IASLC), and the Singapore Society of Oncology (SSO). He is currently an Associate Editor for Lung Cancer and sits on various committees including Medical Oncology Specialist Training Committee, Chapter of Medical Oncology Executive Committee, Long-term International Fellowship (Life) Subcommittee of the Grant Selection Committee of the Conquer Cancer Foundation of ASCO, and Immuno-oncology Program Committee Track WCLC 2019. He is Co-Chair; “Thoracic cancers” track ESMO Asia Congress 2018, Chair of the National Healthcare Group Domain-Specific Ethics Review Board, and is the immediate past Chair of the IASLC Communications Committee.
DAY 2

The 2nd International Cancer Research Symposium of Training Plan for Oncology Professionals
February 3 (Sun), 2019 Yamato-no-Ma

Poster Session-2

Poster 2-1/Poster 2-2  9:00–10:00

Oral Session

Mini Lecture 4  10:10–10:40
Session 5  Thoracic Oncology 2  10:40–11:25
Luncheon Seminar 2  11:35–12:25
Mini Lecture 5  12:35–13:05
Session 6  Immunotherapy  13:05–13:50

Chairpersons

Session 5  Thoracic Oncology 2
Tomoya Kawaguchi, M.D.,Ph.D.  (Graduate School of Medicine, Osaka City University)
Nobuyuki Yamamoto, M.D.,Ph.D.  (Wakayama Medical University)

Session 6  Immunotherapy
Kenji Chamoto, Ph.D.  (Kyoto University Graduate School of Medicine)
Hidetoshi Hayashi, M.D.,Ph.D.  (Kindai University Faculty of Medicine)

Poster Session-2

Shosaku Nomura, M.D.,Ph.D.  (Kansai Medical University)
Masanori Toyoda, M.D.,Ph.D.  (Kobe University Graduate School of Medicine)
Hajime Monzen, Ph.D.  (Kindai University Faculty of Medicine)
**Poster Session 2**

### P2-1

**Development of an oral pemetrexed pro-drug for lung cancer treatment**

#### Education

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<tr>
<td>December 2013</td>
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#### Work Experience

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<tr>
<td>April 2006-Mar 2011</td>
<td>Associate professor at Faculty of Pharmacy, Kindai University</td>
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<tr>
<td>April 1990-Mar 2006</td>
<td>Pharmacist at Tenri Yorozu Hospital</td>
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#### Abstract

Toru Otori, 1, Tetutaro Kimachi2, Tomohiro Maegawa 1, Hyuji Ota 1, Sumio Mazuno 1, Masahiro Iwaki 1 and Renji Matsuyama 3

1 Faculty of Pharmacy Kindi University, 3-4-1, Kowakae, Higashi-OSaka 577-8502, Japan, E-mail: totori@phar.kindai.ac.jp
2 School of Pharmacy Mukogawa Women’s University, 11-68, Koshien - kyubantyou, Nishinomiya, 663-8179, Japan, E-mail : tkimachi@mukogawa-u.ac.jp
3 Daichi University of Pharmacy, 22-1 Tamagawa-cho, Minami-ku Fukuoka 815-8511 Japan, E-mail : matsuyama@daichi-cps.ac.jp

More than one million people worldwide die from lung cancer every year. Historically, standard first-line treatment for lung cancer is carried out with platinum-based chemotherapy. In addition, cetuximab and bevacizumab (antibodies) have been shown to improve survival in specific patient populations. If these antibodies are not effective, pemetrexed (PTX) is often used.

Pemetrexed exerts its action by disrupting folate-dependent metabolism. There is no difference in effectiveness between pemetrexed and docetaxel. Pemetrexed is injectable, but oral preparations have not been developed. Because pemetrexed has strong hydrophilicity it is not absorbed in the gastrointestinal tract. Therefore, pemetrexed injection therapy is inconvenient for lung cancer patients undergoing chemotherapy. To address this problem, we have set out to develop an oral pemetrexed pro-drug to improve the QOL of cancer patients.

In this study, a di-medoxxomil ester of pemetrexed (PTX-DM) was synthesized as a pro-drug which can be absorbed in the gastrointestinal tract. Pemetrexed at doses of 60 mg/kg in rat was evaluated. The area under the plasma concentration-versus-time curve from zero to 24 h (AUC 0-24h) of PTX-DM was significantly larger than PTX. PTX-DM was rapidly hydrolyzed in small intestinal mucosal, lung and liver. PTX-DM is converted to PTX by enzymes, first during the process of absorption from the intestine, and the remaining in the liver and lung.

### P2-2

**Biologic profiling of patient-matched primary lung cancer and its brain metastasis**

#### Education

April 2013 - Faculty of Medicine, Kansai Medical University

#### Degree

Medical student

#### Work Experience

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#### Abstract

Kohei Ofune 1, Tomohito Saito 2, Ryochi Iwata 1, Mikio Hayashi 3, Kunikazu Yoshimura 1, Masahiro Nonaka 1, Tomohiro Murakawa 2, and Akio Asai 1

1 Department of Neurosurgery, Kansai Medical University, 2 Department of Thoracic Surgery, Kansai Medical University, and 3 Department of Cell Physiology, Kansai Medical University, 2-5-1, Shin-machi, Hirakata City, Osaka 573-1010, Japan, E-mail: baghk309@gmail.com

**Background:** Brain metastasis is a common and lethal complication of non-small cell lung carcinoma. Ion channels have been reported to play crucial roles in proliferation and invasion of cancer cells. Biologic profiling of brain metastasis may help better understanding of the mechanism and ultimately lead to develop novel targeted therapy.

**Aim:** Our aim is to characterize brain metastasis by comprehensive analysis of ion channels, and evaluate them as potential therapeutic targets.

**Method:** Total RNA was extracted from archived formalin-fixed paraffin-embedded sections of patient-matched primary lung cancer and its brain metastasis (n = 3) and analyzed by nCounter Advanced Analysis(Nanostring Technologies, Inc.) with KMU ion channel panel. The cancer stem cell lines were established from patients of metastatic brain tumors (n = 2). The whole-cell currents of cancer stem cells were measured using patch-clamp technique, and pharmacological properties were analyzed.

**Result:** Metastatic brain tumors significantly increased the expression of MCOLN3 which coded mucolpin protein. TRP currents were observed in cancer stem cells. The currents were blocked by an anti-arrhythmic drug.

**Conclusion:** The results indicated that the mucolpin composed TRP channels in cancer stem cells from metastatic brain tumors. The mucolpin may be useful for therapeutic target of metastasis. We are promising to reposition the anti-arrhythmic drug to cancer therapy.
Molecular characteristics of human leukemia cell line after the long-term exposure to the Bcl-2 inhibitor ABT-199

**Education**
- Apr 2007-Mar 2013: Himeji Dokkyo University
- Apr 2018-Present: Kobe University Graduate School of Medicine

**Degree**
- BPharm (Bachelor of Pharmacy)

**Work Experience**
- Apr 2013-Present: Research Assistant, Himeji Dokkyo University

**Abstract**
Yuko Nakayama 1, 2, Kohji Takara 2, Tetsuya Minegaki 3, Kazuhiro Yamamoto 1, and Ikuko Yano 1

1 Kobe University Graduate School of Medicine, 2 Faculty of Pharmaceutical Sciences, Himeji Dokkyo University, and 3 Kyoto Pharmaceutical University, E-mail: yu-na@gm.himeji-du.ac.jp

ABT-199 (Venetoclax®) is a selective, first-in-class B-cell lymphoma-2 (Bcl-2) inhibitor which was approved by the US FDA in 2016, but has not yet been approved in Japan. Numerous clinical trials for ABT-199 demonstrated high efficacy and safety in the treatment of various hematologic malignancies. However, multidrug resistance remains a significant problem for cancer chemotherapy, and thus it is important to identify potential mechanisms of resistance to ABT-199. The aims of the present study are to establish ABT-199-resistant leukemia cells and to examine their molecular characteristics.

Human promyelocytic leukemia HL60 cells were exposed to 1 μM ABT-199 for ca. 3 months, and several clones were isolated. Sensitivities to ABT-199 were about 3-fold lower in the clone than HL60 cells by the WST-1 assay, and this resistant clone was named HL60/ABT-199. These resistant cells also exhibited multidrug resistance to vinblastine, vincristine, paclitaxel, doxorubicin, etoposide, and mitoxantrone. However, the sensitivities to SN-38, 5-fluorouracil, and cisplatin were comparable in both cell lines. The expression of ABCB1 mRNA was higher in HL60/ABT-199 as compared with HL60 cells by real-time RT-PCR. Treatment with 5 μM ABT-199 for 24 h induced apoptosis at ca. 50% and 20% of total cells in HL60 and HL60/ABT-199 cells, respectively, by the Annexin V assay. Collectively, the novel ABT-199-resistant HL60 cells were shown to have multidrug resistance. Further investigation is necessary to elucidate the mechanistic details of the resistance to ABT-199.

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Short-term exposure to a high concentration of carfilzomib stimulates type I IFN-producing capacity of plasmacytoid dendritic cells

**Education**
- Apr 2016-: Kansai Medical University Graduate School
- Apr 2005-May 2011: Kansai Medical University

**Work Experience**
- Apr 2011-: Kansai Medical University

**Abstract**
Yuta Yamanaka 1, Tomoki Ito 1, Munee Inaba 1, Yusuke Sawai 1, KI Imai 1, Yoshiko Azuma 1, Minoru Shigesaka 1, Atsushi Satake 2, Shosaku Nomura 1

1 First Department of Internal Medicine, Kansai Medical University, 2-5-1, shinmachi, HirakataCity, Osaka, 573-1010, Japan. E-mail: yamanayt@hirakata.kmu.ac.jp

**Background:** Carfilzomib (CARF), a selective proteasome inhibitor (PI), has an antitumor activity for multiple myeloma. Clinical pharmacokinetics of CARF is different from other PIs. T1/2 of CARF is very short and plasma concentration of CARF rapidly declines and reaches a plateau at low concentration in a biphasic manner. To assess immunomodulatory effects of CARF, we focused on the effects of CARF on the IFN-producing capacity of human plasmacytoid DCs (pDCs), which are the major source of IFN-α in the blood and play a central role in antiviral immune response.

**Results:** We used a biphasic culture including 20 min-culture with 1000nM as followed 24 h with 1 nM, which is an in vitro mimic culture of a biphasic manner of CARF plasma concentration, we found short-term exposure to a high concentration of CARF triggered enhanced IFN-α production by pDCs during post culture of CpG2216 with 1 nM CARF for 24 h. In the biphasic culture system with prior stimulation of 100 nM CARF (but not 1000 nM), addition of lenalidomide into the post culture enhanced pDC-derived IFN-α production. **Conclusions:** The short duration of clinical CARF peak-concentration potentially stimulated pDC function. Therefore, our findings suggest a therapeutic potential of CARF without preventing the DC function and an advantage of combination use with CARF and lenalidomide from an immunological point of view.
P 2-5

**Investigation of pharmacological action of anti-SLAMF7 antibody (Elotuzumab) on human dendritic cells (DC)**

**Education**

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**Abstract**

Yoshiko Azuma 1 and Tomoki Ito 1, Minoru Shigesaka 1 and Kai Imai 1 and Muneco Inaba 1 and Shosaku Nomura 1

1 First Department of Internal Medicine Kansai Medical University Hirakata Hospital, 2-5-1, Shinmachi, Hirakata-city, Osaka 573-1010, Japan, E-mail: azumays@hirakata.kmu.ac.jp

The immune-based cancer treatments are currently important in multiple myeloma (MM) therapy. Series of analyses have clarified a functional plasticity of DCs to induce Th1 or Th2 response. Here, we focused on the effects of myeloma environment to modulate the human myeloid DCs (mDCs), which are the major regulators to induce Th1 or Th2 responses. Soluble form of SLAMF7 (sSLAMF7) is a pivotal environmental component of MM and functions as a self-ligand of myeloma cells. sSLAMF7 has been detected in the serum of patients with MM at higher levels than healthy individuals. To evaluate the functions of soluble factors/components derived from myeloma cells, we analyzed whether supernatants of myeloma cell lines could modulate mDC functions. Our data suggest that the MM micro-environment, while suppress the Th1-inducing capacity, rather lead to enhance Th2 response at DC phase. As sSLAMF7 is detected in the serum of patients with MM but not in the supernatants of MM cell lines in the experimental setting, there is a limitation that our data does not consider the action of sSLAMF7.

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P 2-6

**Immunomodulatory effect of lenalidomide after allogeneic hematopoietic stem cell transplantation**

**Education**

| April 2006-March 2012 | Wakayama Medical University |

**Work Experience**

| April 2012-March 2016 | Kansai Medical University Hospital |

**Abstract**

Yukie Tsubokura 1, Atsushi Satake 1, Hideaki Yoshimura, Masaaki Hotta, Shosaku Nomura

1 First Department of Internal Medicine, Kansai Medical University, 2-5-1 Shinmachi, Hirakata City, Osaka 573-1010, Japan. E-mail: fujitayu@hirakata.kmu.ac.jp

Lenalidomide (Len) is a thalidomide derivative for the treatment of cancers such as multiple myeloma, myelodysplastic syndrome, and adult T-cell leukemia/lymphoma. Originally anti-tumor mechanism caused by Len was unknown; however, previous reports suggested Len has direct anti-tumor effects and immunomodulatory effects. Len can stimulate NK cell activation and promote IL-2 and IFN-γ production from T cells. Additionally, several reports suggested that Len inhibits the proliferation and function of regulatory T cells (Treg) by suppressing the expression of Foxp3 in the syngeneic setting. Actually, Len slightly expanded NK cells and decreased Treg in the steady state when wild-type mice were treated with Len.

In contrast, the effect of Len for alloimmune responses remains unknown. Allogenic hematopoietic stem cell transplantation (aHSCT) is the only curative therapy for hematological malignancies, but many patients suffer from disease recurrences even if they undergo aHSCT. Thus, treatment with Len may be a useful treatment option for disease recurrences after aHSCT. The clinical effects, immunomodulatory effect and safety of Len for patients who underwent aHSCT have not been elucidated. Finally, this study aims to clarify the effect of Len for T cells including Treg using a mouse acute graft versus host disease model because Treg plays an important role in establishment of immune tolerance after aHSCT.
**Poster Session 2**

### P2-7

**Sulforaphane has a liver-protective effect through the suppression of inducible nitric oxide synthase in primary cultured rat hepatocytes.**

**Education**

2017.4-present  
Kansai Medical University Graduate School of Medicine  
2005.4-2011.3  
Kansai Medical University

**Work Experience**

2016.4-2017.3  
Department of Surgery, Pref Osaka Saiseikai Izu Hospital  
2013.4-2016.3  
Department of Surgery, Kansai Medical University  
2011.4-2013.3  
Kansai Medical University Hirakata Hospital

**Abstract**

Yuki Hashimoto 1, Richi Nakatake 1, Tatsuma Sakaguchi 1, Masaya Kotsuka 1, Masahiko Hatta 1, Mikio Nishizawa 2, Tadayoshi Okumura 1,3 and Masaki Kaitori 1

1 Department of Surgery, Kansai Medical University, 2-5-1, Shinmachi, Hirakata City, Osaka, 573-1010, Japan, E-mail: hashimoy@hirakata.kmu.ac.jp  
2 Department of Biomedical Sciences, and 3Research Organization of Science and Technology, College of Life Sciences, Ritsumeikan University, Kusatsu, Shiga, Japan

**Introduction:** Sulforaphane is a natural isothiocyanate that is present in cruciferous vegetables such as broccoli. As reported previously, sulforaphane has anti-inflammatory effects on a variety of organ injury. However, there is a few scientific evidence that sulforaphane influences inflammatory mediators, such as tumor necrosis factor (TNF)-α and nitric oxide (NO). In inflamed liver, proinflammatory cytokines stimulate liver cells, followed by induction of inducible NO synthase (iNOS) and others. Excessive NO produced by iNOS is one of the factors in liver injury. Therefore, inhibiting iNOS induction for preventing liver injury is important. This study aimed to investigate the protective effects of sulforaphane on the liver by examining interleukin (IL)-1β-stimulated hepatocytes.

**Results:** Simultaneous addition of IL-1β and sulforaphane decreased expression levels of iNOS protein, resulting in inhibition of NO production dose- and time-dependently. Sulforaphane inhibited one of the essential signaling pathways for iNOS induction, NF-κB activation, although sulforaphane had no effect on the degradation of IκB. Sulforaphane decreased the levels of iNOS mRNA expression. Transfection experiments revealed that sulforaphane reduced iNOS mRNA levels at the promoter activation and mRNA stabilization steps.

**Conclusion:** Sulforaphane inhibited the induction of inflammatory mediators, such as iNOS, in part through inhibition of NF-κB activation in hepatocytes. Sulforaphane may have therapeutic potential for organ injuries, including the liver.

### P2-8

**New knowledge of carcinogenesis of colorectal cancer through splice variants in MUTYH gene**

**Education**

April 2017-  
Master of Science, Graduate School of Science & Engineering, Kindai University  
April 2012-May 2017  
Department of Life Science, Faculty of Science & Engineering, Kindai University  
April 2008-May 2011  
Kansai Okura High School

**Degree**

May 2017  
Bachelor of Science, Kindai University

**Abstract**

Motohide Kaneda 1, Musha Futagawa 1, Miho Takeshita 1, Fumino Katou 1, Maki Taniguchi 1, Akihito Babaya 2, Michiko Hamanaoka 2, Tomoki Yamano 2, Masataka Ikeda 2, Naohiro Tomita 2 and Kazuo Tamura 1

1 Master of Science, Graduate School of Science & Engineering, Kindai University, 3-4-1 Kowakaes, Higashi-Osaka City, Osaka 577-8502, Japan, E-mail:1733310115sw@kindai.ac.jp  
2 Division of Lower Gastrointestinal Surgery, Department of Surgery, Hyogo College of Medicine

The human MUTYH gene encodes the A/G specific adenine DNA glycosylase (α-glycosylase), which plays a crucial role in the base excision repair (BER) system and is essential for maintaining the genome integrity. The MUTYH product (α-glycosylase) contributes to DNA repair by deleting misincorporated adenine base.

The purpose of our study is to search for various splice variants between exon 1-4, and to form the foundation for the construction of a concern risk assessment system due to new knowledge of carcinogenesis of colorectal cancer through splice variants in MUTYH gene.

First, we sequenced 18 samples of control (disease free control group; 18 samples of blood) to search for splice variants. We identified two new variants and three known variants. Both of new variants showed nonsense mutation caused by frameshift. They were predicted to be pathologic variants by genome annotation.

Second, we performed quantitative analysis of each splicing variants, and compared between the disease free control group and patient group with colorectal cancer. The patient group was significant increasing by 3.83-fold in the pathologic variants as compared with the control. The patient group was significant decreasing by 0.63-fold in the reference sequence as compared with the control.

Our study suggested that the possibility of constructing a risk assessment system for colorectal cancer using quantitative analysis of splice variant of the MUTYH.
**P 2-9**

**Ectopic band 3 expression under control of hypoxic condition stimulates autoantibody production causing colorectal cancer-related anemia**

**Akihito Kitao, M.D.**

The cause of cancer-related anemia at onset is generally attributed to bleeding in patients with gastrointestinal cancer. However, anemia due to other etiologies is also observed, such as autoimmune hemolytic anemia (AIHA) that develops as a paraneoplastic syndrome. To investigate the relationship between the extent of ectopic band 3 expression, an erythrocyte membrane protein that is the target of IgG autoantibodies in AIHA, and the degree of anemia in colorectal cancer (CRC), we conducted this prospective observational study. From September 2016 to August 2018, 50 patients with CRC and 26 healthy controls were enrolled. Although clinical AIHA was not observed in any patient, a direct Coombs test was positive in 10 CRC patients (20%, p=0.01). When erythrocyte membrane-bound IgG was measured via flow cytometry, the mean ± standard deviation fluorescence intensity was significantly higher among patients with CRC compared to healthy controls (38.8 ± 14.7 vs. 29.9 ± 15.6, p=0.012). Immunohistochemical staining of band 3 in CRC surgical specimens showed a positive rate of 97%. BALB/c mice transplanted with Colon-26, a band 3 protein expressing mouse CRC cell line, showed an increase in erythrocyte membrane-bound IgG as compared with mice not transplanted with Colon-26. The effect was moderate in athymic BALB/c-nu mice. We also confirmed that band 3 expression in CRC cell is controlled by hypoxic stimuli. This is the first description of elucidates a reliable mechanism underlying immune anemia in patients with cancer.

**Poster Session 2**

**P 2-10**

**Dosimetric Effect of Rotational Setup Errors in Brain SRS with HyperArc**

**Tomohiro Sagawa**

In the treatments using single isocenter for multiple metastases, rotational setup errors caused considerable effects on dose coverage to targets. The aim of this study is to evaluate the dosimetric effects of rotational setup errors in stereotactic radiosurgery for brain metastases with HyperArc. For 29 patients (1-8 brain metastases), HyperArc plans (“Base plan”) with a prescription dose of 20-24 Gy for D95 of planning target volume (PTV) were retrospectively generated. For all patients, reference computed tomography (CT) sets was registered with cone-beam CT to create the rotated CT sets involving rotational setup errors. By copying “Base plan” on the rotational CT sets and recalculating dose distributions, we created “Rotation plan” and compared dosimetric parameters for PTV and normal brain tissues of both plans. The rotational setup errors for three axes were 0.29 ± 1.23” for Pitch, 0.00 ± 1.22” for yaw and 0.32 ± 1.27” for roll. Although, for single metastasis cases, rotational setup errors did not affect significantly, for multiple metastases cases, they caused considerable underdosage of D95; 10.4% on average and 37.4% for maximum. The V12 for normal brain tissues was increased by 0.09 ± 0.17 cc. In multiple metastases cases, rotational setup errors caused considerable underdosage of target dose and made brain tissues doses higher during HyperArc. Precise patient setup using a six degrees of freedom couch is required to minimize the effects of rotational setup errors.
Para-caval and caudate lobe hepatocellular carcinoma treated with combination of selective chemoembolization and stereotactic body radiotherapy.

Masayoshi Inoue, M.D.

**Education**

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<td>April 2015-present</td>
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**Work Experience**

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<td>Higashiosaka City Medical Center</td>
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<td>Chief Radiation Oncologist, Department of Radiology</td>
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<td>January 2015-December 2015</td>
<td>Nara Medical University</td>
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<td>Assistant Professor, Department of Radiation Oncology</td>
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<td>April 2009-December 2014</td>
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<td>April 2004-March 2009</td>
<td>Staff Diagnostic Radiologist, Department of Radiology</td>
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**Abstract**

Masayoshi Inoue, 1,2, Emiko Shimoda 1, and Masatoshi Hasegawa 2

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**Background & Objectives:** Because there are many feeding arteries of hepatocellular carcinoma (HCC) in the para-caval and caudate lobe of the liver, the local recurrence rates of selective chemoembolization for the para-caval and caudate lobe HCC were higher than those for in other segments. The role of percutaneous ablation therapies such as radiofrequency ablation and ethanol ablation is still limited, because of the deep location of HCC and the adjacent large vessels. Here we report 3 cases of para-caval and caudate lobe HCC treated with combination of selective chemoembolization and stereotactic body radiotherapy (SBRT).

**Material & Methods:** Three patients with unresectable HCC in the para-caval or caudate lobe underwent this treatment, comprised of 1 man and 2 women. Age was 71, 77, and 80 years. Two cases were located in the para-caval lobe, one was located in the caudate lobe. Tumor size was 1.3, 1.5, and 4 cm, respectively. All three patients received SBRT. In 2 cases, a total dose of 60 Gy in 20 daily fractions was delivered, and in 1 case a total dose of 60 Gy in 15 daily fractions was delivered. Selective chemoembolization was also performed with an emulsion of iodized oil and epirubicin hydrochloride.

**Results:** Prescribed course of treatments were completed in all patients. Follow-up period after radiotherapy was 12, 15, and 16 months, respectively. All patients achieved complete response 6 months after SBRT. No local recurrence and severe adverse event was observed.

**Conclusion:** Combination of selective chemoembolization and SBRT seemed to be safe and effective for para-caval and caudate lobe HCC.
Recent topics of ALK/BRAF altered lung cancer

Seiji Yano, M.D., Ph.D.
Professor, Division of Medical Oncology,
Cancer Research Institute, Kanazawa University

Education
1990 M.D. University of Tokushima Medical School, Tokushima, Japan
1995 Ph.D. University of Tokushima, Graduate School of Medicine, Tokushima

Postdoctoral Training
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1995-1996 Senior Resident, Third Department of Internal Medicine, University of Tokushima

Hospital or Affiliated Institution Appointments & Research History
1997 Assistant Professor, Third Department of Internal Medicine, University of Tokushima
1997-1999 Visiting Assistant Professor, Department of Cancer Biology (Professor Isaiah J Fidler), MD Anderson
Cancer Center, University of Texas, Houston TX, USA
1999-2000 Assistant Professor, Third Department of Internal Medicine, University of Tokushima
2000-2007 Lecturer, Department of Internal Medicine and Molecular, University of Tokushima
2007-present Professor, Division of Medical Oncology, Cancer Research Institute, Kanazawa University
Head, Kanazawa University Hospital Cancer Center, Japan
2012-2015 Head, Out Patient Chemotherapy Unit, Kanazawa University Hospital, Japan
2014-2017 Head, Innovative Clinical Research Center, Kanazawa University Hospital, Japan
2017-present Deputy Director, Cancer Research Institute, Kanazawa University
2018-present Principal Investigator, WPI Nano Life Science Institute, Kanazawa University, Japan
2018-present Deputy Director, Kanazawa University Hospital, Japan
Paired Genomic Analysis of Squamous Cell Carcinoma Transformed From EGFR-mutated Lung Adenocarcinoma

Sehhoon Park, MD, Joon Ho Shim, MD, Boram Lee, MD, Inju Cho, MD, PhD, Woong-Yang Park, MD, PhD, Youjin Kim, MD, Se-Hoon Lee, MD, PhD, Yoon La Choi, MD, PhD, Joungho Han, MD, PhD, Jin Seok Ahn, MD, PhD, Myung-Ju Ahn, MD, PhD, Keunchil Park, MD, PhD, Jong-Mu Sun, MD, PhD.

1 Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
2 Samsung Genome Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
3 Department of Health Science and Technology, Samsung Advanced Institute of Health Science and Technology, Sungkyunkwan University, Seoul, Republic of Korea
4 Department of Hospital Pathology, Yeouido St. Mary’s Hospital, The Catholic University, Seoul, Republic of Korea
5 Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background: Adenocarcinoma (ADC) to squamous cell carcinoma (SCC) transformation (AST) is reported in epidermal growth factor receptor (EGFR)-mutated non–small cell lung cancer after tyrosine kinase inhibitor (TKI) failure. However, little is known about the underlying genomic changes during the AST process.

Methods: We performed deep target sequencing (381 genes) using paired samples from 4 patients with AST after EGFR TKI treatment. The histology of each sample was confirmed by TTF-1 and p63 immunohistochemistry. The patients received first- or second-generation EGFR TKI as an initial treatment.

Results: Transformed SCC acquired genomic alterations related to the PI3K/AKT/mTOR pathway, in addition to the initial EGFR mutation. In a representative case, two separate sub-clones, with a PTEN nonsense mutation and EGFR p.T790M mutation, were observed without histologic transformation at the time of gefitinib resistance. After subsequent treatment with osimertinib, SCC transformation was observed with the disappearance of the EGFR p.T790M mutation and acquired copy number loss in PTEN. Adopting the adjusted tumor cell fraction model elucidates the sub-clonal evolution process of the PTEN mutant sub-clone toward AST under the background of EGFR mutation. The rest of the transformed samples also had acquired genomic alterations in PTEN, LKB1, PI3KCA, or RICTOR, which are related to the PI3K/AKT/mTOR pathway.

Conclusions: Paired genomic analysis from our sample provides early clinical evidence of the ADC to SCC lineage transition that might be provoked by an alteration in the PI3K/AKT/mTOR pathway during EGFR TKI treatment. This finding could potentially broaden the known spectrum of EGFR TKI resistance mechanisms.
**Thoracic Oncology 2**

*Satomi Watanabe, M.D., Ph.D.* (Kindai University Faculty of Medicine)

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**Education**

- April 2006-March 2012: Osaka City University school of Medicine, Osaka, Japan
- April 2014-March 2018: Graduate school of Medical Science, Kindai University Faculty of Medicine, Osaka, Japan
- July 2016-July 2017: Harvard Medical School, Global Clinical Scholars Research Training Program

**Work Experience**

- April 2012-March 2014: Resident doctor, Bell-land general hospital, Osaka, Japan
- April 2014-present: Assistant Professor, Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan

**Awards/Honors**

- Merit Award, 4th International Symposium of Training Plan for Oncology Professionals
- Travel Grant, 18th Lynn Sage Breast Cancer Symposium

**Academic/Professional Memberships and Other Professional Activities**

- The Japanese Society International Medicine (Board Certified Member)
- The Japanese Society of Medical Oncology
- The Japan Lung Cancer Society
- The Japanese Breast Cancer Society

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**Abstract**

*Mutational activation of the epidermal growth factor receptor down-regulates MHC class I expression via the ERK signaling pathway in non‒small cell lung cancer*

Satomi Watanabe 1, Hidetoshi Hayashi 1, Koji Haratani 1, Shigeki Shimizu 2, Junko Tanizaki 1, Kazuko Sakai 3, Hisato Kawakami 1, Kimio Yonesaka 1, Junji Tsurutani 1, Yosuke Togashi 4, Kazuto Nishio 3, Akihiko Ito 2, and Kazuhiko Nakagawa 1

1 Department of Medical Oncology, 2 Department of Pathology, and 3 Department of Genome Biology, Kindai University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan, 4 Division of Cancer Immunology, Research Institute/EPOC, National Cancer Center, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan

The recognition by T cells of tumor antigens presented by major histocompatibility complex class I (MHC-I) molecules is essential for an antitumor immune response. We examined the effects of EGFR tyrosine kinase inhibitors (TKIs) on MHC-I expression in NSCLC cell lines. Appropriate EGFR-TKIs increased MHC-I expression at the mRNA and cell surface protein levels in NSCLC cells positive for EGFR mutations including those with the T790M secondary mutation. Trametinib, an inhibitor of the extracellular signal-regulated kinase (ERK) kinase MEK, also increased MHC-I expression, whereas the phosphatidylinositol 3-kinase (PI3K) inhibitor buparlisib did not, suggesting that the MEK-ERK pathway mediates the down-regulation of MHC-I expression in response to EGFR activation. Our results suggest that mutational activation of EGFR inhibits MHC-I expression through the MEK-ERK pathway in NSCLC and thereby contributes to the poor response of such tumors to immunotherapy. Further studies are warranted to evaluate the relation between EGFR-MEK-ERK signaling in and the immune response to *EGFR*-mutated NSCLC.
The efficacy of a Histone deacetylase inhibitor in combination with a MEK inhibitor in lung cancer cells harboring RAS mutations

Tadaaki Yamada and Koichi Takayama

Department of Pulmonary Medicine, Kyoto Prefectural University of Medicine, 465, Kajii-cho, Kamigyo-ku, Kyoto City, Kyoto 602-8566, Japan, E-mail: tayamada@koto.kpu-m.ac.jp

Non-small cell lung cancer (NSCLC) can be identified by precise molecular subsets based on genomic alterations that drive tumorigenesis and include mutations in EGFR, KRAS, and various ALK fusions. However, despite effective treatments for EGFR and ALK, promising therapeutics have not been developed for patients with KRAS mutations. It has been reported that one way the RAS-ERK pathway contributes to tumorigenesis is by affecting stability and localization of FOXO3a protein, an important regulator of cell death and the cell cycle. This is through regulation of apoptotic proteins BIM and FASL and cell-cycle regulators p21Cip1 and p27Kip1.

We now show that an HDAC inhibitor affects the expression and localization of FOXO proteins and wanted to determine whether the combination of a MEK inhibitor with an HDAC inhibitor would increase the sensitivity of NSCLC with KRAS mutation. Combined treatment with a MEK inhibitor and an HDAC inhibitor showed synergistic effects on cell metabolic activity of RAS-mutated lung cancer cells through activation of FOXOs, with a subsequent increase in BIM and cell-cycle inhibitors. Moreover, in a mouse xenograft model, the combination of belinostat and trametinib significantly decreases tumor formation through FOXOs by increasing BIM and the cell-cycle inhibitors p21Cip1 and p27Kip1.

These results demonstrate that control of FOXOs localization and expression is critical in RAS-driven lung cancer cells, suggesting that the dual molecular-targeted therapy for MEK and HDACs may be promising as novel therapeutic strategy in NSCLC with specific populations of RAS mutations.
Luncheon Seminar 2

Chair
Takayasu Kurata, M.D.,Ph.D.
Professor, First Department of Internal Medicine
Professor, Department of Thoracic Oncology, Kansai Medical University Hospital

Pemetrexed enhances anti-tumor efficacy of PD-1 pathway blockade by promoting intra-tumor immune response via immunogenic tumor cell death and T cell-intrinsic mechanisms

Nelusha Amaladas
Principal Research Associate, Cancer Immunobiology Department, Eli Lilly and Company

Nelusha Amaladas is a Principal Research Associate in the Cancer Immunobiology Department at Eli Lilly and Company located at the Alexandria Center for Life Sciences in NYC. She received her Bachelor’s degree in Microbiology at the University of California-San Diego and her Master’s degree in Molecular Biology at San Diego State University. She spent 3 years at the National Institutes of Health (NIH/NIDDK) in the lab of Dr. Hsieh working on mismatch repair protein biochemistry. This was followed by 2 years at Schering Plough Research Institute (now Merck & Co.) where she was part of the Pre-clinical and Clinical Bioanalytics team recognized for scientific achievement for the development of an HCV mutational analysis validation assay. Since joining Lilly 10 years ago, she has worked in multiple areas ranging from novel target discovery, expression systems development, cell based assays and more recently pre-clinical biomarkers. For the last 3 years as a member of the pre-clinical biomarker team she has been involved in investigating novel non-IO/IO combination strategies through mouse modeling and high content biomarker approaches.
Mini Lecture 5

Chair
Yosuke Togashi, M.D., Ph.D.
National Cancer Center Japan

Application of Clinical Sequencing for Cancer Genomic Medicine

Shuta TOMIDA, Ph.D.
Associate Professor, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University

Resume

1998 • 3  BS, Engineering, Nagoya University
2002 • 5  Ph.D., Engineering, Nagoya University
2002 • 6  JSPS Research Fellowship for Young Scientists
2003 • 2  Researcher, Aichi Cancer Center Research Institute
2006 • 5  Assistant Professor, Nagoya University School of Medicine
2008 • 11 Postdoctoral Fellow/Research Fellow, University of California Los Angeles
2013 • 4  Lecturer, Kinki University School of Medicine
2015 • 7  Associate Professor, Okayama University School of Medicine
Immunomodulatory effects of small molecule targeted agents in triple negative breast cancer

Chun-Yu Liu¹,²

¹ Division of Transfusion Medicine, Department of Medicine, and Comprehensive Breath Health Center, Taipei Veterans General Hospital, Taipei, Taiwan; ² School of Medicine, National Yang-Ming University, Taipei, Taiwan

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Triple-negative breast cancer (TNBC) has been associated with a robust tumor immune infiltrate. Tumor-infiltrating lymphocytes (TILs) in TNBC have been demonstrated a prognostic value. Some targeted pathways, such as the mitogen-activated protein kinase (MAPK) signaling pathway have been shown to regulate the immune response with the production of immunomodulatory cytokines, such as TNFα, interleukin (IL)-1, IL-10, and IL-12. Clinical studies have shown that the high expression level of Extracellular signal–related kinase (ERK), a member of the MAPK pathway, correlates with shorter survival in TNBC patients. Accordingly, ERK is a potential target for anti-tumor and cancer immunotherapy. In this talk, we will introduce our recent laboratory findings on small molecule targeted agents regarding their implication in immunogenic cell death (ICD) and/or other immunomodulatory effects in TNBC models.


Session 6

Immunotherapy

Koji Haratani, M.D., Ph.D. (Kindai University Faculty of Medicine)

Education

2004-2010 Osaka City University (MD)
2015-2018 Kindai University (PhD)

Work Experience

2013-2015 Tokyo Bay Urayasu-Ichikawa Medical Center (General Internal Medicine)
2015- Kindai University (Medical Oncology)

Academic/Professional Memberships and Other Professional Activities

- The Japanese Society of Medical Oncology
- The Japan Lung Cancer Society
- The West Japan Oncology Group
- The Japanese Society of Internal Medicine
- The American College of Physician
- The American Society of Clinical Oncology

Abstract

Tumor immune microenvironment and prognosis of cancer of unknown primary.

Koji Haratani¹, Hidetoshi Hayashi¹, Takayuki Takahama¹,², Nakamura Yasushi³, Takahiro Sawada⁴, Shuta Tomida⁵, Yasutaka Chiba⁶, Kazuko Sakai², Akihiko Ito³, Kazuto Nishio²,⁴, Kazuhiko Nakagawa¹

¹Department of Medical Oncology, Kindai University Faculty of Medicine.
²Department of Genome Biology, Kindai University Faculty of Medicine.
³Department of Pathology, Kindai University Faculty of Medicine.
⁴Kindai University Life Science Research Institute.
⁵Department of Biobank, Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University.
⁶Clinical Research Center, Kindai University.

Cancer of unknown primary (CUP) accounts for 1-5% of all cancers, and have poor prognosis. We retrospectively analyzed 165 CUP cases including 95 cases whose archival tumor tissue were available, of 209 cases who were treated in our institute between 2009 and 2017. Immunohistochemistry (IHC) and immune-related gene expression analyses with archival tumor tissue were examined to evaluate tumor immune microenvironment. Of these, 31 were favorable subset, and 134 were unfavorable subset. Median of overall survival time (OS) was 29.8 months in the favorable subset and 7.2 months in the unfavorable subset (Log rank test: P=0.001). Immunohistochemistry (IHC) showed that PD-L1 TPS, CD8+TILs density and FOXP3+TILs density did not predict overall survival, suggesting that pre-treatment immune activity is not utilized by conventional chemotherapy. Furthermore, immune-related gene expression analyses suggested that there were clinically significant candidates who would potentially benefit from immunotherapy.
Abstract

Development of chimeric antigen receptor T cell therapy for human rhabdomysarcoma

Shigeki Yagyu 1, Daisuke Morita 2, Miyuki Tanaka 2, Ken Kikuchi 1, Tomoko Iehara 1, Yozo Nakazawa 2, Hajime Hosoi 1

1 Department of Pediatrics, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan, E-mail: shigeky@koto.kpu-m.ac.jp
2 Department of Pediatrics, Shinshu University School of Medicine, Matsumoto, Japan

**Background:** The survival rate of rhabdomyosarcoma (RMS) is dismal. The EPHB4 receptor, which is associated with the malignant phenotype of various tumors, is strongly expressed in RMS, but at extremely low levels in normal tissue. In this study, we developed novel chimeric antigen receptor (CAR)-T cells that can target EPHB4 and kill RMS cells.

**Material and methods:** We generated a *piggyBac* transposon-mediated CAR-T cells, which enabled transduced cells to recognize EPHB4-positive RMS cells. The positivity of CAR transgene and the phenotype of transduced cells were analyzed by flow cytometry. To evaluate the cytotoxic activity, the transduced cells were co-cultured with an RMS cell line, Rh30, and the transduced cells were injected via tail vein of RMS xenograft-bearing mice.

**Results:** We successfully generated EPHB4-CAR-T cells, with a positivity of 27.95 ± 3.85% for EPHB4-CAR at day 14 after transduction. Notably, EPHB4-CAR-T cells exhibited naive/memory stem cell phenotype, indicating their proliferative potential in response to antigen stimulation. When co-cultured with Rh30 cells, EPHB4-CAR-T cells effectively eliminated Rh30 cells. Furthermore, EPHB4-CAR-T cells could debulk the RMS tumor in vivo.

**Conclusion:** We have demonstrated that EPHB4-CAR-T cells effectively eliminate RMS cells. The EPHB4-CAR-T cells may therefore be used as a novel adoptive T-cell therapy for RMS.