### 乳癌に発現する新規薬物トランスポーター human breast cancer transport 1 (hBCT1) の機能解析

梅本 岳宏[1]、中村 清吾[2]、日比 健志[1] ([1]昭和大学藤が丘病院　消化器外科、[2]昭和大学医学部乳腺外科)

We attempted to identify factors predicting the effectiveness of anticancer drug Paclitaxel. To search for a novel organic solute transport protein, we screened a human breast cancer cDNA library using an EST clone as a probe. To determine the functional characterization of the isolated transporter, we employed a Xenopus laevis oocyte expression system. After multiple rounds of screening, we isolated fifteen positive clones, and isolated a novel gene encoding human breast cancer transport 1 (hBCT1), from a human breast cancer cDNA library. Isolated hBCT1 cDNA consisted of 1,581 base pairs that encoded a 327-amino acid protein. By RT-PCR analysis, hBCT1 mRNA was detected in the normal breast and the breast cancer tissues. When expressed in X. oocytes, hBCT1 mediated the high affinity transport of [3H] Paclitaxel in time- and pH-dependent, and Na+-independent manners. Immunohistochemical analysis revealed that the hBCT1 protein is localized in the lactiferous duct epithelium and breast cancer.
A newly isolated hBCT1 is a key molecule for the breast handling of Paclitaxel in humans, and a predictor of the therapeutic effect of Paclitaxel .

*Keywords:* transporter, Paclitaxel

### P-2393 Thymidylate synthase copy number as a predictive biomarker for pemetrexed sensitivity in lung cancer

Daishi Kasai, Tetsuya Oguri, Hiroaki Ozasa, Takehiro Uemura, Eiji Kunii, Osamu Takakuwa, Mikinori Miyazaki, Ken Maeno, Shigeki Satou, Akio Niimi (Dept. of Internal Med., Nagoya City Univ. Sch. of Med.)

### チミジレートシンターゼコピー数は、肺癌におけるペメトレキセド感受性の予測因子となり得るか

笠井 大嗣、小栗 鉄也、小笹 裕晃、上村 剛大、國井 英治、高桑 修、宮崎 幹規、前野 健、佐藤 滋樹、新実 彰男 (名古屋市立大学 医学部 第２内科)

In this study, we examined whether thymidylate synthase (TS) copy number is the biomarker for pemetrexed (MTA) sensitivity. First, we confirmed that the lung adenocarcinoma cell lines have lower TS copy numbers and show higher susceptibility to MTA than those of squamous cell carcinoma. Next, we examined the correlation of TS copy numbers and 50% cell survival of MTA about 17 non-small cell lung cancer cell lines. Then, there was a meaningful relationship that the higher the copy numbers of TS, the lower the sensitivity for MTA. In addition, we examined TS copy numbers in clinical specimens of non-squamous cell lung cancers treated with MTA and platinum as first line, non-response cases exhibited higher TS copy numbers than response cases, and a meaningful relationship was observed between TS copy number and response rate( $P=0.0109$ ). Our study suggests that TS copy number is a predictive biomarker for MTA sensitivity in lung cancer.

*Keywords:* Thymidylate synthase, pemetrexed

Room R-P4 Sep. 20 (Thu) 17:20 - 18:10

## P17-5 Drus sensitivity test and prediction (2)
薬理効果の評価と予測 (2)

Chairperson: Tohru Obata (Aichi Gakuin Univ.)
座長：小幡 徹 (愛知学院大学　薬学部)

### P-2394 Prediction of response to chemotherapy for esophageal cancer by anti-p53 antibody

KOJI TANAKA, Hiroshi Miyata, Keijiro Sugimura, Makoto Yamasaki, Tsuyoshi Takahashi, Yukinori Kurokawa, Shuji Takiguchi, Kiyokazu Nakajima, Masaki Mori, Yuichiro Doki (Osaka Univ., Grad. school of Med., Dept. of Gastroentelorogical surgery)

### 食道癌における血清 p53抗体価を用いた抗癌剤感受性予測

田中 晃司、宮田 博志、杉村 啓二郎、山崎 誠、高橋 剛、黒川 幸典、瀧口 修司、中島 清一、森 正樹、土岐 祐一郎 (大阪大学消化器外科)

*Background*
We examine usefulness of anti-p53 antibody titer for prediction of response to chemotherapy in the patients with advanced esophageal cancer.
*Methods*
Total of 100 patients with advanced esophageal cancer who received chemotherapy from December 2011 to January 2008 were analyzed.
p53 antibody titer and the clinical response were compared.
*Results*
Among 100 patients, there were 38 patients (38.0%) whose p53 antibody titer became the positive and 30 patients (30%) whose p53 antibody titer became more than the twice the standard value (more than 2.6: high titer group).
The background factor were not different between high titer group and low titer group.
There were 8 responders (26.7%) in the high titer group and 41 patients (58.6%) in the low titer group (p=0.0045). As for the FAP, there were 3 responders (25%) in the high titer group and 27 patients (52.9%) in the low titer group (p=0.1120). As for the DCF, there were 5 responders (27.8%) in the high titer group and 14 patients (73.7%) in the low titer group (p=0.0086).
*Conclusion*
This study shows that possibility of prediction of response to chemotherapy for esophageal cancer by anti-p53 antibody.

*Keywords:* P53, Esophageal cancer

### P-2395 Mechanisms of resistance to EGFR tyrosine kinase inhibitors involving HER-family ligands and receptors in lung cancer

Kentaro Iwanaga[1,2], Naoko Aragane[2], Akemi Sato[2], Tomomi Nakamura[2], Naomi Kobayashi[2], Eisaburou Sueoka[3], Shinya Kimura[2] ([1]Dept. of Internal Med., Saga Prefectural Hosp. Koseikan, [2]Dept. of Internal Med., Faculty of Med., Saga Univ., [3]Dept. of Lab. Med., Saga Univ. Hosp.)

### HERリガンドとレセプターを標的とした EGFRチロシンキナーゼ阻害薬耐性化機序の解明

岩永 健太郎[1,2]、荒金 尚子[2]、佐藤 明美[2]、中村 朝美[2]、小林 直美[2]、末岡 榮三朗[3]、木村 晋也[2] ([1]佐賀県立病院好生館　内科、[2]佐賀大学　医学部 内科学講座、[3]佐賀大学病院　検査部)

To investigate novel mechanisms of resistance to EGFR-TKI in lung cancer, we examined expression levels of HER-family ligands and phosphorylation status of HER-family receptors in EGFR-TKI primary and acquired resistant NSCLC cell lines. As for the mechanisms of primary resistant, Her3 and Her4 binding ligands such as neuregulin(NRG)1, NRG2, NRG3, epigen and epiregulin were highly expressed in resistant cell lines than sensitive cell lines. Phosphorylation of EGFR was elevated in sensitive cell lines, whereas other HER-family receptors did not. Next we established HCC827 gefitinib resistant (HCC827GR) or erlotinib resistant (HCC827ER) cells, and analyzed mechanisms of acquired resistance. These cells did not show EGFR-T790M mutation, MET amplification and HGF overexpression which have been known to involve in mechanisms of acquired resistance. EGFR binding ligands were up-regulated in HCC827GR but down-regulated in HCC827ER. However, NRG2 was remarkably elevated in HCC827ER. Phosphorylation status of Her4 and its downstream STAT5 were increased in both cells. These results indicate that Her3, Her4 and its binding ligands may contribute to primary and acquire resistance to EGFR-TKI.

*Keywords:* Lung cancer, gefitinib

### P-2396 Curcumin Reverses doxorubicin-Induced Epithelial-Mesenchymal Transition in Breast Cancer Cells

WEI-CHIH CHEN[1], SHENG-CHU KUO[2], TZONG-DER WAY[3] ([1]The Ph.D. Program for Cancer Biol. and Drug Discovery, Taiwan, [2]Grad. Inst. of Pharmaceutical Chemistry, China Medical Univ.,Taiwan, [3]Dept. of Biological Science and Technology, China Medical Univ., Taiwan)

Chemotherapeutic agents not only have therapeutic effects but also increase the malignancy in treatment cancers. Epithelial-mesenchymal transition (EMT) might possess tumor progression and drug resistance. Recent studies indicated that chemotherapeutic drug doxorubicin-induced EMT associated with drug resistance and invasive potential in breast cancer cells. Curcumin exhibited inhibition of cell invasion and motility. We aimed to investigate whether curcumin reverse doxorubicin-induced EMT in breast cancer cells. BT-20 breast cancer cell line was used in this study. Here, we found that curcumin could abrogate doxorubicin-induced migration and invasion. Curcumin also inhibited doxorubicin-induced activation of $\beta$ -catenin and AKT/GSK3$\beta$ pathway by twist. In addition, combination treatment of doxorubicin with curcumin enhanced the anti-proliferative effects in BT-20 cells. These observation suggest that curcumin could improve the efficiency of doxorubicin and suppress doxorubicin-induced EMT.

*Keywords:* curcumin, Doxorubicin

### P-2397 Molecular mechanism underlying ALA-PDT resistance in human cancer cells

Yoshio Endo[1], Shun-ichiro Ogura[2], Yutaka Yonemura[3], Masahiro Ishizuka[3], Katsushi Inoue[4], Kiwamu Takahashi[4], Motowo Nakajima[4], Masashi Kimura[5] ([1]Cancer Res. Inst., Kanazawa Univ, [2]Frontier Res. Ctr., Tokyo Inst. Tech, [3]NPO Org. support Peritoneal Dissemination Treat., [4]SBI pharmaceutical Co.,Ltd, [5]Shizuoka Cancer Ctr.)

### 5-アミノレブリン酸を用いるがんの光線力学的療法における耐性化機構

遠藤 良夫[1]、小倉 俊一郎[2]、米村 豊[3]、石塚 昌宏[4]、井上 克司[4]、高橋 究[4]、中島 元夫[4]、木村 仁[1,5] ([1]金沢大・がん研、[2]東工大・フロンティア研究・生体代謝工学、[3]腹膜播種治療支援機構、[4]SBI ファーマ、[5]静岡がんセ・薬剤部)

5-Aminolevulinic acid (ALA) is a metabolic precursor of protoporphyrin (PpIX), an endogenous photosensitizer. PpIX-dependent photodynamic diagnosis and therapy (ALA-PDD and ALA-PDT) initiated by the metabolic precursor ALA are widely accepted as novel therapeutic strategies for the