P-2461 **Demethoxycurcumin preferentially inhibits HER2-overexpressing bladder cancer cells**

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Bladder cancer is the malignancy arising from the epithelial lining of the urinary bladder. HER2-mediated signaling has also been demonstrated to be involved in anti-apoptosis induced by certain proapoptotic stimuli. Curcuma long a orturmeric is widely consumed in the countries of its origin for a variety of uses. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin are major forms of curcuminoids found in the rhizomes of turmeric. The anti-tumor effect of curcuminoids has been successfully demonstrated in a wide range of humanmalignant cell lines. Here, we evaluated whether curcumin, demethoxycurcumin,and bisdemethoxycurcumin could repress the expression of HER2 protein in bladder cancer cells. Western blotting was performed to investigate the effects on reducing the expression of HER2 protein. Among the test compounds,demethoxycurcumin significantly suppressed the expression of HER2, and preferentially inhibited cell proliferation and induced apoptosis inHER2-overexpressing cancer cells. These findings show that demethoxycurcuminshould be developed further as a new antitumor drug candidate for treatment ofHER2-overexpressing bladder cancer.

Keywords: Demethoxycurcumin, HER2

P-2462 **The BMP signaling pathway leads to enhanced proliferation in serous ovarian cancer-------A potential therapeutictarget**

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Objectives:
We would like to identify the function of BMP/SMAD5 signaling in serous ovarian cancer.
Methods:
The expression of SMAD5 and phosphorylated SMAD5 (pSMAD5) protein were investigated by immunohistochemicalanalysis using clinical samples of serous ovarian cancer. Following treatment with recombinant BMP2(rBMP2) and dorsomorphin(DM) separately, western blotting was performed to observe the cytoplasm and the nucleus of pSMAD5 protein; cell proliferations detected by WST-1 assay and FACS in SK-OV-3 and IOSE cell line. The impact of DM or rBMP2 on tumor growth was observed in a mouse model of serous ovarian cancer.
Results:
Inverse correlation observed between pSMAD5 expression in nucleus and the prognosis of patients with serous ovarian cancer. Treatment of SK-OV-3 with BMP2 stimulated pSMAD5 translocation cell percentage, and the effects were inhibited by DM. In vitro and in vivo experiments, clearly demonstrated BMP2 stimulated proliferation of serous ovarian
cancer and this effect was inhibited by DM.
Conclusions:
Our data suggests BMP/SMAD5 signaling play an important role and is promising as a potential therapeutic target in serous ovarian cancer.

Keywords: BMP2, SMAD5

Room R-P7 Sep. 20 (Thu) 17:20 - 18:10

P21-4 Gene therapy (4)
遺伝子治療 (4)

Chairperson: Kazunori Aoki (National Cancer Ctr. Res. Inst., Div. of Gene and Immune Med.)
座長：青木 一教（国立がん研究センター研究所　遺伝子免疫細胞医学研究分野）

P-2463 **Genetically engineered oncolytic measles virus shows antitumor activity against non-small cell lung cancer stem cells.**

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遺伝子改変腫瘍溶解性麻疹ウイルスは肺癌幹細胞に対し抗腫瘍効果を呈する

井上 博之[1,2]、安成 啓祐[1]、松村 友美子[1]、宮本 将平[1]、野崎 要[1,2]、坂本 一[1]、高山 浩一[2]、中西 洋一[2]、谷 憲三朗[1]（[1]九州大学　生医研　ゲノム病学、[2]九州大学　胸部疾患研究施設）

Development of novel therapeutic modality targeting cancer stem cells (CSCs) offers great promise for cancer treatment.
Here we demonstrated that our newly developed Edmonston strain of measles virus (MV) genetically engineered by replacing the N, P,and L genes with those of the wild-type MV strain (MV-NPL) showed stronger oncolytic activity against human non-small cell lung cancer (NSCLC) stem cells (NSCLC-CSCs) while sparing human normal lung cells, than parental MV Edmonston strain. Our results of caspase inhibition assay showed that caspase-dependent apoptosis significantly contributed to the oncolysis of NSCLC-CSCs by MV-NPL, despite their higher expression levels of anti-apoptotic protein of both XIAP and Mcl-1. In addition, combination of MV-NPL with PI3K inhibitor enhanced the oncolytic effects of MV-NPL. Furthermore, consecutive intratumoral MV-NPL administrations into subcutaneous NSCLC-CSCs xenografts preestablished in nude mice significantly inhibited the outgrowth of NSCLC-CSCs without severe side effects.
This study suggested that MV-NPL would become a promising oncolytic virotherapy candidate for NSCLC patients resistant to conventional therapies.

Keywords: Oncolytic virus, cancer stem cell

P-2464 **Oncolytic Herpes Simplex Virus Type 1 Targetting Glioma-derived Cancer Stem-like Cells**

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脳腫瘍由来がん幹細胞を標的としたがん治療用 HSV-1の開発

稲生 靖[1]、中坪 拓也[1]、高橋 雅道[2]、福原 浩[3]、藤堂 具紀[1]（[1]東京大学医科学研究所先端がん治療分野、[2]東京大学医学部附属病院脳神経外科、[3]東京大学大学院医学系研究科泌尿器科）

Cancer stem-like cells (CSCs) are reported to be resistant to conventional therapies, and likely responsible for the recurrence of the disease. We have reported previously that oncolytic herpes simplex viruses type 1 (HSV-1), G47Δ and T-01, exhibit a potent cytopathic effect on CSCs isolated from surgical specimens of glioblastoma patients. A new oncolytic HSV-1, T-hTERT, was created by restoring the ICP6 gene regulated by the human telomerase reverse transcriptase (hTERT) promoter. The efficacy of T-hTERT was evaluated *in vitro* and *in vivo*. Secondary sphere forming assays showed that CSCs that survived 7 days after T-01 or T-hTERT treatment had significantly lower self-renewal abilities compared with mock treated cells. Both T-01 and T-hTERT prolonged the survival of mice bearing intracerebral TGS-01 tumors compared with mock, and T-hTERT was significantly more efficacious than T-01. These results suggest that both T-01 and T-hTERT are effective in killing glioblastoma-derived CSCs, and T-hTERT is more efficacious in slowly-growing CSCs. This new oncolytic HSV-1, T-hTERT, may be particularly useful in eradicating tumors that are abundant with CSCs.

Keywords: Oncolytic virus, cancer stem cell

P-2465 **Contribution of the 3'-UTR fo Sindbis virus to the oncolytic activity of the sindbis replicon**

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シンドビス・レプリコン 3'-UTRの腫瘍融解活性への関与

趙 莎莎、元 清華、蟻 瑞栄、齋藤 謙悟、白澤 浩（千葉大学大学院医学研究院　分子ウイルス学）

Sindbis virus AR339 induces cytopathic effects on cancer cells but less on normal cells. To elucidate the mechanisms which underlie the oncolytic features, the cytotoxicities of Sindbis AR339 replicons expressed from the CMV promoter or transcribed in vitro were assessed using HeLa, HSC4, MKN45, HepG2 cells as well as Vero cells and normal human fibroblasts. In cancer cells, the replicons expressed from the CMV promoter exhibited cytotoxicities, which were more intense when the replicons without the 3'-UTR of SIN AR339 were expressed. In contrast, both of the replicons with 3'-UTR and without 3'-UTR showed less cytotoxicity to Vero cells and normal human fibroblasts, when expressed from the CMV promoter. On the other hand, the RNA replicons with 3'-UTR transcribed from the T7 promoter exhibited as much cytotoxicities as the replicons expressed from the CMV promoter to cancer cells and no cytotoxicities to Vero cells and human fibroblasts. The different cytotoxicities of replicons between with and without 3'-UTR suggested the involvement of the 3'-UTR sequences in the cancer-specific oncolytic activity of the Sindbis virus AR339.

Keyword: Vector

P-2466 **New Method to Produce Peptide-displaying Adenovirus Library**

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