病態生化学分野　Division of Pathogenic Biochemistry

教　授	済木　育夫	Professor	Ikuo　Saiki　(D. Med. Sci.)
助教授	櫻井　宏明	Associate Professor	Hiroaki Sakurai (Ph.D.)
助　手	小泉　桂一	Assistant Professor	Keiichi Koizumi (Ph.D.)
研究員	秋　旼京（COE）	Postdoctoral Fellow	Choo Min-kyung (Ph.D.)

◇研究目的

本分野は、病態の生化学的研究を行うとともに、和漢薬を含む種々の薬物の病態に及ぼす効果を生化学的、免疫学的、あるいは遺伝学的に研究することを目的としている。

和漢薬を中心に、構造の明らかにされた成分あるいは化合物を用いて、種々の病態に有効な薬物の探索とその作用機序を分子レベルで解明する。「証」といわれる病態変化／徴候を遺伝子工学的、免疫学的手法等を駆使してその遺伝的背景を解析し、薬物の効果発現との関連性からその科学的基盤を解明する。現在、癌、免疫、アレルギー疾患などを中心にして検討を行っている。

◇研究概要

Ⅰ）がん転移機構の解明とその制御

1) がん転移に対するケモカインの作用機序解明と治療への応用
2) がん癌転移病態モデルの作製とその形成に関与する標的分子の探索
3) 伝統薬物を中心としたがん転移の抑制物質の探索

Ⅱ）シグナル伝達分子による病態制御機構の解析

1) TAK1 キナーゼ活性化の分子機構
2) TNF-α シグナルと ErbB 受容体シグナルのクロストーク
3) 自然免疫シグナルに影響を及ぼす漢方薬の探索

Ⅲ）漢方方剤テーラーメード治療法の開発

1) 漢方医学の証の解明を目指した血漿プロテオミック・パターン解析

◇原著論文

1) **Matsuo M., Sakurai H., Ueno Y., Ohtani O. and Saiki I.: Activation of ERK and PI3K/Akt pathways by fibronectin requires integrin αv-mediated ADAM activity in hepatocellular carcinoma: a novel functional target for gefitinib. Cancer Sci., 97: 155-162, 2006.**

Abstract: We have shown that the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) inhibits the development of intrahepatic metastases of hepatocellular carcinoma CBO140C12, and EGFR transactivation by tumor necrosis factor-α is a possible target of gefitinib. In the present study, we focused on the fibronectin (FN)-dependent signaling pathway to further elucidate the antimetastatic activity of gefitinib in CBO140C12 cells. We initially observed that FN induced activation of extracellular signal-regulated kinase (ERK), p38 and Akt, as well as cell proliferation and CBO140C12 cell invasion. These responses were mediated by EGFR tyrosine kinase, because gefitinib inhibited these effects of FN. FN-induced ERK, p38 and Akt activation was partly blocked by the Arg-Gly-Asp (RGD)-pseudo-peptide FC-336, anti-αv integrin antibody RMV-7, the broad-spectrum matrix metalloprotease inhibitor GM6001 and the broad spectrum a disintegrin and metalloprotease (ADAM) inhibitor TAPI-1. But these inhibitors had no effect on EGF-induced signaling pathways, suggesting that integrins and ADAM may be upstream components of EGFR in these responses. These results suggest that FN-induced activation of ERK, p38, Akt, cell proliferation and invasion was mediated, at least in part, via integrins, ADAM and EGFR, and that this FN-induced signaling pathway might be involved in the antimetastatic activity of gefitinib.

2) **Lee S-J., Sakurai H., Koizumi K., Song G.Y., Bae Y.S., Kim H-M., Kang K-S., Surh Y-J., Saiki I. and Kim S.H.: MAPK regulation and caspase activation are required in DMNQ S-52 induced apoptosis in Lewis lung carcinoma cells. Cancer Lett., 233: 57-67, 2006.**

Abstract: 6-(1-Hydroxyimino-4-methylpentyl)5,8-dimethyoxy 1,4-naphthoquinone S-52 (DMNQ S-52) was reported to have cytotoxic activity against L1210 leukemia cells. In the present study, we investigated the apoptotic mechanism of DMNQ S-52 in vitro and in vivo in murine solid cancer cells. DMNQ S-52 exerted cytotoxicity against Lewis lung carcinoma (LLC) cells (IC50=12.3 μM). DMNQ S-52 increased Annexin V positive cell population in a concentration-dependent manner. DMNQ S-52 also induced apoptosis through caspase-mediated pathway, including activation of caspase-3, cleavage of Poly(ADP-ribose) polymerase (PARP) and decreased expression of Bcl-2 in LLC cells in a time and concentration-dependent fashion. DMNQ S-52 activated the phosphorylation of c-Jun N-terminal kinase (JNK) and p38 as well as abrogated the expression of extracellular signal-regulated kinase (ERK) in a time-dependent manner at 10 microM. Similarly, cell proliferation inhibition by DMNQ S-52 was masked by caspase inhibitor Z-Asp-Glu-Val-Asp-fluoromethylketone (Z-VAD-FMK), JNK inhibitor SP600125 and p38 inhibitor SB203580, but not by MEK inhibitor U0126. Furthermore, i.p. administration of DMNQ S-52 at 5 mg/kg resulted in a potent inhibition of the growth of LLC cells implanted on the right flank of C57BL/6 mice compared to untreated control. Immunohistochemical analysis revealed the decreased tumor cell proliferation and increased tumor cell apoptosis in DMNQ S-52 treated tumor sections using terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) and proliferation cell nuclear antigen (PCNA). Taken together, these findings demonstrate that DMNQ S-52 may exhibit anti-tumor activity by inducing apoptosis via caspases and mitogen activated protein (MAP) kinase-dependent pathways.

3) **Yasumoto K., Koizumi K., Kawashima A., Saitoh Y., Arita Y., Shinohara K., Minami T., Nakayama T., Takahashi Y., Yoahie O. and Saiki I.: Role of CXCL12 in peritoneal carcinomatosis of gastric cancer. Cancer Res., 66: 2181-2187, 2006.**

Abstract: Peritoneal carcinomatosis is a frequent cause of death in patients with advanced gastric carcinoma. Because chemokines are now considered to play an important role in the metastasis of various malignancies, we hypothesized that they may be involved in the development of peritoneal carcinomatosis by gastric carcinoma. Human gastric carcinoma cell lines, which were all highly efficient in generating malignant ascites in nude mice upon i.p. inoculation, selectively expressed CXCR4 mRNA and protein. In particular, NUGC4 cells expressed CXCR4 mRNA at high levels and showed vigorous migratory responses to its ligand CXCL12. CXCL12 enhanced proliferation and rapid increases in phosphorylation of protein kinase B/Akt and extracellular signal-regulated kinase of NUGC4 cells. We also showed that AMD3100 (a specific CXCR4 antagonist) effectively reduced tumor growth and ascitic fluid formation in nude mice inoculated with NUGC4 cells. Additionally, we examined human clinical samples. Malignant ascitic fluids from patients with peritoneal carcinomatosis contained high concentrations of CXCL12 (4.67 ng/mL). Moreover, immunohistochemical analysis showed that 22 of 33 primary gastric tumors with peritoneal metastasis were positive for CXCR4 expression (67%), whereas only 4 of 16 with other distant metastasis were positive (25%). Notably, 22 of 26 CXCR4-expressing primary tumors developed peritoneal metastases (85%). CXCR4 positivity of primary gastric carcinomas significantly correlated with the development of peritoneal carcinomatosis ($P < 0.001$). Collectively, our results strongly suggest that the CXCR4/CXC12 axis plays an important role in the development of peritoneal carcinomatosis from gastric carcinoma. Thus, CXCR4 may be a potential therapeutic target for peritoneal carcinomatosis of gastric carcinoma.

4) **Fukasawa K., Fujii H., Saitoh Y., Koizumi K., Aozuka Y., Sekine K., Yamada M., Saiki I. and Nishikawa K.: Aminopeptidase N (APN/CD13) is selectively expressed in vascular endothelial cells and plays multiple role in angiogenesis. Cancer Lett., 243: 135-143, 2006.**

Abstract: Proteolytic enzyme-mediated degradation of the extracellular matrix (ECM) is crucial for the formation of both tumor metastasis and angiogenesis. Recently, several reports have suggested that aminopeptidases are involved in this process, but precisely how is largely unknown. We found here that aminopeptidase N (APN/CD13) was selectively expressed in vascular endothelial cells including human umbilical vein endothelial cells (HUVEC) and human aortic endothelial cells (HAEC), and was not detectable in a majority of normal cells and tumor cell lines we examined. RNA interference (RNAi) of APN resulted in the inhibition of capillary tube formation of HUVEC on Matrigel. APN siRNA suppressed the migration of HUVEC through a fibronectin-coated Transwell membrane, and reduced the cellular adhesion to Matrigel and various adhesion molecules including type IV collagen, type I collagen and fibronectin. These findings suggest that APN is a multifunctional protein with important roles in vascular endothelial morphogenesis during angiogenesis.

5) **Choo M-K., Sakurai H., Koizumi K., and Saiki I.: TAK1-mediated stress signaling pathways are essential for TNF-α-promoted pulmonary metastasis of murine colon cancer cells. Int. J. Cancer, 118: 2758-2764, 2006.**

Abstract: We have recently established a TNF-α-promoted metastasis model, in which the ability to metastasize to the lung was enhanced by stimulation of cultured colon 26 cells with TNF-α before intravenous inoculation. To investigate intracellular events in metastatic cascades of TNF-α-treated cancer cells, we have focused on the stress signaling pathways to c-Jun N-terminal kinase (JNK) and p38. Treatment with a specific inhibitor, SP600125 or SB203580, in vitro suppressed TNF-α-induced migration and pulmonary metastasis. Activation of endogenous TAK1, a mitogen-activated protein kinase (MAP3K) regulating the JNK and p38 MAPK pathways, was induced rapidly by TNF-α, and co-transfection of TAK1 with its activator protein TAB1 stimulated activation of JNK and p38 MAPKs, which led to activation of the transcription factor AP-1. The activation of stress signaling pathways by TAK1 resulted in enhanced migration to fibronectin in vitro and metastasis to the lung in vivo without

affecting cell proliferation in vitro and tumor growth in vivo. Moreover, knockdown of endogenous TAK1 using small interfering RNA (siRNA) suppressed the TNF-α-induced JNK/p38 activation, migration and pulmonary metastasis. These results indicate that TAK1-mediated stress signaling pathways in cancer cells are essential for TNF-α-promoted metastasis to the lung.

6) **Saitoh Y., Koizumi K., Minami T., Sekine K., Sakurai H. and Saiki I.: A derivative of aminopeptidase inhibitor (BE15) has a dual inhibitory effect of invasion and motility on tumor and endothelial cells. Biol. Pharm. Bull., 29: 709-712, 2006.**

Abstract: Bestatin is an inhibitor of aminopeptidase N (APN)/CD13 and aminopeptidase B. In our previous report, bestatin inhibited the tumor cell invasion and the angiogenesis induced by the inoculation of B16-BL6 melanoma cells into mice and capillary formation on human umbilical vein endothelial cells (HUVECs) in vitro. The results show that the enzymatic activity of APN is deeply involved in tumor invasion and angiogenesis. We investigated the effect of three bestatin derivatives on A375 human melanoma cells and in vitro. All the derivatives inhibited the activity of APN, but BE15 was most effective and controlled the migration of A375 cells and HUVECs and capillary formation of HUVECs. Furthermore, the bestatin derivatives had an inhibitory effect not only on aminopeptidase activity but also on cell motility. Compared with bestatin and the other derivatives, BE15 had a marked inhibitory effect on the formation of capillary structure by HUVECs in vitro. These results suggest that new anti-metastatic and anti-angiogenic agents, which have a dual inhibitory effect on the degradation of the extra cellular matrix and cell motility, may be developed from bestatin.

7) **Fuke Y., Shinoda S., Nagata I., Sawaki S., Nomura T., Ryoyama K., Koizumi K. and Saiki I.: Preventive effect of oral administration of 6-(methylsulfinyl)hexyl isothiocyanate from wasabi (*Wasabia japonica* Matsum) against pulmonary metastasis of B16-BL6 mouse melanoma cells. Cancer Detection Prevention, 30: 174-179, 2006.**

Abstract: AIM: Effect of oral administration of 6-(methylsulfinyl)hexyl isothiocyanate (6-MITC) or a 6-MITC-containing T-wasabi fraction from wasabi root (Wasabia japonica Matsum) to inhibit the macroscopic pulmonary metastasis was studied with a murine B16-BL6 melanoma model. METHOD: Two administration routes, subcutaneous or intravenous, and two administration times, prior to or concomitant with tumor inoculation, of 6-MITC or T-wasabi against the metastatic foci formation in C57BL/6J mouse lungs were compared. RESULTS: The number of metastasized foci per lung in either subcutaneous or intravenous injection was significantly reduced by intake of 6-MITC or a T-wasabi fraction. The maximum reduction by a T-wasabi fraction reached to 82%. Fifty-six percent of foci formation was inhibited by a 2 week-prior administration of 6-MITC (200 μM), whereas only 27% inhibition was obtained by a concomitant administration with tumor inoculation. Neither 6-MITC nor T-wasabi at tested concentrations showed any toxic effects. DISCUSSION: Together with our previous results, a component of the Japanese pungent spice, wasabi appears to inhibit not only tumor cell growth but also tumor metastasis. Therefore, 6-MITC from wasabi is apparently a useful dietary candidate for controlling tumor progression.

8) **Nakamura E-S., Koizumi K., Kobayashi M., Saitoh Y., Nakayama T., Sakurai H., Kameda Y., Yoshie O. and Saiki I.: Osteoclasts constitutively produce CC chemokine ligand CCL22 /macrophage-derived chemokine and potentially promote bone metastasis of lung cancer expressing its CCR4. Clin. Exp. Metastasis, 23: 9-18, 2006.**

Abstract: Chemokines are now known to play an important role in cancer growth and metastasis. Here we report that differentiating osteoclasts constitutively produce CCL22 (also called macrophage-derived chemokine) and potentially promote bone metastasis of lung cancer expressing its receptor CCR4. We first examined expression of chemokines by differentiating osteoclasts. CCL22 was selectively upregulated in osteoclast-like cells derived from RAW264.7 cells and mouse bone marrow cells upon

stimulation with RANKL (receptor activator of nuclear factor-kappaB ligand). In addition, a human lung cancer cell line SBC-5 that efficiently metastasized to bone when intravenously injected into NK cell-depleted SCID mice was found to express CCR4. Stimulation of SBC-5 cells with CCL22 induced cell migration and also enhanced phosphorylation of protein kinase B/Akt and extracellular signal-regulated kinase (ERK). Furthermore, immunohistochemical analysis of bone metastasis lesions demonstrated close co-localization of tartrate-resistant alkaline phosphatase (TRAP)-positive osteoclasts expressing CCL22 and SBC-5 cells expressing CCR4. Collectively, these results suggest that osteoclasts may promote bone metastasis of cancer cells expressing CCR4 in the bone marrow by producing its ligand CCL22.

9) **Ogawa H., Gomi T., Nishizawa M., Hayakawa Y., Endo S., Hayashi K., Ochiai H., Takusagawa F., Pitot H.C., Mori H., Sakurai H., Koizumi K., Saiki I., Oda H., Fujishita T., Miwa T., Maruyama M., and Kobayashi M. Enzymatic and biochemical properties of a novel human serine dehydratase isoform. Biochim Biophys Acta, 1764: 961-971, 2006.**

Abstract: A cDNA clone similar to human serine dehydratase (SDH) is deposited in the GenBank/EMBL databases, but its structural and functional bases remain unknown. Despite the occurrence of mRNA, the expected protein level was found to be low in cultured cells. To learn about physicochemical properties of the protein, we expressed the cDNA in Escherichia coli, and compared the expressed protein with that of a hepatic SDH. The purified protein showed l-serine and l-threonine dehydratase activity, demonstrating to be an isoform of SDH. However, their Km and Vmax constants were different in a range of two-order. Removal of Pro128 from the hepatic SDH consisting of 328 residues, which is missing in the corresponding position of the isoform consisting of 329 residues, significantly changed the Michaelis constants and Kd value for pyridoxal 5'-phosphate, whereas addition of a proline residue to the isoform was without effect. These findings suggest the difference in the structures of the active sites of the two enzymes. Another striking feature was that the expressed level of the isoform in E. coli was 7-fold lower than that of the hepatic SDH. Substitution of Val for Leu287 in the isoform dramatically increased the protein level. The high yield of the mutated isoform was also confirmed by the in vitro transcription and translation experiment. The poor expression of the isoform could be explained by the more stable secondary structure of the mRNA than that of the hepatic SDH mRNA. The present findings may provide a clue as to why the protein level in cultured cells is low.

10) **Matsuo M., Koizumi K., Yamada S., Tomi M., Takahashi R., Ueda M., Terasaki T., Obinata M., Hosoya K., Ohtani O. and Saiki I.: Establishment of lymphatic and venous endothelial cell limes from tsA58/EGFP transgenic rats. Cell Tissue Res. 326: 749-758, 2006.**

Abstract: The basic biology of blood vascular endothelial cells has been well documented. However, little is known about that of lymphatic endothelial cells, despite their importance under normal and pathological conditions. The lack of a lymphatic endothelial cell line has hampered progress in this field. The objective of this study has been to establish and characterize lymphatic and venous endothelial cell lines derived from newly developed tsA58/EGFP transgenic rats harboring the temperature-sensitive simian virus 40 (SV40) large T-antigen and enhanced green fluorescent protein (EGFP). Endothelial cells were isolated from the transgenic rats by intraluminal enzymatic digestion. The cloned cell lines were named TR-LE (temperature-sensitive rat lymphatic endothelial cells from thoracic duct) and TR-BE (temperature-sensitive rat blood-vessel endothelial cells from inferior vena cava), respectively, and cultured on fibronectin-coated dishes in HuMedia-EG2 supplemented with 20% fetal bovine serum and Endothelial Mitogen at a permissive temperature, 33 degrees C. A temperature shift to 37 degrees C resulted in a decrease in proliferation with degradation of the large T-antigen and cleavage of poly (ADP-ribose) polymerase. TR-LE cells expressed lymphatic endothelial markers VEGFR-3 (vascular endothelial growth factor receptor), LYVE-1 (a lymphatic endothelial receptor), Prox-1 (a homeobox gene product), and podoplanin (a glomerular podocyte membrane mucoprotein), together with

endothelial markers CD31, Tie-2, and VEGFR-2, whereas TR-BE cells expressed CD31, Tie-2, and VEGFR-2, but no lymphatic endothelial markers. Thus, these conditionally immortalized and EGFP-expressing lymphatic and vascular endothelial cell lines might represent an important tool for the study of endothelial cell functions in vitro.

11) Mori A., Sakurai H., Choo M-K., Obi R., Koizumi K., Yoshida C., Shimada Y. and Saiki I.: Severe pulmonary metastasis in obese and diabetic mice. Int. J. Cancer., 119: 2760-2767, 2006.

Abstract: Although obesity is known as a risk factor for several human cancers, the association of obesity with cancer recurrence and metastasis remains to be characterized. Here, B16-BL6 melanoma and Lewis lung carcinoma cells were intravenously injected into diabetic (*db/db*) and obese (*ob/ob*) mice. The number of experimental lung colonies was markedly promoted in these mice when compared with C57BL/6 mice. In contrast, tumor growth at the implanted site was comparable when cells were inoculated orthotopically. The use of B16-BL6 cells stably transfected with the luciferase gene revealed that the increased metastasis reflected a difference mainly within 6 hr after the intravenous inoculation of tumor cells. Administration of recombinant leptin in *ob/ob* mice abolished the increase in metastasis early on as well as the decrease in the splenic NK cell number. In addition, depletion of NK cells by an anti-asialo-GM1 antibody abrogated the enhanced metastasis in *db/db* mice. These results demonstrate that metastasis is markedly promoted in diabetic and obese mice mainly because of decreased NK cell function during the early phase of metastasis.

12) Awale S., Linn T.Z., Than M.M., Swe T., Saiki I. and Kadota S.: *News Letter*, The healing art of traditional medicines in Myanmar. J. Trad. Med., 23: 47-68, 2006.

Abstract: Traditional medicines are an integral part of people's culture and are used extensively by the peoples in developing countries for their primary health care. A rich heritage of traditional medical knowledge and the use of plants as medicines still exist in Myanmar which have been inherited from earlier generations. However, many areas in Myanmar are now experiencing rapid changes. Traditional knowledge as well as plants that the traditional healers rely upon are being lost at an alarming rate. Therefore, it is important that immediate steps be taken to protect the important source of traditional knowledge as well as medicinal plant diversity. This paper highlights information and observations on the art of healing performed by the traditional medicine practitioners in Myanmar, their success stories, together with an inventory of some medicinal plants, and traditional knowledge pertaining to their use, including preparation and administration.

13) Suzuki S., Singhirunnusorn P., Nakano H., Doi T., Saiki I. and Sakurai H.: Identification of TNF-α-responsive NF-κB p65-binding element in the distal promoter of the mouse serine protease inhibitor *SerpineE2*. FEBS Lett. 580: 3257-3262, 2006.

Abstract: Serine protease inhibitor SerpinE2 is known as a cytokine-inducible gene. Here, we investigated whether tumor necrosis factor α (TNF-α)-induced expression of SerpinE2 is mediated by the nuclear factor-κB (NF-κB) p65 subunit. Both steady state and TNF-α-induced expression of SerpinE2 mRNA were abrogated in p65-/- murine embryonic fibroblasts (MEFs). Reconstitution with wild-type p65 rescued SerpinE2 mRNA expression in an IκB kinase beta-dependent manner. Electrophoresis mobility shift assay and ChIP assay demonstrated that p65 bound to the κB-like DNA sequence located at approximately -9 kbp in the SerpinE2 promoter. In addition, TNF-α stimulated luciferase gene expression driven by the κB-like element in the reconstituted MEFs, but not in p65-/- MEFs. These results indicated that activation of NF-κB p65 plays an important role in TNF-α-induced expression of SerpinE2.

14) Sakurai H., Choo M-K., Chino A., Tega E., Iwasaki T., Kobayashi H. and Saiki I.: Antimetastatic and immunostimulatory properties of fermented brown rice and rice bran.

J. Trad. Med., 23: 112-116, 2006.

Abstract: The antimetastatic effect of fermented brown rice by *Aspergillus oryzae* (FBRA), a processed food, was examined in an animal model of metastasis to the liver using mouse colon cancer cells. Mice fed a diet containing 10% FBRA were inoculated with colon 26-L5 cells via the portal vein on day 14. Liver metastasis on day 28 was significantly inhibited by the FBRA-containing diet without an increase in body weight. To investigate the immunostimulatory activity, the cellular functions of macrophages were examined. Intracellular glutathione levels were increased in peritoneal macrophages (PEMs) prepared from mice fed FBRA for 18 days. FBRA did not induce the production of interferon-γ (IFN-γ) by itself, though enhanced the ability of PEMs to produce IFN-γ, but not interleukin-12 or tumor necrosis factor-α, in response to lipopolysaccharide (LPS). These results indicated that oral administration of FBRA inhibited the metastasis of colon 26-L5 cells to the liver through a mechanism leading to a Th1-dominant immune state and activation of macrophages via anti-oxidative properties.

15) **Akashi T., Koizumi K., Nagakawa O., Fuse H. and Saiki I.: Andorogen receptor negatively influences the expression of chemokine receptors (CXCR4, CCR1) and ligand-mediated migration in prostate cancer DU-145. Oncol. Rep., 16:831-836, 2006.**

Abstract: We previously reported that androgen receptor (AR) plays a role in the regulation of adhesion to the extracellular matrix and invasion of human prostate cancer cells by influencing the expression of specific integrin subunits. It is now considered that chemokines play a significant role in organ-selective cancer metastasis. In this study, we hypothesized that AR may influence the expression of these chemokine receptors and cell function. The mRNA expression of chemokine receptors in human prostate cancer cell line DU-145 and DU-145 cells expressing AR (DU-145/AR) was investigated by RT-PCR. DU-145 cells selectively expressed CXCR4 and CCR1 mRNA at high levels compared with DU-145/AR cells. DU-145 showed vigorous migratory responses to its ligand CXCL12 (also called stromal-derived factor-1alpha, SDF-1α) and CCL3 (also called macrophage inflammatory protein-1, MIP-1α). In contrast, neither CXCL12 nor CCL3 affected the migration of DU-145/AR cells. These results indicate that expression of AR down-regulates the migratory responses of human prostate cancer cells via chemokine and its receptor systems.

16) **Thiefes A., Wolf A., Doerrie A., Grassl G. A., Matsumoto K., Autenrieth I., Bohn E., Sakurai H., Niedenthal R., Resch K. and Kracht M.: The *Yersinia enterocolitica* effector YopP inhibits host cell signaling by inactivating the protein kinase TAK1 in the IL-1 signalling pathway. EMBO reports, 7: 838-844, 2006.**

Abstract: The mechanism by which YopP simultaneously inhibits mitogen-activated protein kinase (MAPK) and nuclear factor-κB pathways has been elusive. Ectopic expression of YopP inhibits the activity and ubiquitination of a complex consisting of overexpressed TGF-β-activated kinase 1 (TAK1) and its subunit TAK1-binding protein (TAB)1, but not of MEK kinase 1. YopP, but not the catalytically inactive mutant YopP (C172A), also suppresses basal and interleukin-1-inducible activation of endogenous TAK1, TAB1 and TAB2. YopP does not affect the interaction of TAK1, TAB1 and TAB2 but inhibits autophosphorylation of TAK1 at Thr 187 and phosphorylation of TAB1 at Ser 438. Glutathione S-transferase-tagged YopP (GST-YopP) binds to MAPK kinase (MAPKK) 4 and TAB1 but not to TAK1 or TAB2 in vitro. Furthermore, YopP in synergy with a previously described negative regulatory feedback loop inhibits TAK1 by MAPKK6-p38-mediated TAB1 phosphorylation. Taken together, these data strongly suggest that YopP binds to TAB1 and directly inhibits TAK1 activity by affecting constitutive TAK1 and TAB1 ubiquitination that is required for autoactivation of TAK1.

17) **Yamamoto M., Okamoto Y., Takeda T., Sato S., Sanjo H., Uematsu S., Saitoh T., Yamamoto N., Sakurai H., Ishii K.J., Yamaoka S., Kawai T., Matsuura Y., Takeuchi O., and Akira S.: Key function for the Ubc13 E2 ubiquitin-conjugating enzyme in immune receptor signaling. Nature Immunol., 7: 962-970, 2006.**

Abstract: The Ubc13 E2 ubiquitin-conjugating enzyme is key in the process of 'tagging' target proteins

with lysine 63-linked polyubiquitin chains, which are essential for the transmission of immune receptor signals culminating in activation of the transcription factor NF-κB. Here we demonstrate that conditional ablation of Ubc13 resulted in defective B cell development and in impaired B cell and macrophage activation. In response to all tested stimuli except tumor necrosis factor, Ubc13-deficient cells showed almost normal NF-κB activation but considerably impaired activation of mitogen-activated protein kinase. Ubc13-induced activation of mitogen-activated protein kinase required, at least in part, ubiquitination of the adaptor protein IKKγ. These results show that Ubc13 is key in the mammalian immune response.

18) **Yamamoto M., Sato S., Saitoh T., Sakurai H., Uematsu S., Kawai T., Ishii K.J., Takeuchi O., and Akira S.: Cutting Edge: pivotal function of Ubc13 in Thymocyte TCR signaling. J. Immunol., 177: 7520-7524, 2006.**

Abstract The Ubc13 E2 ubiquitin-conjugating enzyme is essential for BCR-, TLR-, and IL-1 receptor (IL-1R)-mediated immune responses. Although Ubc13-deficient mice show defects in BCR-, TLR/IL-1R-, or CD40-mediated activation of mitogen-activated protein kinases, the function of Ubc13 in TCR-mediated signaling and responses remains uncertain. To address this, we here generated T cell-specific conditional Ubc13-deficient mice. The frequency of T lymphocytes was severely reduced in spleens from Ubc13-deficient mice. Moreover, Ubc13-deficient thymocytes displayed defective proliferation in response to anti-CD3/CD28 or PMA/ionophore stimulation. Regarding the signal transduction, although NF-κB activation was modestly affected, PMA/ionophore-induced activation of Jnk and p38 was profoundly impaired in Ubc13-deficient thymocytes. In addition, PMA/ionophore-mediated ubiquitination of NF-κB essential modulator (NEMO)/IκB kinase gamma (IKKγ) and phosphorylation of TGF-β-activated kinase 1 (TAK1) were nearly abolished in Ubc13-deficient thymocytes. Thus, Ubc13 plays an important role in thymocyte TCR-mediated signaling and immune responses.

19) **Miyanaga S., Obata T., Onaka H., Fujita T., Saito N., Sakurai H., Saiki I., Furumai T. and Igarashi Y.: Absolute configuration and antitumor activity of myxochelin A produced by *Nonomuraea pusilla* TP-A0861. J. Antibiotics, 59: 698-703, 2006.**

Abstract: In the screening of antitumor compounds from microbial secondary metabolites, myxochelin A was isolated from a culture broth of Nonomuraea pusilla TPA0861. The absolute configuration was determined to be S by synthesizing both enantiomers from an L- or D-lysine derivative and comparing their specific rotations. Both enantiomers of myxochelin A showed remarkable inhibitory effects on the invasion of murine colon 26-L5 carcinoma cells at non-cytotoxic concentrations.

20) **Choo M.K., Kawasaki N., Singhirunnusorn P., Koizumi K., Sato S., Akira S., Saiki I., and Sakurai H.: Blockade of transforming growth factor-β-activated kinase 1 activity enhances TRAIL-induced apoptosis through activation of a caspase cascade. Mol. Cancer Ther, 5: 2970-2976, 2006.**

Abstract: Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL/Apo2L) is a member of the tumor necrosis factor-α (TNF-α) ligand family that selectively induces apoptosis in a variety of tumor cells. To clarify the molecular mechanism of TRAIL-induced apoptosis, we focused on TAK1 mitogen-activated protein kinase kinase kinase (MAP3K), a key regulator of the TNF-α-induced activation of p65/RelA and JNK/p38 MAPKs. In human cervical carcinoma HeLa cells, TRAIL induced the delayed phosphorylation of endogenous TAK1 and its activator protein TAB1 and TAB2, which contrasted to the rapid response to TNF-α. Specific knockdown of TAK1 using small interfering RNA (siRNA) abrogated the TRAIL-induced activation of p65 and JNK/p38 MAPKs. TRAIL-induced apoptotic signals including caspase-8, -3, and -7 and PARP were enhanced by TAK1 siRNA. Flow cytometry demonstrated that the binding of annexin-V to cell surface was also synergistically increased by TRAIL in combination with TAK1 siRNA. In addition, pretreatment of cells with 5Z-7-oxozeaenol, a selective TAK1 kinase inhibitor, enhanced the TRAIL-induced cleavage of caspases and binding of annexin-V. The TAK1-mediated anti-apoptotic effects were also observed in human lung adenocarcinoma

A549 cells. In contrast, TAK1-deficient mouse embryonic fibroblasts (MEFs) are resistant to TRAIL-induced apoptosis, and treatment of control MEFs with 5Z-7-oxozeaenol did not drastically promote the TRAIL-induced activation of a caspase cascade. These results suggest that TAK1 plays a critical role for TRAIL-induced apoptosis, and the blockade of TAK1 kinase will improve the chances of overcoming cancer.

◇総　説

1) 済木育夫：特集「癌の漢方療法–新しい展開」、1.漢方薬による癌転移阻害のメカニズム、Biotherapy. **20**: 23-32, 2006.
2) 済木育夫：Serial 東洋医学と生命科学の融合を目指して、漢方医学における「証」の科学的解析、Biophilia. **6**: 54-58, 2006.
3) 済木育夫：学術講演会「漢方薬によるがん転移の抑制とその作用機序の解析」、神戸市医師会報、**547**: 67-75, 2006.
4) Tani T., Shimada Y. and Saiki I.: Invension of a new crude drug formation. A new formulation containing eleven crude drugs devised by the cooperative research project in Toyama. J. Trad, Med., **23**: 5-15, 2006.

◇学会報告　(*: 特別講演、シンポジウム、ワークショップ等)

* 1) Sakurai H., Choo M-K, Singhirunnusorn P., Koizumi K., and Saiki I.:TAK1-mediated stress signaling pathways are essential for TNF-α-promoted pulmonary metastasis of murine colon cancer cells. Keystone Symposia, NF-κB: 20 Years on the Road from Biochemistry to Pathology, March 23-28, 2006, Banff, Alberta, Canada.
2) 松尾圭祐、宇都口直樹、鈴木 亮、岡田直貴、中川晋作、小泉桂一、済木育夫、丸山一雄：腫瘍組織血管内皮細胞を標的とした樹状細胞ワクチンによる癌免疫療法の開発、日本薬剤学会第 21 年会、2006.03.16-18　金沢.
3) 小泉 桂一、済木 育夫、櫻井 宏明、木我 千鶴、後藤 博三、中川 孝子、嶋田 豊、引網 宏彰、高橋 宏三、小川 和生、山本 雅浩、 松本 千波、小嶋 徹子、 鈴木 祥子、 柴垣 ゆかり、尾山 卓也、村元 浩、亀谷 聡：シンポジウム S34「プロテオミクス研究の現状とその創薬への展開」プロテオミクス解析による漢方医学診断基準(証)の客観的評価法構築への試み、日本薬学会第 126 年会、2006、03.28-31、仙台.
* 4) 済木 育夫：シンポジウム SS2「アレルギーの解明と制御を目指して - 遺伝子から機能分子・細胞・生体まで -」、心理的ストレスによるアレルギー性皮膚炎の増悪と漢方薬による改善、日本薬学会第 126 年会、2006、03.28-31、仙台.
5) 小泉桂一、松尾光浩、山田紗奈衣、登美斉俊、上田正次、寺崎哲也、帯刀益夫、細谷健一、大谷　修、済木育夫: 新規条件的不死化リンパ管内皮細胞株の樹立とリンパ管新生関連分子の探索、日本薬学会第 126 年会、2006、03.28-31、仙台.
6) 松尾光浩、山田紗奈衣、小泉桂一、大谷　修、済木育夫: 温度感受性 SV40 ラージ T 抗原 /EGFP ダブルトランスジェニックラットを用いた血管およびリンパ管内皮細胞株の樹立、第 111 回日本解剖学会、2006、03.29-31、東京.
7) Choo M-K, Sakurai H., Koizumi K., and Saiki I.: TAK1-mediated stress signaling pathways are essential for TNF-α-promoted pulmonary metastasis of murine colon cancer cells. The 97th AACR Annual Meeting., April 1-5, 2006, Wasington DC, U.S.A
8) 串田茂樹、大前比呂思、菅間 博、戸塚瑠美子、松村雅幸、竹内 晃、済木育夫、柳川 徹、鬼澤浩司郎、石井哲郎、大野忠夫:マウス肺癌と悪性黒色腫モデルにおけるサイトカインカクテルによる温熱療法の抗腫瘍効果増強、全身ハイパーサーミア研究会、2006.04.22、東京.
9) 済木育夫：第２８回日本小児東洋医学会　主催、2006.04.22、金沢.
* 10) 済木育夫：漢方薬によるがん転移の抑制と作用機序、日本生薬学会北海道支部第 30 回例会、2006.05.13、札幌.

* 11) 済木育夫：漢方補剤のがん転移抑制効果とその作用機序、第 133 回癌研有明病院学術講演会、2006.05.16、東京.

* 12) 済木育夫：がん治療と和漢薬、和漢薬によるがんの進展と転移の阻害に関する分子機構、第 12 回癌治療増感研究会、2006.05.19-20、富山.

13) 櫻井宏明、川崎範隆、Min-Kyung Choo、Pattama Singhirunnusorn、済木育夫：TRAIL 誘導性アポトーシスにおける TAK1 の役割、第 24 回日本生化学会北陸支部大会、2006.05.27 富山.

14) 櫻井 宏明、小泉桂一、済木育夫: TRAIL 誘導性アポトーシスにおける TAK1 の役割、第 10 回がん分子標的治療研究会総会、2006.06.15-16、東京.

15) 小泉桂一、小林光夫、中村エリアネ静、中山　隆志、義江修、済木育夫：破骨細胞分化に伴う CCL22 の発現亢進と肺がんの骨転移機序、第 71 回日本インターフェロン・サイトカイン学会、2006.07.07.

16) 山田　紗奈衣、松尾光浩、小泉桂一、済木育夫: 条件的不死化リンパ管内皮細胞株の樹立とリンパ管新生における FGF-2 の役割、第 18 回日本薬学会北陸支部会、2006.07.08、富山

* 17) 櫻井 宏明: TAK1:NF-κB 活性化を制御する炎症関連キナーゼ、第 27 回日本炎症・再生医学会、2006、07.11-12、東京.

* 18) 済木育夫：特別講演：漢方薬による癌転移の抑制とその作用機序　日本東洋医学会北陸支部　第１３回夏季講習会、2006.07.23、富山.

* 19) Saiki I.: Proteomic analysis of pathogenic alteration (SHO) diagnosed by Kampo medicine and establishment of Tailor-made treatment, The 6th International Symposium on Natural Medicine and Microflora (6th ISNMM), 2006.08.06-08, Korea.

* 20) 済木育夫：プロテオミクスによる「証」の科学的解析ーマルチマーカーの探索ー、第 23 回和漢医薬学会総会、2006.08.26-27、岐阜.

21) 後藤博三、木我千鶴、中川孝子、小泉桂一、櫻井宏明、引網宏彰、嶋田 豊、済木育夫：脳卒中易発症高血圧ラットの血漿プロテオミクス解析と黄連解毒湯の効果に関する検討、第 23 回和漢医薬学会総会、2006.08.26-27、岐阜.

22) 松本千波、小嶋徹子、尾山卓也、柴垣ゆかり、藤永　洋、高橋宏三、木我千鶴、小泉桂一、竹田秀一、済木育夫：プロテオミクス技術を用いた於血診断システム確立の試み、第 23 回和漢医薬学会総会、2006.08.26-27、岐阜.

23) 小川和生、尾山卓也、柴垣ゆかり、高橋宏三、引網宏彰、後藤博三、櫻井宏明、嶋田 豊、竹田秀一、済木育夫：関節リウマチ患者における桂枝茯苓丸奏効患者予測マーカーの探索、第 23 回和漢医薬学会総会、2006.08.26-27、岐阜.

* 24) Saiki I., Koizumi K. and Yasumoto K.: Role of chemokine/their receptors in the formaton of cancer metastasis, "From postgenomics to the clinic for Control of Cancer Metastasis" The 11th International Congress of Metastasis research society Jointed with the 15th Annual Meeting of Japanese association for Metastasis Research, 2006.09.03-06, Tokushima.

25) Tsunoda S., Nakamura T., Sakurai H. and Saiki I.: Recombinant human fibroblast growth factor-2 stimulates expression of endogenous vascular endothelial growth factor to enhance the growth and metastasis of B16-BL6 mouse melanoma cells, "From postgenomics to the clinic for Control of Cancer Metastasis" The 11th International Congress of Metastasis research society Jointed with the 15th Annual Meeting of Japanese association for Metastasis Research, 2006.09.03-06, Tokushima.

26) 串田茂樹、菅間 博、竹内　晃、済木育夫、大野忠夫:マウス肺癌と悪性黒色腫モデルにおけるサイトカインカクテルによる温熱療法の抗腫瘍効果増強、第 65 回日本癌学会総会、2006.09.29-30、横浜.

27) 北條荘三、小泉桂一、有田貴久、中山隆志、義江修、塚田一博、済木育夫：大腸癌における CXCL16 の発現と予後との関連、第 65 回日本癌学会総会、2006.09.29-30、横浜.

28) 小泉桂一、松尾光浩、櫻井宏明、済木育夫: 条件的不死化リンパ管内皮細胞株の樹立とリンパ管新生機序の解明、第 65 回日本癌学会総会、2006.09.29-30、横浜.

29) 保田賢司、永川 修、明石拓也、小泉桂一、済木育夫、布施秀樹: 前立腺癌における HAI-1

の発現について、第65回日本癌学会総会、2006.09.29-30、横浜.

30) 松尾光浩、山田紗奈衣、小泉桂一、大谷　修、済木育夫：条件的不死化リンパ管内皮細胞株 TR-LE に及ぼす FGF-2 のリンパ管新生誘導機構、第 65 回日本癌学会総会、2006.09.29-30、横浜.

31) 櫻井宏明、川崎範隆、Min-Kyung Choo、Pattama Singhirunnusorn、小泉桂一、済木育夫: TAK1 を標的とした TRAIL 誘導性アポトーシスの増強効果、第 65 回日本癌学会総会、2006.09.29-30、横浜.

* 32) Saiki I.: Proteomic analysis of pathogenic alteration (Sho) diagnosed by Kampo medicine and establishment of tailor-made treatment. The 2nd Internatinal Symposium for herbal medicines. "Highlights in Standardization and Drug Discovery", 2006, Oct. 31st, Seoul.

33) 済木育夫：漢方医学における「証」の科学的解析−プロテオミクス解析と診断支援マーカーの探索、「天然資源から抗感染症薬と病態制御へのアプローチ」　−東洋の知と生命科学の融合−北里大学 21 世紀 COE プログラム・富山大学 21 世紀 COE プログラムジョイントシンポジウム、2006.11.09、東京.

* 34) Sakurai H.: The role of TAK1 in TNF signaling. 2nd International Hannover Workshop on Cytokine Receptors and Cytokine Signaling, 2006, 11. 16-18, Kloster Wennigsen, Germany.

* 35) Saiki I.: Inhibition of tumor metastasis by Kampo medicine Juzen-taiho-to and its inhibitory mechanism of action. The 10th Internatinal Conference on Oriental Medicine of Dong-Eui & Daegu hanny University 2006, 2006, 11. 23, Busan.

* 36) Saiki I.: Proteomic analysis of pathogenic alteration (Sho) diagnosed by Kampo medicine and establishment of tailor-made treatment. COE/JSPS-NRCT Joint Evening Conference on Advanced Technologies to Evaluate Kampo Medicine-based Diagnosis and Clinical Therapy, 2006, 12. 01, Toyama.

37) Lirdprapamongkol K., Sakurai H., Kawasaki N., Choo M-K., Saitoh Y., Aozuka Y., singhirunnusorn P., Ruchirswat S., Svasti J. and Saiki I.: Vanillin (Vanilla) suppresses in vitro invasion and in vivo metastasis of mouse breast cancer cells. JSPS-NRCT core University Program on Natural Medicine in Pharmaceutical Sciences. The 7th Joint Seminar "Recent Advances in Natural Product Research and its Application", 2006, Dec. 2-4, Toyama.

* 38) Sakurai H., Chino A., Shimada Y., Terasawa K., and Saiki I.: Selective modulation of Toll-like receptor 4 singlinag pathways by juzentaihoto, a Japanese Kampo Medicine. JSPS-NRCT core University Program on Natural Medicine in Pharmaceutical Sciences. The 7th Joint Seminar "Recent Advances in Natural Product Research and its Application", 2006, Dec. 2-4, Toyama.

39) 鈴木俊輔、Pattama Singhirunnusorn、山岡昇司、北島 勲、済木育夫、櫻井宏明：HTLV-1 Tax による恒常的 TAK1 活性化とその細胞内シグナル機構における役割、日本分子生物学 2006 フォーラム、2006.12.6-8、名古屋.

40) Singhirunnusorn P., Ueno Y., Matsuo M., Suzuki S., Saiki I. and Sakurai H.: Transient suppression of ligand-mediated activation of EGFR by TNF-α through the TAK1-p38 signaling pathway, 日本分子生物学 2006 フォーラム、2006.12.06-08、名古屋.

* 41) 済木育夫：薬用人参の効果発現と腸内細菌、「健康長寿に向かう個の医療と薬食同源」静岡県立大学 21 世紀 COE プログラム・富山大学 21 世紀 COE プログラムジョイントシンポジウム、2006.12.13、東京.

◇その他

1) 済木育夫：和漢研セミナー「NK 細胞の腫瘍免疫監視機構における役割」、講師：早川芳弘、2006、01. 25、富山.

2) 済木育夫：癌転移に関する漢方薬の可能性、富山漢方セミナー冬の陣、2006、01. 29、富山.

3) 済木育夫：オリジナルブランド医薬品開発研究会報告「パナワンの開発と評価から販売まで」、フォーラム富山「創薬」第 18 回研究会、2006、02. 07、富山.

4) 済木育夫：補剤の癌転移抑制効果とその作用機序、臨床研修指定病院指導医のための横

浜漢方医学セミナー2006、2006、02. 11、横浜.

5) 済木育夫：漢方薬の新潮流　西洋医学との融合、NHK 教育テレビ「サイエンス ZERO」、2006、02. 11、放送

6) 済木育夫：補剤の癌転移抑制効果とその作用機序　ー21 世紀 COE プログラムー、第４回東海耳鼻咽喉科漢方研究会、2006、02. 12、名古屋.

7) 済木育夫：和漢薬研究の最前線ーがんの転移と漢方薬ー、ツムラ神奈川県・薬剤師のための漢方セミナー、2006、02. 25、横浜.

8) 済木育夫：補剤のがん転移抑制効果とその作用機序、大学勤務医のための漢方医学セミナー、2006、02. 25、東京.

9) 済木育夫：肥満マウスにおける転移亢進および QR-32 細胞の悪性化に対する FBRA の効果、第 14 回 FBRA 全国研究会、2006. 02. 26、東京.

10) 済木育夫：ダイオキシンの排出には葉緑素と食物繊維が有効で、補給食 No.1 は高栄養藻スピルリナ、わかさ, 2006 新年号、64-67.

11) 済木育夫：教育講演「がん転移に関する漢方薬の可能性」、学術講演会、2006.03. 17、富山

12) 済木育夫：高齢化社会に対しての漢方の役割 ー補剤の免疫機能への働きー、神戸東 易しい漢方研究会　第１７回学術講演会、2006、03. 18、神戸.

13) 済木育夫：セミナー「証」を科学する東洋医学によるオーダーメイド医療、医と薬とバイオのサミット 、2006、05. 12、金沢.

14) 済木育夫：補剤のがん転移抑制効果とその作用機序、臨床研修医のための漢方医学セミナー、2006.05.27、大阪.

15) 済木育夫、小松かつ子：土曜スペシャル「封印されたオーパーツ」、テレビ朝日、19：00-21：00、2006.06.03

16) 済木育夫：補剤のがん転移抑制効果とその作用機序、漢方医学入門セミナー　ー漢方との出会い　温故知新ー、2006.06.03、大阪.

17) 済木育夫：生活習慣病と免疫ーいつまでも若く元気でいるためにー、第 6 回（株）丸大サクライ薬局　健康づくりセミナー、2006.06.06-07、青森.

18) 済木育夫：癌転移抑制と漢方　−十全大補湯の免疫賦活作用を中心に−、上越漢方学術講演会、2006.06.20、上越.

19) 済木育夫：漢方薬による癌転移抑制効果 第 1 回漢方医学学術講演会、2006.07.21、帯広.

20) 済木育夫：がん転移モデルにおける FBRA と抗がん剤の併用効果、第 15 回 FBRA 全国研究会、2006. 08. 27、札幌.

21) 済木育夫：ここまでわかった漢方薬の効果 第 11 回和漢医薬学総合研究所夏期セミナー「ふれてみよう和漢薬！」、2006.08.29-30、富山.

22) 済木育夫：漢方医学における「証」の科学的解明　BioJapan 2006 World Business Forum、2006.09.13-15、大阪.

23) 済木育夫：特別講演「漢方薬理の基礎」　漢方医が区カンファレンス東京、2006.09.02、東京

24) 済木育夫：生活習慣病と免疫ーいつまでも若く元気でいるためにー　2006 ザ・スピルリナ会、2006.09.08、東京.

25) 済木育夫：癌転移抑制と漢方薬　富山入門 II 漢方セミナー、2006.09.10、富山.

26) 済木育夫：補剤によるがん転移抑制効果とその作用機序、第３回三重東洋医学教育研究会、2006、10.19、三重.

27) 済木育夫：漢方医学における「証の科学的解析」と薬理作用、2006 年横浜漢方医学セミナー・秋、2006、10.29、横浜.

28) 済木育夫：癌転移抑制と漢方薬、EBM 漢方、2006、11.25、大阪.

◇共同研究

国内

1) 永井博弐：岐阜薬科大学薬理学、「アトピー性皮膚炎モデルにおける伝統薬物の効果」、1994, 04ー2006.03
2) 鶴岡伸夫：サントリー株式会社、「プロテオーム解析による健康食品の機能発現に関する研究」、2004、10ー
3) 岩崎輝明：玄米酵素（株)、「がん転移モデルにおける FBRA と抗がん剤の併用効果」、2002, 4ー
4) 義江 修：近畿大学医学部、「ケモカインを中心としたがん転移メカニズムの解明」、2001.9ー
5) 加瀬 義夫、山本 雅浩、小川 和生、松本 千波、小嶋 徹子、鈴木 祥子：（株）ツムラ、知的クラスター創成事業「とやま医薬バイオクラスター」、2003, 4ー
6) 小森 隆、柴垣 ゆかり、尾山 卓也、亀谷 聡：ｲﾝﾃｯｸ･ｳｪﾌﾞ･ｱﾝﾄﾞ･ｹﾞﾉﾑ･ｲﾝﾌｫﾏﾃｨｸｽ株式会社、知的クラスター創成事業「とやま医薬バイオクラスター」、2003, 4ー
7) 嶋田 豊、引網 宏彰：富山医科薬大学医学部和漢診療学、知的クラスター創成事業「とやま医薬バイオクラスター」、2003, 4ー
8) 柴原 直利、後藤 博三、酒井 伸也：富山医科薬科大学和漢薬研究所臨床科学部門漢方診断学分野、知的クラスター創成事業「とやま医薬バイオクラスター」、2003, 4ー
9) 高橋 宏三：富山県立中央病院和漢診療科、知的クラスター創成事業「とやま医薬バイオクラスター」、2003, 4ー
10) 木我 千鶴：富山県新世紀産業機構、知的クラスター創成事業「とやま医薬バイオクラスター」、2003, 4ー
11) 正川康明、塩井保彦：株式会社 廣貫堂、産業クラスター連携プロジェクト「生活習慣の乱れに基づく健康不調に関連するプロテオーム発現解析と天然薬物の開発研究」2005、04ー
12) 村元 浩、柴垣 ゆかり、尾山卓也：ｲﾝﾃｯｸ･ｳｪﾌﾞ･ｱﾝﾄﾞ･ｹﾞﾉﾑ･ｲﾝﾌｫﾏﾃｨｸｽ株式会社、産業クラスター連携プロジェクト「生活習慣の乱れに基づく健康不調に関連するプロテオーム発現解析と天然薬物の開発研究」2005、04ー
13) 木我千鶴：富山県新世紀産業機構、産業クラスター連携プロジェクト「生活習慣の乱れに基づく健康不調に関連するプロテオーム発現解析と天然薬物の開発研究」2005、04ー
14) 鶴岡伸夫、別府佳紀：サントリー株式会社　健康科学研究所、産業クラスター連携プロジェクト「生活習慣の乱れに基づく健康不調に関連するプロテオーム発現解析と天然薬物の開発研究」2005、04ー
15) 加藤敏光：大日本インキ化学工業（株)、「エンドトキシンショックモデルにおけるサイトカイン産生におけるスピルリナの効果」、2005, 04ー
16) 審良静男：大阪大学微生物病研究所「免疫細胞シグナルにおける TAK1 の役割」2006、01ー
17) Michael Kracht : Hannover Medical School、「サイトカインシグナルにおける TAK1 の役割」2006、01ー

◇非常勤講師

1) 済木育夫：富山大学大学院医学系研究科修士過程 講義「東洋医学概論」2006.01.11、富山
2) 済木育夫：富山大学医学部専門教育 講義「免疫学」2006, 04, 21, 富山
3) 済木育夫：富山大学薬学部専門教育 講義「薬理学 III」2006, 04, 24, 富山.

4) 済木育夫：富山大学共通専門教育 講義「和漢医薬学入門」2006, 0428, 富山
5) 済木育夫：富山県立いずみ高等学校看護学科 講義 「がん転移と漢方薬」2006, 07, 26, 富山
6) 済木育夫、櫻井宏明、小泉桂一：富山高校スーパーサイエンスハイスクール事業　講義実習　テーマ「がん転移の機序解明及び治療方法構築に関する基礎実験」

◇研究費取得状況

1) 平成 18 年度 知的クラスター創成事業「とやま医薬バイオクラスター」(代表：済木育夫) 漢方方剤テーラーメード治療法の開発について
2) 平成 18 年度 21 世紀 COE プログラム「東洋の知に立脚した個の医療の創生」(分担：済木育夫) 臨床研究 (遺伝子多型と血漿プロテオーム解析)
3) 平成 17 年度研究奨励金 財団法人上原記念生命科学財団 (代表：小泉桂一) プロテオミクスによる漢方診断基準の解析
4) 独立行政法人科学技術振興機構のシーズ育成試験助成 (代表：小泉桂一) 新規リンパ管新生評価の構築とリンパ管新生関連病態を標的とした治療薬の開発
5) 平成 18 年度文部科学省科学研究費補助金基盤研究 (C) (代表：櫻井宏明)「ストレス応答キナーゼ TAK1 によるがん転移促進作用の分子機構解析」
6) 平成 18 年度文部科学省科学研究費補助金基盤研究 (B) (分担：櫻井宏明)「漢方薬の薬効を利用した脳血管性痴呆治療標的分子の探索・同定とその生理機能解析」
7) 平成 18 年度文部科学省科学研究費補助金基盤研究 (C) (分担：櫻井宏明)「新規酵素群グリセロホスホジエステルホスホジエステラーゼを分子標的とした基盤研究」
8) 平成 17 年度小野医学研究財団 研究奨励助成 (代表：櫻井宏明)「肥満および糖尿病モデルマウスにおけるがん転移亢進の分子機構解析」
9) 平成 18 年度富山県受託研究：和漢薬・バイオテクノロジー研究 (分担：櫻井宏明)「遺伝子解析技術を活用した和漢薬の薬効評価と効率的生産システムの開発」
10) 平成 18 年度文部科学省科学研究費補助金若手研究 B (代表：小泉桂一)「温度感受性リンパ管内皮細胞株の樹立及び組織アレイによる腫瘍リンパ管新生分子の検索」

◇研究室在籍者

学部 3 年生：竹野伸洋
学部 4 年生：杉嶋祐巳子
大学院前期 1 年：南　貴久
大学院前期 2 年：篠原看奈、山田紗奈衣
大学院後期 1 年：角田　聡 (社会人入学、2005.10ー)
大学院後期 2 年：鈴木俊輔、上野陽子、齊藤百合花、小川和生 (社会人入学、2005.04ー)
大学院後期 3 年：植田康嗣 (社会人入学、2003.04ー2006.03)
協力研究員：木我千鶴 (2003.11.01ー、新世紀産業機構)
Pattama Singhirunnusorn (2006.05.01ー、新世紀産業機構)
COE 研究員：Choo Min-Kyung (2006.04.01ー)
技術補佐員：林　和子 (2005.04.01ー)
事務補佐員：笠井直美 (2004.04.01ー)
学内研究生：明石拓也 (富山大学医学部・泌尿器科学、2002.04ー)
薄田勝男 (富山大学附属病院・光学医療診療部、2002.01ー2006.03)
森　昭憲 (富山大学医学部・和漢診療学、2004.05ー)
北條荘三 (富山大学医学部・第二外科、2005.04ー)
橋本伊佐也 (富山大学医学部・第二外科、2006.04ー)

外国人客員研究員：Juthamaus Chuethong (Ubon Ratchathani University, Thailand)
2006. 03. 01～2006. 05. 31
Chantana Boonyarat (Khon Kaen University, Thailand)
2006. 10. 01～2006. 12. 05

◇学位（修士、博士）取得者

卒業論文：

南　貴久：骨代謝におけるケモカイン fractalkine およびその受容体 CX3CL1 の関与

修士論文：

有田貴久：膜結合型ケモカイン Fractalkine/CX3CL1 による同所性移植モデルを用いたマウス肺癌細胞の増殖抑制効果の検討

川崎範隆：TRAIL 誘導性アポトーシスにおける TAK1 の役割

博士論文：

Min-Kyung Choo：Role of TNF-α Signaling Pathways in Metastasis of Murine Colon Cancer Cells

Pattama Singhirunnusorn：Critical Role of Threonine 187 Phosphorylation in Activation of TAK1 Mitogen-activated Protein Kinase Kinase Kinase