病態生化学分野　Division of Pathogenic Biochemistry

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◇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，がん，免疫疾患などを中心にして検討を行っている。

◇研究概要

Ⅰ）和漢薬に関する基礎的研究

1) 漢方方剤およびその構成成分によるがん転移抑制とその機構
2) 和漢薬による免疫応答および免疫疾患の制御に関する研究

Ⅱ）がん転移機構の解明とその制御

1) がん転移におけるケモカインの作用機序の解明と治療への応用
2) がん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

Ⅲ）ストレス応答シグナルによる病態制御機構の解析

1) プロテインキナーゼ TAK1 によるがん悪性化の分子機構の解明
2) がん分子標的治療に関与する細胞内シグナルの制御に関する研究

◇原著論文

1) Tsunoda S., Sakurai H., Saitoh Y., Ueno Y., Koizumi K., and Saiki I.: Massive T lymphocyte infiltration into the host stroma is essential for FGF-2-promoted growth and metastasis of mammary tumors via neovascular stability. *Am. J. Pathol.*, 174: 671-683, 2009.

Abstract: Inflammation in the tumor stroma greatly influences tumor development. In the present study, we investigated the roles of fibroblast growth factor (FGF)-2-induced chronic inflammation in the development of 4T1 murine mammary tumors. Administration of FGF-2 into the tumor inoculation site during the initial phase of tumor growth enhanced tumor growth and pulmonary metastasis as well as microvessel density in tumor tissues in normal but not in nude mice. Infiltration of T lymphocytes and macrophages, recruitment of pericytes/vascular mural cells in neovascular walls, and the expression levels of cyclooxygenase (COX)-2 and vascular endothelial growth factor A (VEGFA) were also enhanced in the FGF-2-activated host stroma of normal mice. In addition, FGF-2-induced tumor growth and metastasis was abrogated by administration of either an immunosuppressant, FK506, or a COX-2 inhibitor. FGF-2 enhanced prostaglandin E(2) secretion in cultured T lymphocytes. In addition, VEGFA secretion was

increased in a co-culture of T lymphocytes and fibroblasts in vitro. These results indicate that the massive infiltration of T lymphocytes into FGF-2-activated host stroma during the initial phase of tumor growth enhances neovascular stability by regulating endogenous COX-2 and VEGFA levels because both compounds are known to play important roles in marked 4T1 mammary tumor development via FGF-2-induced inflammatory reactions.

2) **Yasuda K., Nagakawa O., Akashi T., Fujiuti Y., Koizumi K., Saiki I., and Fuse H.: Serum active hepatocyte growth factor (AHGF) in benign prostatic disease and prostate cancer. *Prostate.*, 69: 346-351, 2009.**

Abstract: BACKGROUND: Hepatocyte growth factor (HGF) is secreted as an inactive single-chain precursor called pro-HGF. Pro-HGF is converted to an active two-chain form by HGF activator and matriptase. We attempted to clarify whether serum levels of active HGF (AHGF) could be used as a marker of prostate cancer. METHODS: Serum levels of AHGF and total HGF (THGF; pro-HGF + AHGF) were measured by enzyme-linked immunosorbent assay in 38 patients with benign prostatic disease and 160 patients with prostate cancer. RESULTS: Serum levels of AHGF in patients with untreated prostate cancer (0.37 +/- 0.12 ng/ml) were significantly higher than those in patients with benign prostatic disease (0.28 +/- 0.08 ng/ml) (P = 0.0001). Serum AHGF levels were increased in patients with stage D or D3 compared with stage B. In addition, there were significant differences in serum AHGF levels between patients with well-differentiated and poorly differentiated adenocarcinoma. Furthermore, the mean serum AHGF/THGF ratio in patients with stage D3 prostate cancer was significantly higher than that in patients with stage B. CONCLUSIONS: AHGF may be a potential tumor marker for prostate cancer. Further studies in large groups of patients are needed to define the clinical value of AHGF. 2008 Wiley-Liss, Inc..

3) **Sunghwa F., Sakurai H., Saiki I., and Koketsu M.: Iodine-catalyzed etherification of morroniside. *Chem. Pharm. Bull.*, 57: 112-115, 2009.**

Abstract: In this study, we describe a highly selective etherification procedure of unprotected morroniside catalyzed by molecular iodine in acetone. The etherification reaction furnished 7-O-alkyl ether derivatives in reasonable yields within few hours under neutral conditions. Studies of the obtained products on cytotoxicity activity in colon 26-L5 cell line were examined. Among the tested compounds, 7-O-dodecylmorroniside showed moderate cytotoxic activity, having IC50 values equal to 20.9 microM.

4) **Kammasud N., Boonyarat C., Sanphanya K., Tsunoda S., Sakurai H., Saiki I., Andre I., Grierson D.S., and Vajragupt O.: 5-Substituted pyrido[2,3-d]pyrimidine, an inhibitor against three receptor tyrosine kinases. *Bioorg. Med. Chem. Lett.*, 19: 745-750, 2009.**

Abstract:NP506,the3-{2,4-dimethyl-5-[2-oxo-5-(N'-phenylhydrazinocarbonyl)-1,2-dihydro-indol-3-ylid enemethyl]-1H-pyrrol-3-yl}-propionic acid, was designed as FGF receptor 1 inhibitor by computational study and found to be more active against endothelial proliferation of HUVEC after the rhFGF-2 stimulation than SU6668 with minimum effective dose of 10 microM. NP506 inhibited the tyrosine phosphorylation in FGF, VEGF, and PDGF receptors and the activation of extracellular signal-regulated kinase (ERK), c-Jun-N-terminal-kinase (JNK) and AKT after the rhFGF-2 stimulation. The introduction of the phenyl hydrazide motif to the position 5 of the pyrido[2,3-d]pyrimidine scaffold led to the inhibitory effect in two signaling pathways: inhibition of AKT activation in the phosphatidyl inositol 3'-kinase (PI13K)/AKT signaling pathway and the inhibition of ERK and JNK activation in MAPK pathway.

5) **Minoda Y., Sakurai H., Kobayashi T., Yoshimura A., and Takaesu G.: An F-box protein FBXW5 negatively regulates TAK1 MAPKKK in the IL-1β signaling pathway. *Biochem. Biophys. Res. Commun.*, 381: 412-417, 2009.**

Abstract: TAK1, a member of the MAP3K family, plays an essential role in activation of JNK/p38 MAPKs and IKK in the IL-1β and TNFα signaling pathway. Upon stimulation, TAK1 is rapidly and transiently activated. While the activation mechanism of TAK1 in these signaling pathways is well characterized, how its activity is terminated still remains unclear. To identify the molecule(s) involved in TAK1 regulation, we performed tandem affinity purification (TAP) in HeLa cells stably expressing TAP-tagged TAK1. FBXW5, an F-box family protein, was identified as a previously unknown component of the IL-1β-induced TAK1 complex. FBXW5 associated with endogenous TAK1 in an IL-1β-dependent

manner. Overexpression of FBXW5 inhibited IL-1β-induced activation of JNK/p38 MAPKs and NF-κB as well as phosphorylation of TAK1 on Thr187. Conversely, knockdown of FBXW5 resulted in the prolonged activation of TAK1 upon IL-1β stimulation. These results suggest that FBXW5 negatively regulates TAK1 in the IL-1β signaling pathway.

6) **Cho S., Koizumi K., Takeno N., Kato S., Hashimoto I., Sakurai H., Tsukada K., and Saiki I.: Anti-tumor effect of combining CC chemokine 22 (CCL22) and an anti-CD25 antibody on myeloma cells implanted subcutaneously into mice. *Mol. Med. Rep.*, 2: 773-777, 2009.**

7) **Miyanaga S., Sakurai H., Saiki I., Onaka H., and Igarashi Y.: Synthesis and evaluation of myxochelin analogues as antimetastatic agents. *Bioorg. Med. Chem.*, 17: 2724-2732, 2009.**

Abstract: Myxochelin A (1) is an inhibitor of tumor cell invasion produced by the bacterium belonging to the genus Nonomuraea. In order to obtain more potent inhibitors, a series of myxochelin analogues [2 and (S)-3-17] were synthesized through the coupling of lysine or diaminoalkane derivatives and appropriately protected hydroxybenzoate, followed by modification of functional groups and deprotection. These compounds were evaluated for their inhibitory activity against invasion of murine colon 26-L5 carcinoma cells. Among the synthetic analogues tested, compound (S)-6 which possesses carbamoyl group at C-1 was found to be the most potent antiinvasive agent and is considered to be a promising lead molecule for the antimetastasis. Compound (S)-6 was also shown to inhibit gelatinase activities of MMP-2 and MMP-9 and *in vivo* lung metastasis in mice.

8) **Senda K., Koizumi K., Prangsaengtong O., Minami T., Suzuki S., Takasaki I.,Tabuchi Y., Sakurai H., Doki Y., Misaki T., and Saiki I.: Inducible capillary formation in lymphatic endothelial cells by blocking lipid phosphate phosphatase-3 activity. *Lymphat. Res. Biol.*, 7: 69-74, 2009.**

Abstract: Lymphangiogenesis plays critical roles under normal and/or pathological conditions; however, the molecular contributors to this event were unknown until recently. In the present study, we first employed gene chip analysis and confirmed that lipid phosphate phosphatase-3 (LPP3) expression was increased until capillary formation in the conditionally immortalized rat lymphatic endothelial cell line. Signaling responses occur when several lipids induce acute biological functions; further, lipid phosphate phosphatases (LPPs) control their functions via dephosphorylation; however, there is no report on the association between LPP3 and lymphangiogenesis. siRNA-targeted LPP3 significantly increased capillary formation of human lymphatic endothelial cells; in contrast, it decreased cell adhesion to the basement membrane matrix. Furthermore, the inducible effect of the LPP inhibitor on capillary formation was observed. For the first time, we report that LPP3 abolishes accelerated abnormal lymphangiogenesis. Blocking LPP3 activities may aid in the development of novel therapy for lymph vessel defects.

9) **Shin M.S., Singhirunnusorn P., Sugishima Y., Nishimura M., Suzuki S., Koizumi K., Saiki I., and Sakurai H.: Cross interference with TNF-α-induced TAK1 activation via EGFR-mediated p38 phosphorylation of TAK1-binding protein 1. *Biochim. Biophys. Acta*, 1793: 1156-1164, 2009.**

Abstract: Transforming growth factor-α-activated kinase 1 (TAK1) has been widely recognized as a kinase that regulates multiple intracellular signaling pathways evoked by cytokines and immune receptor activation. We have recently reported that tumor necrosis factor-α (TNF-α) triggers internalization of epidermal growth factor receptor (EGFR) through a TAK1-p38α signaling pathway, which results in a transient suppression of the EGFR. In the present study, we investigated the pathway of intracellular signaling in the opposite direction. Ligand-induced activation of EGFR caused phosphorylation of the TAK1-binding proteins TAB1 and TAB2 in a TAK1-independent manner. EGFR-mediated phosphorylation of TAB1 was completely inhibited by a chemical inhibitor and siRNA of p38α. The phosphorylation of TAB1 was occurred at Ser-423 and Thr-431, the residues underlying the p38-mediated feedback inhibition of TAK1. In contrast, phosphorylation of TAB2 was sustained, and largely resistant to p38 inhibition. The inducible phosphorylation of TAB1 interfered with a response of EGF-treated cells to TNF-α-induced TAK1 activation, which led to the reduction of NF-κB activation. Collectively, these results demonstrated that EGFR activation interfered with TNF-α-induced TAK1 activation via p38-mediated phosphorylation of TAB1.

10) **Igarashi Y., Mogi T., Yanase S., Miyanaga S., Fujita T., Sakurai H., Saiki I., and Ohsaki A.: Brartemicin, an inhibitor of tumor cell invasion from the Actinomycete Nonomuraea sp. *J. Nat. Prod.*, 72: 980-982, 2009.**

Abstract: Brartemicin (1), a new trehalose-derived metabolite, was isolated from the culture broth of the actinomycete of the genus Nonomuraea. Its structure and absolute configuration were determined by spectroscopic analyses. The new compound inhibited the invasion of murine colon carcinoma 26-L5 cells with an IC(50) value of 0.39 muM in a concentration-dependent manner without showing cytotoxic effects.

11) **Isono T., Kim C.J., Ando Y., Sakurai H., Okada Y., and Inoue H.: Suppression of cell invasiveness by periostin via TAB1/TAK1. *Int. J. Oncol.*, 35: 425-432, 2009.**

Abstract: We have previously shown that the expression of periostin is significantly downregulated in human bladder cancer tissues and that periostin suppresses cell invasiveness and metastasis of cancer cells. To clarify the molecular mechanism of this suppression by periostin, we searched for periostin-binding proteins and identified TAB1, which interacts with and activates TAK1, by mass analysis of proteins co-precipitated with periostin in 293T cells expressing periostin. The association between periostin and TAB1 was confirmed by a pulldown assay in 293T cells co-tranfected with expression plasmids of periostin, TAB1 and TAK1. TAK1 was also co-precipitated with periostin in this assay. Co-transfection experiments in 293T also showed that periostin could activate TAK1. Introduction of siRNA for TAB1 suppressed TAK1 activation by periostin. Analyses with deletion mutants of periostin revealed that the C-terminal region of periostin was necessary and sufficient for the association with TAB1 and the TAK1 activation. The suppression of invasiveness by periostin was attenuated by siRNA targeting TAK1 or TAB1 in 293T (human embryonic kidney) and T24 (human bladder carcinoma) cell lines. These findings indicate that periostin is involved in the suppression of cell invasiveness via the TAB1/TAK1 signaling pathway.

12) **Nishimura M., Shin M.S., Singhirunnusorn P., Suzuki S., Kawanishi M., Koizumi K., Saiki I., and Sakurai H.:TAK1-mediated serine/threonine phosphorylation of epidermal growth factor receptor via p38/extracellular signal-regulated kinase: NF-κB-independent survival pathways in tumor necrosis factor alpha signaling. *Mol. Cell. Biol.*, 29: 5529-5539, 2009.**

Abstract: The kinase TAK1, a mitogen-activated protein kinase kinase kinase (MAP3K), has been widely accepted as a key kinase activating NF-κB and MAPKs in tumor necrosis factor alpha (TNF-α) signaling. We have recently reported that TAK1 regulates the transient phosphorylation and endocytosis of epidermal growth factor receptor (EGFR) in a tyrosine kinase activity-independent manner. In the present study, we found that Thr-669 in the juxtamembrane domain and Ser-1046/1047 in the carboxyl-terminal regulatory domain were transiently phosphorylated in response to TNF-α. Experiments using chemical inhibitors and small interfering RNA demonstrated that TNF-α-mediated phosphorylation of Thr-669 and Ser-1046/7 were differently regulated via TAK1-extracellular signal-regulated kinase (ERK) and TAK1-p38 pathways, respectively. In addition, p38, but not ERK, was involved in the endocytosis of EGFR. Surprisingly, modified EGFR was essential to prevent apoptotic cellular responses; however, the EGFR pathway was independent of the NF-κB antiapoptotic pathway. These results demonstrated that TAK1 controls two different signaling pathways, IκB kinase-NF-κB and MAPK-EGFR, leading to the survival of cells exposed to the death signal from the TNF-α receptor.

13) **Zaidi S.F., Yamamoto T., Refaat A., Ahmed K., Sakurai H., Saiki I., Kondo T., Usmanghani K., Kadowaki M., and Sugiyama T.: Modulation of activation-induced cytidine deaminase by curcumin in *H. pylori*-infected gastric epithelial cells. *Helicobacter*, 14: 588-595, 2009.**

Abstract: BACKGROUND: Anomalous expression of activation-induced cytidine deaminase (AID) in Helicobacter pylori-infected gastric epithelial cells has been postulated as one of the key mechanisms in the development of gastric cancer. AID is overexpressed in the cells through nuclear factor (NF)-κB activation by H. pylori and hence, inhibition of NF-κB pathway can downregulate the expression of AID. Curcumin, a spice-derived polyphenol, is known for its anti-inflammatory activity via NF-κB inhibition. Therefore, it was hypothesized that curcumin might suppress AID overexpression via NF-κB inhibitory activity in H. pylori-infected gastric epithelial cells. MATERIALS AND METHODS: MKN-28 or MKN-45 cells and H. pylori strain 193C isolated from gastric cancer patient were used for co-culture

experiments. Cells were pretreated with or without nonbactericidal concentrations of curcumin. Apoptosis was determined by DNA fragmentation assay. Enzyme-linked immunosorbent assay was performed to evaluate the anti-adhesion activity of curcumin. Real-time polymerase chain reaction was employed to evaluate the expression of AID mRNA. Immunoblot assay was performed for the analysis of AID, NF-κB, inhibitors of NF-κB (IκB), and IκB kinase (IKK) complex regulation with or without curcumin. RESULTS: The adhesion of H. pylori to gastric epithelial cells was not inhibited by curcumin pretreatment at nonbactericidal concentrations (< or =10 micromol/L). Pretreatment with nonbactericidal concentration of curcumin downregulated the expression of AID induced by H. pylori. Similarly, NF-κB activation inhibitor (SN-50) and proteasome inhibitor (MG-132) also downregulated the mRNA expression of AID. Moreover, curcumin (< or =10 micromol/L) has suppressed H. pylori-induced NF-κB activation via inhibition of IKK activation and IκB degradation. CONCLUSION: Nonbactericidal concentrations of curcumin downregulated H. pylori-induced AID expression in gastric epithelial cells, probably via the inhibition of NF-κB pathway. Hence, curcumin can be considered as a potential chemopreventive candidate against H. pylori-related gastric carcinogenesis.

14) Yamazaki K., Gohda J., Kanayama A., Miyamoto Y., Sakurai H., Yamamoto M., Akira S., Hayashi H., Su B., and Inoue J.: Two Mechanistically and Temporally Distinct NF-κB Activation Pathways in IL-1 Signaling. *Sci Signal.*, 2: ra66, 2009.

Abstract: The cytokine interleukin-1 (IL-1) mediates immune and inflammatory responses by activating the transcription factor nuclear factor κB (NF-κB). Although transforming growth factor-β-activated kinase 1 (TAK1) and mitogen-activated protein kinase (MAPK) kinase kinase 3 (MEKK3) are both crucial for IL-1-dependent activation of NF-κB, their potential functional and physical interactions remain unclear. Here, we showed that TAK1-mediated activation of NF-κB required the transient formation of a signaling complex that included tumor necrosis factor receptor-associated factor 6 (TRAF6), MEKK3, and TAK1. Site-specific, lysine 63-linked polyubiquitination of TAK1 at lysine 209, likely catalyzed by TRAF6 and Ubc13, was required for the formation of this complex. After TAK1-mediated activation of NF-κB, TRAF6 subsequently activated NF-κB through MEKK3 independently of TAK1, thereby establishing continuous activation of NF-κB, which was required for the production of sufficient cytokines. Therefore, we propose that the cooperative activation of NF-κB by two mechanistically and temporally distinct MEKK3-dependent pathways that diverge at TRAF6 critically contributes to immune and inflammatory systems.

15) Koizumi K., Saitoh Y., Minami T., Tsuneyama K., Miyahara T., Nakayama T., Sakurai H., Takano Y., Nishimura M., Imai T., Yoshie O., and Saiki I.: Role of CXCL1/fractalkine in osteoclast differentiation and bone resorption. *J. Immunol.*, 183: 7825-7831, 2009.

Abstract: The recruitment of osteoclast precursors toward osteoblasts and subsequent cell-cell interactions are critical for osteoclast differentiation. Chemokines are known to regulate cell migration and adhesion. CX3CL1 (also called fractalkine) is a unique membrane-bound chemokine that has dual functions for cells expressing its receptor CX3CR1: a potent chemotactic factor in its soluble form and a type of efficient cell adhesion molecule in its membrane-bound form. In this paper, we demonstrate a novel role of CX3CL1 in osteoblast-induced osteoclast differentiation. We found that osteoclast precursors selectively expressed CX3CR1, whereas CX3CL1 is expressed by osteoblasts. We confirmed that soluble CX3CL1 induced migration of bone marrow cells containing osteoclast precursors, whereas immobilized CX3CL1 mediated firm adhesion of osteoclast precursors. Furthermore, a blocking mAb against CX3CL1 efficiently inhibited osteoclast differentiation in mouse bone marrow cells cocultured with osteoblasts. Anti-CX3CL1 also significantly suppressed bone resorption in neonatal mice by reducing the number of bone-resorbing mature osteoclasts. Collectively, CX3CL1 expressed by osteoblasts plays an important role in osteoclast differentiation, possibly through its dual functions as a chemotactic factor and adhesion molecule for osteoclast precursors expressing CX3CR1. The CX3CL1-CX3CR1 axis may be a novel target for the therapeutic intervention of bone resorbing diseases such as rheumatoid arthritis, osteoporosis, and cancer bone metastasis.

16) **Saiki I.: Award of Medical and Pharmaceutical Society for WAKAN-YAKU 2008, To elucidate individual pathogenic alteration (so-called "Sho") diagnosed by Kampo medicine –Evidence-based objective evaluation of the efficacy of Kampo Formulations–** ***J. Tad. Med.*****, 26: 141-159, 2009.**

◇総　説

1) 済木育夫，山崎美佳子，松本欣三：Review 日本薬学会第 128 年会誌上シンポジウム タイ拠点大学交流事業「薬学分野：天然薬物」，薬学雑誌，**129** 巻 4 号 387-391, 2009,
2) 竹野伸洋，小泉桂一，済木育夫：総説：根拠に基づく漢方治療実践への基礎研究からのフィードバック，日本病院薬剤師会雑誌，**45** 巻 6 号 761-765, 2009,
3) 櫻井宏明，小泉桂一，済木育夫：漢方薬・生薬と臨床検査，トピックス：漢方の効き目を決める「証」の解析，臨床検査，**53** 巻 8 号 950-954, 2009,

◇学会報告　（*：特別講演，シンポジウム，ワークショップ等）

* 1) 櫻井宏明：和漢薬を用いたケミカルバイオロジーの展開に向けて，科学研究費特定領域「ゲノム」ワークショップ-生薬のバイオインフォーマティクス–，2009, 1, 14-15, 富山.
* 2) Saiki I.: Chair for Honorary Keynote Lecture "Structure and biological diversities of Thai Natural products" by Professor Dr. H.R.H. Princes Chulabhorn Mahidol. The 8th Joint Seminar : Innovative Research in Natural Products for sustainable development. 2009, 2, 3-4, Thailand.
* 3) 櫻井宏明：和漢薬ライブラリーを用いたケミカルバイオロジーの展開，第 2 回和漢薬の科学研究シンポジウム-和漢薬の標準化とは–，2009, 2, 27-28, 富山.
4) 周 越，鈴木俊輔，アラー・リファート，高崎一朗，小泉桂一，山岡昇司，田渕圭章，済木育夫，櫻井宏明：HTLV-1 Tax 発現細胞における TAK1 を介したインターフェロン応答遺伝子の発現誘導とその分子機構，第 27 回日本生化学会北陸支部大会，2009, 5, 23, 福井.
* 5) 済木育夫：特別講演 I 漢方医学における「証」の科学的解明を目指したプロテオミクス解析～マルチマーカーの探索～，第 19 回日本臨床検査専門医会春季大会，2009, 6, 13, 富山.
6) 櫻井宏明，小泉桂一，済木育夫: TNF-α による EGFR の Ser/Thr リン酸化と細胞内局在化–新しい抗アポトーシス経路–，第 13 回がん分子標的治療学会総会，2009, 6, 25-26, 徳島.
7) 長野一也，岡村賢孝，中川晋作，小泉桂一，済木育夫，角田慎一，堤　康央：抗体プロテオミクス技術による肺がんリンパ節転移関連蛋白質の探索 1，第 18 回がん転移学会，2009, 7, 23-24, 旭川.
8) 岡村賢孝，長野一也，小泉桂一，済木育夫，角田慎一，堤　康央：抗体プロテオミクス技術による肺がんリンパ節転移関連蛋白質の探索 2, 第 18 回がん転移学会, 2009, 7, 23-24, 旭川.
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* 11) 済木育夫：シンポジウム基調講演「がん転移と漢方」日本東洋医学会 第 66 回関東甲信越支部学術総会，2009, 9, 27, 宇都宮.
12) Sakurai H., Nishimura M., Shin M-S., Suzuki S., Koizumi K., and Saiki I.: TAK1-mediated Ser/Thr phosphorylation of EGFR: NF-κB-independent survival pathway in TNF-α signaling. 第 68 回日本癌学会学術総会，2009, 10, 1-3, 横浜.
13) Zhou Y., Suzuki S., Refaat A., Koizumi K., Yamaoka S., Saiki I., and Sakurai H.: HTLV-1 manipulates interferon regulatory signals by activating TAK1-IRF3 pathway and controlling negative factor IRF4. 第 68 回日本癌学会学術総会，2009, 10, 1-3, 横浜.

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* 15) Saiki I.: Anti-metastatic effect of intestinal bacterial metabolites of Ginseng saponins and their molecular mechanism of action. Symposium on “The Metabolism of Foods and Drugs by Inrestinal Microflora”. 2009, 10, 20, Seoul.

16) 櫻井宏明，西村美紀, 申 明淑，河西美保，鈴木俊輔，小泉桂一，済木育夫：TNF-α による EGFR の Ser/Thr リン酸化と細胞内局在化，第 82 回日本生化学会大会，2009, 10, 21-24, 神戸.

* 17) 済木育夫：がん転移と漢方薬，第 18 回日本脳神経外科漢方医学会，2009, 10, 31, 東京.

18) 申 明淑，西村美紀，Pattama Singhirunnusorn，鈴木俊輔, 河西美保, 小泉桂一, 済木育夫, 櫻井宏明：TNF-α による EGF 受容体のリン酸化と細胞局在化：新しい抗アポト−シス経路，第 32 回日本分子生物学会年会，2009,12, 9-12, 横浜.

19) 山崎孔輔, 合田 仁, 金山敦宏, 櫻井宏明, 井上純一郎：Two mechanistically and temporally distinct NF-κB activation pathways in IL-1 signaling，第 32 回日本分子生物学会年会， 2009, 12, 9-12, 横浜.

◇受賞

1) 中田千鶴：平成 21 年度和漢医薬学会奨励賞（2009, 8, 29）

◇その他

1) 済木育夫：漢方薬によるがん転移の抑制に関する基礎的研究，第 5 回補完医療を考える会，2009, 1, 23，大阪.
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◇共同研究

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4) 大鵬薬品工業(株)：免疫調整に関わる漢方薬のスクリーニング」，2008, 10〜
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◇非常勤講師

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3) 櫻井宏明：富山大学薬学部専門教育 講義「薬物代謝学」2009, 7, 1, 富山
4) 済木育夫：富山大学薬学部専門教育 講義「和漢医薬学入門」2009, 7, 4, 富山.
5) 小泉桂一：富山大学薬学部専門教育 講義「薬物代謝学」 2009, 7, 8, 富山
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◇研究費取得状況

1) 平成 21 年度文部科学省科学研究費補助金挑戦的萌芽研究（代表：櫻井宏明）2,200 千円「Kampo-Kinome 解析によるケミカルバイオロジーの展開」
2) 平成 21 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） 700 千円「免疫調節作用を有する和漢薬・漢方薬の科学的薬効評価と新規和漢薬製剤開発」
3) 平成 21 年度 文部科学省知的クラスター創成事業ほくりく健康増進クラスター（分担：櫻井宏明）2,600 千円，広域化プログラム 「天然薬物の遺伝子解析等に基づく標準化研究」
4) 平成 21 年度 富山大学和漢医薬学総合研究所公募型共同研究(A)特定共同研究（本学研究代表者：小泉桂一）1,600 千円「標準和漢薬ライブラリーならびに細胞パネルシステム

を用いたケモカイン受容体アンタゴニストの網羅的な探索および創薬への展開～はじめに，アレルギー疾患を標的として～」

5) 平成 21 年度独立行政法人科学技術振興機構重点地域研究開発推進プログラム（地域ニーズ即応型）（分担：小泉桂一）1,000 千円「含有アミノ酸成分を増強した脱塩海洋深層水を原料とする，アンチメタボリック機能を有する新規機能性飲料の研究開発」

6) 平成 21 年度富山県新世紀産業機構新商品・新事業創出公募委託事業（代表：小泉桂一）1,000 千円「含有アミノ酸成分を増強した海洋深層水を原料とする，新機能性外用剤の研究開発」

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卒業論文：

伊東 彩：非アルコール性脂肪肝の発症・進行における NKT 細胞の関与 ～NKT 細胞は敵か味方か～

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