病態生化学部門　Department of Pathogenic Biochemistry

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◇研究目的　Aims of the research projects

病態生化学部門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，構造の明かにされた成分あるいは化合物を用いて，種々の病態（癌，アレルギーなどの疾患）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。また，「証」といわれる病態変化を遺伝子工学的，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。

◇研究概要　Research projects

Ⅰ．癌および癌転移の抑止に関する基礎的研究

1）癌および癌転移の抑制物質の探索（伝統薬物を中心に）
2）癌の悪性化・進展モデルの確立とその分子機序の解析
3）癌ワクチンを指向した免疫遺伝療法の開発と免疫力増強物質の検索
4）同所移植性転移モデルにおける転移の臓器特異（選択）性とその機序の解析
5）細胞接着の制御に基づく浸潤・転移の抑制
6）基底膜分解酵素の転写・産生・分解レベルでの阻害物質の探索

Ⅱ．免疫抑制に関する基礎的研究

1）アレルギー性／炎症性疾患モデルの確立と有効物質（抑制／増強）の探索
2）免疫応答調節機構解明と和漢薬への応用

Ⅲ．細胞の機能制御とシグナル伝達機構の解析

1）自己分泌型運動抑制因子の単離・精製とその構造解析
2）細胞運動と細胞内調節分子の関連性の解析
3）神経ペプチドによる細胞浸潤の制御と細胞内機能分子の関与

◇原　著　original papers

1）**Takeda K., Hayakawa H., Smyth M.J., Kayagaki N., Yamaguchi N., Kakuta S., Iwakura Y., Yagita H. and Okumura K.: Involvement of tumor necrosis factor-related apoptosis-inducing ligand in surveillance of tumor metastasis by liver natural killer cells.** ***Nature Med.*****, 7: 94-100, 2001.**

Abstract: Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induces apoptosis in various tumor cells in vitro, but its physiological role in tumor surveillance remains unknown. Here, we report that TRAIL is constitutively expressed on murine natural killer (NK) cells in the liver and plays a substantial role in suppressing tumor metastasis. Freshly isolated NK cells, but not natural killer T cells or ordinary T cells, from the liver expressed cell surface TRAIL, which was responsible for spontaneous cytotoxicity against TRAIL-sensitive tumor cells in vitro along with perforin and Fas ligand (FasL). Administration of neutralizing monoclonal antibody against TRAIL significantly increased experimental liver metastases of several TRAIL-sensitive tumor cell lines. Such an anti-metastatic effect of TRAIL was not observed in NK cell-depleted mice or interferon-gamma-deficient mice, the latter of which lacked TRAIL on liver NK cells. These findings provide the first evidence for the physiological function of TRAIL as a tumor suppressor.

2）**Tatsumi T., Yamada T., Nagai H., Terasawa K., Tani T., Nunome S. and Saiki I.: A Kampo medicine: Byakko-ka-ninjin-to (Bai-Hu-Jia-Ren-Sheng-Tang) inhibits IgE-mediated triphasic skin reaction in mice: the role of its constituents in the expression of the efficacy.** ***Biol. Pharm. Bull.*****, 24: 284-290, 2001.**

Abstract: We have demonstrated that oral administration of a Kampo formulation, Byakko-ka-ninjin-to (Bai-Hu-Jia-Ren-Sheng-Tang), inhibited IgE-mediated triphasic skin reaction, including immediate phase response (IPR), late phase response (LPR) and very late phase response (vLPR), in passively sensitized mice with anti-DNP IgE antibody. Variant formulations of Byakko-ka-ninjin-to without Gypsum Fibrosum (Sekko), Glycyrrhizae Radix (Kanzo) or Oryzae Semen (Kobei) attenuated the inhibitory effect as compared with that of Byakko-ka-ninjin-to. The decreased effect of Byakko-ka-ninjin-to without Kanzo was restored by the addition of Kanzo to the variant formulations before oral administration, while the decreased effect of Byakko-ka-ninjin-to without Sekko could not be recovered by the addition of Sekko. Comparison of HPLC profiles of variant formulations without one crude drug with that of original Byakko-ka-ninjin-to revealed that some peaks could be detected only when five constituent crude drugs were simultaneously present during the preparation of Byakko-ka-ninjin-to formulation. Since elimination of Sekko from the Byakko-ka-ninjin-to constituents attenuated the efficacy although it did not show any activity per se, mutual interaction of Sekko with other constituents during the preparation may result in the production of new components. These findings suggest that the effect of Byakko-ka-ninjin-to formulation on cutaneous inflammatory disease can differ from the sum of the effect of the individual constituents.

3）**Sawada S., Murakami K., Yamaura T., Sakamoto T., Ogawa K., Tsukada K. and Saiki I.: Intrahepatic metastasis by orthotopic implantation of a fragment of murine hepatoma and its related molecules.** ***Tumor Biol.*****,22: 154-161, 2001.**

Abstract: Intrahepatic metastasis is a major modality in the recurrence of hepatoma. Establishment of the intrahepatic metastasis model would be useful for evaluating new anticancer therapies and analyzing the molecular mechanisms of tumor metastasis. Orthotopic implantation of a fragment of CBO140C12 hepatoma into the liver resulted in the formation of a solitary tumor nodule and its intrahepatic metastasis. In contrast, implantation of ADras3 cancer cells did not show any metastasis on day 21. CBO140C12 cells showed enhancement of the invasive, adhesive and migratory capabilities, as compared with ADras3 cells. Furthermore, mRNA expression and gelatinolytic activity of MMP-9 were detected in CBO140C12 cells, and the expression of mRNA for MT1-MMP in CBO140C12

cells was greater than that in ADras3 cells. Thus, intrahepatic metastasis of CBO140C12 tumor might be involved in the enhancement of the invasiveness of tumor cells via marked expression of MMP-9 and MT1-MMP. Copyright 2001 S. Karger AG, Basel

4) **Mitani N., Murakami K., Yamaura T., Ikeda T. and Saiki I.: Inhibitory effect of berberine on the mediastinal lymph node metastasis produced by orthotopic implantation of Lewis lung carcinoma.** ***Cancer Lett.*****, 165: 35-42, 2001.**

Abstract: We examined the effect of berberine, a major component with anti-fungal properties contained in Coptidis Rhizoma and Phellodendri Cortex, on the lymph node metastasis of murine lung cancer. Oral administration of berberine for 14 days significantly inhibited the spontaneous mediastinal lymph node metastasis produced by orthotopic implantation of Lewis lung carcinoma (LLC) into the lung parenchyma in a dose-dependent manner, but did not affect the tumor growth at the implantation site of the lung. Combined treatment with berberine and an anti-cancer drug, CPT-11, resulted in a marked inhibition of tumor growth at the implantation site and of lymphatic metastasis, as compared with either treatment alone. Anti-activator protein-1 (anti-AP-1) transcriptional activity of non-cytotoxic concentrations of berberine caused the inhibition of the invasiveness of LLC cells through the repression of expression of urokinase-type plasminogen activator (u-PA).

5) **Nagakawa O., Ogasawara M., Murata J., Fuse H. and Saiki I.: Effect of prostatic neuropeptides on migration of prostate cancer cell lines.** ***Int. J. Urology*****, 8: 65-70, 2001.**

Abstract: BACKGROUND: A previous study by the same authors demonstrated that among various neuropeptides in the prostate, calcitonin gene-related peptide (CGRP) and gastrin-releasing peptide (GRP) increased the invasive capacity of PC-3 prostate cancer cells through enhancement of cell motility, while substance P (SP) inhibited the invasiveness through suppression of motile response. METHODS: The effect of 10 kinds of neuropeptides were investigated, including CGRP, GRP, SP, neuropeptide Y (NPY), vasoactive intestinal polypeptide (VIP), calcitonin (CT), leucine-enkephalin (L-ENK), methionine-enkephalin (M-ENK), glucagon and parathyroid hormone-related protein (PTH-rP), on the invasion of DU-145 prostate cancer cells through a reconstituted basement membrane (Matrigel) and the haptotactic migration of DU-145, TSU-pr1 and LNCaP prostate cancer cells using a Transwell cell culture chamber assay. RESULTS: It was found that GRP, CGRP and PTH-rP increased the invasive capacity of tumor cells. In contrast, SP, VIP, CT, L-ENK, M-ENK, NPY and glucagon had no significant effect. These three neuropeptides also increased the haptotactic migration of tumor cells to fibronectin. In addition VIP, CGRP and GRP increased the haptotactic migration of LNCaP prostate cancer cells and GRP and PTH-rP increased the migration of TSU-pr1 cells. CONCLUSION: The results indicated that some prostatic neuropeptides increased the invasive potential of prostate cancer cells partially through enhancement of cell motility.

6) **Ali S. M., Banskota A.H., Tezuka Y., Saiki I. and Kadota S.: Antiproliferative activity of diarylheptanoids from the seeds of Alpinia blepharocalyx.** ***Biol. Pharm. Bull.*****, 24: 525-528, 2001.**

7) **Hayakawa H., Takeda K., Yagita H., Kaer Luc Van, Saiki I. and Okumura K.: Differential regulation of Th1 and Th2 functions of NKT cells by CD28 and CD40 costimulatory pathways.** ***J. Immunol*****, 166: 6012-6018, 2001.**

Abstract: Valpha14 NKT cells produce large amounts of IFN-gamma and IL-4 upon recognition of their specific ligand alpha-galactosylceramide (alpha-GalCer) by their invariant TCR. We show here that NKT cells constitutively express CD28, and that blockade of CD28-CD80/CD86 interactions by anti-CD80 and anti-CD86 mAbs inhibits the alpha-GalCer-induced IFN-gamma and IL-4 production by splenic Valpha14 NKT cells. On the other, the blockade

of CD40-CD154 interactions by anti-CD154 mAb inhibited alpha-GalCer-induced IFN-gamma production, but not IL-4 production. Consistent with these findings, CD28-deficient mice showed impaired IFN-gamma and IL-4 production in response to alpha-GalCer stimulation in vitro and in vivo, whereas production of IFN-gamma but not IL-4 was impaired in CD40-deficient mice. Moreover, alpha-GalCer-induced Th1-type responses, represented by enhanced cytotoxic activity of splenic or hepatic mononuclear cells and antimetastatic effect, were impaired in both CD28-deficient mice and CD40-deficient mice. In contrast, alpha-GalCer-induced Th2-type responses, represented by serum IgE and IgG1 elevation, were impaired in the absence of the CD28 costimulatory pathway but not in the absence of the CD40 costimulatory pathway. These results indicate that CD28-CD80/CD86 and CD40-CD154 costimulatory pathways differentially contribute to the regulation of Th1 and Th2 functions of Valpha14 NKT cells in vivo.

8) **Sawada S., Murakami K., Murata J., Tsukada K. and Saiki I.: Accumulation of extracellular matrix in the liver induces high metastatic potential of hepatocellular carcinoma to the lung. *Int. J. Oncol.*, 19: 65-70, 2001.**

Abstract: The liver undergoes pathogenic changes such as hepatitis, fibrosis and cirrhosis under continuous stimulation by hepatitis virus or alcohol intake, leading to the development of hepatocellular carcinoma. The metastatic potential of HCC can be positively or negatively regulated by pathogenic alterations of liver. We investigated whether the metastatic abilities of HCC after orthotopic implantation can be influenced in the fibrotic liver by continuous injection of carbon-tetrachloride (CCl4) for seven weeks. The incidence of lung metastasis after orthotopic implantation of murine HCC (CBO140C12) fragments into CCl4-treated livers was higher than into normal livers. The amount of mRNA for MMP-2 increased in the CCl4-treated livers as compared with normal livers, and CBO140C12 cells constitutively expressed mRNA for MT1-MMP in early amplification cycles by RT-PCR. In addition, we found that the culture of CBO140C12 cells on the substrates pre-coated with ECM components increased the expression of MMP-2 mRNA. Thus, enhanced incidence of lung metastasis in the fibrotic liver might be partly due to: i) over-expression of MMP-2 in the fibrotic liver in cooperation with MT1-MMP on the CBO140C12 cell surface, ii) over-expression of MMP-2 in CBO140C12 cells, possibly mediated by the interaction of tumor cells (surface integrins) with accumulated ECM in the fibrotic liver. This is the first report showing that increase of MMP-2 in the fibrotic liver can influence the metastatic potential of HCC cells.

9) **Wu W., Murata J., Hayashi K., Yamaura T., Mitani N. and Saiki I.: Social isolation stress impairs the resistance of mice to experimental liver metastasis of murine colon 26-L5 carcinoma cells. *Biol. Pharm. Bull.*, 24, 772-776, 2001.**

Abstract: Our previous study has demonstrated that the exposure of male BALB/c mice to social isolation stress caused a suppressed immune response and enhanced liver metastasis of colon 26-L5 carcinoma cells. To more precisely understand the influence of psychosocial factors on the metastatic process, here we have investigated the effect of social isolation stress on the vulnerability of the host to develop liver metastasis of colon 26-L5 cells, including the time span and incidence of metastatic formation, survival time and chemotherapy response. Isolation stress decreased the time period required for the metastasis formation relative to that in controls. On day 7 after the tumor injection, the 75% incidence of tumor metastasis in the stressed mice was 5 times the 15% incidence in the unstressed mice. When exposed to the challenge of lower cell numbers (0.025, 0.05, 0.1 x 10(4)/mouse) of colon 26-L5 cells, mice subjected to isolation stress developed an elevated incidence of metastasis (33.3, 66.6, and 100%, respectively) as compared with the controls (0, 33.3 and 50%, respectively). The survival time following the tumor inoculation was also shorter in the stressed mice (21.83 +/- 1.59d) than in the control mice (24.08 +/- 1.68 d). Furthermore, the response of liver metastasis to chemotherapy consisting of 2 mg/kg cisplatin (CDDP) was worse in the stressed mice than that in unstressed mice. These findings suggested that social isolation stress could

significantly impair the resistance of mice to the development of metastasis.

10) Hayakawa H., Takeda K., Yagita H., Kakuta S., Iwakura Y., Kaer Luc Van, Saiki I. and Okumura K.: Critical contribution of IFN-γ and NK cells, but not perforin-mediated cytotoxicity, to the anti-metastatic activities of α-galactosyl ceramide. *Eur. J. Immunol*, 31: 1720-1727, 2001.

Abstract: The glycolipid alpha -galactosylceramide (alpha -GalCer), which is presented by CD1d and specifically activates Valpha 14 NKT cells, exerts a potent anti-metastatic effect when administered in vivo. In this study, we demonstrated that alpha -GalCer administration led to rapid elimination of NKT cells by apoptosis in the liver and spleen, after they produced IFN-gamma and IL-4. In contrast, a more prolonged secretion of IFN-gamma was observed by liver and splenic NK cells after alpha -GalCer administration. Cytotoxic activity of liver mononuclear cells was not augmented 3h after alpha -GalCer administration, but was increased at 24 h when NKT cells were mostly depleted. The alpha -GalCer-induced cytotoxic activity was abolished in IFN-gamma -deficient and NK cell-depleted mice as well as CD1-deficient mice, suggesting that the alpha -Galcer-induced cytotoxicity was mainly mediated by IFN-gamma -activated NK cells. While the alpha -GalCer-induced cytotoxicity in vitro was mostly perforin dependent, anti-metastatic effect of alpha -GalCer was impaired in NK cell-depleted or IFN-gamma -deficient mice but not in perforin-deficient mice. Collectively, these results indicated that the anti-metastatic effect of alpha -GalCer is mainly mediated by NK cells, which are activated secondarily by IFN-gamma produced by alpha -GalCer-activated NKT cells, in a perforin-independent manner.

11) Zhang X., Xu Q. and Saiki I.: Quercetin inhibits the invasion and motility of murine melanoma B16-BL6 cells through inducing apoptosis via decreasing Bcl-2 expression. *Clin. Exp. Metastasis*, 18: 415-421, 2001.

Abstract: Quercetin has been known to have anti-tumor and anti-oxidation activities. In the present study, we have investigated its in vitro anti-metastatic activity. Quercetin inhibited the invasion and mobility of murine melanoma B16-BL6 cells in a dose-dependent manner but did not affect their adhesion to either laminin, fibronectin, or type VI collagen. Moreover, quercetin significantly inhibited the proliferation of B16-BL6 cells only in the case of time incubation longer than 48 h. Quercetin dose-dependently decreased the cell rates in S and G2-M phases of cell cycle. The effect of quercetin to cause a remarkable apoptosis of B16-BL6 cells was also demonstrated by flow cytometric assay as well as DNA fragmentation with a typical 180-bp ladder band in agarose electrophoresis and a quantitative analysis. Furthermore, quercetin markedly inhibited the expression of anti-apoptotic protein Bcl-2 but hardly influenced Bcl-XL. These results suggest that the inhibition of quercetin on invasiveness and migration of B16-BL6 cells are closely associated with the arrest of cell cycle as well as the induction of apoptosis by decreasing the Bcl-2 expression.

12) Zang H.W., Sasamura T., Iida Y., Nojima H., Murata J., Saiki I. and Kuraishi Y.: Algogenic effects of the extract of the tumor mass isolated from mice with orthotopic melanoma inoculation. *Pain Res.*, 16: 43-49, 2001.

13) Tahara E., Wu W., Satoh T., Yamada T., Kurosaki I., Nagai H., Terasawa K. and Saiki I.: psychosocial stress enhances IgE-mediated triphasic cutaneous reaction in mice: antagonism by Yokukan-san (a Kampo medicine) and diazepam. *Allergology International*, 50: 211-222, 2001.

Abstract: We investigated the influence of social isolation stress on IgE-mediated triphasic cutaneous reactions after DNFB challenge in male BALB/c mice passively sensitized with anti-DNP IgE antibody, and examined the effect

of Yokukan-san (a Kampo medicine with anti-psychotic action) and a reference drug, diazepam, on stress-enhanced cutaneous reaction. In response to the challenge with 0.01%, 0.025% and 0.05% DNFB, triphasic skin reactions, including immediate phase response (IPR), late phase response (LPR) and very late phase response (vLPR) at 1 h, 24 h and 8 days after the antigen challenge, respectively, were increased in socially isolated mice in comparison with group-housed mice. Oral administration of Yokukan-san attenuated the isolation stress-exacerbated triphasic skin reactions in a dose-dependent manner, while it had almost no effect on the cutaneous reactions in the unstressed group-housed mice. On the other hand, the i.p. administration of diazepam, a classic benzodiazepine receptor agonist, suppressed the enhanced IPR and LPR in socially isolated mice, but surprisingly stimulated vLPR in both stressed and unstressed mice, differing from the efficacy of Yokukan-san. Moreover, the elevated locomotor activity in socially isolated mice was reduced by Yokukan-san and diazepam, while the isolation stress-induced aggressive behavior was normalized only by diazepam, not by Yokukan-san. The present study indicated that IgE-mediated triphasic cutaneous reaction was exacerbated by social isolation stress, and suggests that Yokukan-san and diazepam antagonizes isolation stress-provoked cutaneous functions in part through their sedative action on social isolation stress.

14) Tran Q.L., Tezuka Y., Banskota A.H., Tran Q. K., Saiki I. and Kadota S.: New spirostanol steroids and steroidal saponins from roots and rhizomes of Dracaena angustifolia and their antiproliferative activity. *J. Nat. Prod.*, 64: 1127-1132, 2001.

15) Ichiki K., Mitani N., Doki Y., Hara H., Misaki T. and Saiki I.: Regulation of activator protein-1 activity in the mediastinal lymph node metastasis of lung cancer. *Clin. Exp. Metastasis*, 18, 539-545, 2001.

Abstract: Orthotopic implantation of a metastatic cell line of Lewis lung carcinoma (LLC-MLN), which was isolated by an in vivo selection method, resulted in greater metastatic growth in mediastinal lymph nodes as compared with that of the original LLC cells. LLC-MLN cells also had increased invasive ability and activator protein-1 (AP-1) transcriptional activity as compared with the original LLC cells. This is well consistent with the previously reported finding that overexpression of AP-1 is associated with lymphatic metastasis in lung cancer patients. Oral administration of curcumin, which downregulates AP-1 transcription, significantly inhibited the mediastinal lymph node metastasis of orthotopically implanted LLC cells in a dose-dependent manner, but did not affect the tumor growth at the implantation site. Combined treatment with curcumin and an anti-cancer drug, cis-diamine-dichloroplatinum (CDDP), resulted in a marked inhibition of tumor growth at the implanted site and of lymphatic metastasis, and a significant prolongation of the survival time. The downregulation of transcriptional AP-1 activity by curcumin as seen in the dual luciferase assay caused inhibition of LLC cell invasion through the repression of expression of the mRNAs for urokinase-type plasminogen activator (u-PA) and its receptor (u-PAR). Inhibition of AP-1 transcriptional activity may offer improved therapeutic efficacy for lung cancer patients with lymphatic metastasis.

16) Ohkoshi M., Hikiji H. and Saiki I.: Inhibition of HT-1080 Human fibrosarcoma cell invasion into Matrigel/fibronectin-coated filters by serine protease inhibitor Foy-305. *Biotherapy*, 14: 1117-1120, 2001.

Abstrac: It is well known that the activites of cell surface serine proteases are especially enhanced in malignant tumors. Using HT human fibrosarcoma cells, we found that a potent serine protease inhibitor, FOY-305, inhibited tumor cell invasion into Matrigel in a dose dependent manner. The filters thus prepared were designated Matrigel/fibronectin -coated filters. The results indicated an imlortant rolefor serine protease inhibitor in invasion of human malignant tumors and suggest a possible application for FOY-305 for the prevention of human fibroblast sarcomainvasion into closed tussues. In this same connection, doxorubicin was used in a contgrol experiment.

17) **Takizawa T., Watanabe C., Saiki I., Wada Y., Tohma T. and Nagai H.: Effect of a new anti-allergic drug, VUF-K-8788, on infiltration of lung parenchyma by eosinophils in guinea pigs and eosinophil-adhesion to human umbilical veinendothelial cells (HUVEC). *Biol. Pharm. Bull.*, 24: 1127- 1132, 2001.**

Abstract: Airway inflammation and reversible airway obstruction are hallmarks of bronchial asthma. In this study, we investigated the effects of a new antiallergic drug, 7-[3-[4-(2-quinolinylmethyl)-1-piperazinyl]-propoxy]-2,3-dihydro-4H-1,4-benzothiazin-3-one (VUF-K-8788), on histopathological changes in lung parenchyma of guinea pigs during late-phase asthmatic reaction (LAR), and on eosinophil-adhesion to human umbilical vein endothelial cells (HUVEC). Repeated exposure to ovalbumin of sensitized guinea pigs induced inflammatory phenomena such as hyperplasia of airway epithelial cells, perivascular edema and infiltration of lung parenchyma by eosinophils. VUF-K-8788 inhibited these histopathological phenomena at 10 mg/kg p.o. Moreover, the eosinophil-adherence to HUVEC was inhibited by VUF-K-8788 at the concentration of 10-30 microM. In conclusion, this inhibitory effect of VUF-K-8788 on eosinophil-adherence might contribute to the prevention of LAR and infiltration by eosinophils in the experimental asthmatic model in guinea pigs.

◇総　説　Review Paper

1) 田澤賢次，小池　潤，並川宏英，八塚美樹，安田智美，大西康晴，大上英夫，斎藤智裕，済木育夫：肝転移を抑制する漢方方剤における活性酸素消去能からみた特徴，漢方医学，25 : 15–19, 2001.
2) 一木克之，澤田成朗，済木育夫：特集「21世紀の癌研究」，癌の転移研究－ 実験動物による転移病態モデル－，Cancer Frontier 2001, 3 : 355–40, 2001.
3) 巽　武司，寺澤捷年，済木育夫：マウス IgE 介在性三相性皮膚反応に及ぼす強力ミノファーゲンシーの効果，Minophagen Medical Review, 46 : 3535–356, 2001.

◇学会報告　Scientific presentation (*: 特別講演，シンポジウム，ワークショップ等)

1) Tsuchiya Y., Sawada S., Tsukada K. and Saiki I.: Molecular mechanism of intrahepatic metastases of hepatocellular carcinoma. Molecular Biology and New Therapeutic Straegies: Cancer Research in the 21st Century. 5th Joint Conference of the American Association for Cancer Research and the Japanese Cancer Association. 2001, 02. 12-16, Hawaii.
2) Ali M.S., Banskota A.H., Tezuka Y., Saiki I. and Kadota S.: Antiproliferative activity of diarylheptanoids from the seed of *Alpinia blepharocalyx*. 日本薬学会第121年会総会，2001, 03. 28–30, 札幌.
3) 土屋康紀，澤田成朗，塚田一博，済木育夫：肝癌肝内転移の分子生物学的解析，第101回日本外科学会総会，2001. 04. 11–13, 仙台.
4) 村石康博，三谷宜靖，布施秀樹，済木育夫：マウス腎細胞癌実験的肺転移モデルにおけるインターフェロン αA/D と十全大補湯の転移抑制効果，第19回泌尿器科漢方研究会，2001, 04. 15, 神戸.
5) 村石康博，三谷宜靖，布施秀樹，村田　純，済木育夫：マウス腎癌細胞の肺転移に及ぼす Matrix metalloproteinase inhibitor (ONO-4817) の効果，第89回日本泌尿器科学会総会，2001, 04. 14–17, 神戸.
6) 永川　修，藤内靖喜，三谷宜靖，村田　純，布施秀樹，済木育夫：ヒト前立腺癌細胞の浸潤能及び増殖能に及ぼす各種 chromogranin A fragment の影響，第89回日本泌尿器科学会総会，2001, 04. 14–17, 神戸.
*7) 済木育夫：シンポジウム「MMPs およびそれら阻害剤研究の基礎と臨床応用」，マトリックスメタロプロテアーゼ阻害剤ONO-4817の癌転移及び血管新生の抑制，第48回マトリックス研究会，2001, 4. 16-17, 富山.
8) 土屋康紀，澤田成朗，塚田一博，済木育夫：RGD 合成擬似ペプチド (FC-336) は肝癌肝内転移を抑制

する，第14回富山癌治療懇話会，2001. 05. 18，富山.

9）村石康博，布施秀樹，三谷宜靖，済木育夫：マウス腎細胞癌実験的肺転移モデルにおけるインターフェロン αA/D と十全大補湯の転移抑制効果，第14回富山癌治療懇話会，2001. 05. 18，富山.

*10）済木育夫：シンポジウム「アレルギー疾患と漢方療法」，精神的ストレスによるアレルギー疾患の増悪と漢方薬による改善，第18回日本小児東洋医学会，2001，05. 19，仙台.

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Pongpun Siripong (Natural Product Research Section, Research Division, National Cancer Institute in Thailand, 2001. 09. 03～2001. 10. 31)

Hamdy T. Taie (Animal Nutrition Department, Faculty of Agriculture, Menufiya University, Egypt 2001. 10. 01～2001. 10. 31)

研究機関研究員：早川芳弘（2001. 04. 1～2001，11.30）

◇人事移動

村田　純：秋田県立大学生物資源科学部応用生物科学科の助教授に転出

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早川芳弘：富山医科薬科大学　研究機関研究員に任用

◇学位（修士，博士）取得者 Academic degrees and theses

卒業論文：

小澤陽子：種々の癌細胞の運動性に及ぼすメラノーマ由来運動阻害因子の影響

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修士論文：

黒崎いずみ：アレルギー性炎症における好酸球浸潤メカニズムの解析

三谷宜靖：肺癌同所性移植による縦隔リンパ節転移に及ぼすベルベリンの抑制効果とその作用機序の解析

博士論文：

早川芳弘：NKT 細胞の活性化機序及び免疫調節細胞としての機能解析

呉　文娟：Study on the effect of social isolation stress on liver metastasis of colon 26-L5 carcinoma cells and the involved mechanism in male BALB/c mice

土岐善紀：Mediastinal lymph node metastasis model by orthotopic intrapulmonary implantation of Lewis lung carcinoma cells in mice.　医学博士（富山医科薬科大学）

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長谷川秀夫：人参サポニンの腸内細菌代謝物による抗腫瘍効果の発現及びその脂肪酸抱合による効果の増強　薬学博士（富山医科薬科大学）

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