病態生化学部門

教授　済木育夫（医学博士）
助教授　中島松一（医学博士）
助手　村田純（理学博士）
技官　林和子

◇研究目的

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

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

◇著　書

1）村田．純，済木育夫：基礎編　－ヒト癌細胞の転移機構の解析－　3．細胞外マトリックスと分解，4）細胞運動性因子，「癌転移　－転移の分子メカニズムと臨床展望－」，渡邊寛，清木元治／編集，医薬ジャーナル社，149–162，1998.

2）田澤賢次，大西康晴，済木育夫：臨床編　－臨床における癌転移の分析－　3．胃，2）肝転移，「癌転移　－転移の分子メカニズムと臨床展望－」，渡邊　寛，清木元治／編集，医薬ジャーナル社，235–246，1998.

3）村上孝司，済木育夫：転移の治療実験，実験医学増刊号 Vol 16 (16)，特集「癌転移のメカニズムと癌治療　その新しいチャレンジ」，入村達郎，中島元夫／編集，羊土社，162–167，1998.

◇原　著

1）**Wakabayashi C., Hasegawa H., Murata J. and Saiki I.: The expression of *in vivo* anti-metastatic effect of Ginseng protopanaxatriol saponin is mediated by their intestinal bacterial metabolite after oral administration. J. Traditional Med.. 14 : 180–185, 1998.**

Abstract: The present study demonstrated *in vivo* and *in vitro* anti-metastatic activities of a major intestinal bacterial metabolite M4 formed from protopanaxatriol saponins of Ginseng (the root of Panax ginseng C.A.MEYER) in comparison with ginsenoside-Re and Rg1. Ginsenosides and M4 at the dose of 500 μg/mouse showed marked inhibiton of lung metastasis of B16-BL6 melanoma cells when they were administred 5 times orally. In contrast, three consecutive i.v. administrations of M4 after tumor inoculation resulted in a significant inhibition of lung metastasis, whereas Re and Rg1 did not show any inhibitroy effect. On the other hand, these ginsenosides hardly inhibited the invasion, migration and the growth of murine B16-BL6 melanoma and human HT-1080 fibrosarcoma cells *in vitro*, whereas the intestinal bacterial metabolite M4 showed inhibitory effect dose-dependently. These findings clearly indicated that the induction of *in vivo* anti-metastatic effect by oral administration of ginsenosides may be primarily mediated by their metabolic component M4.

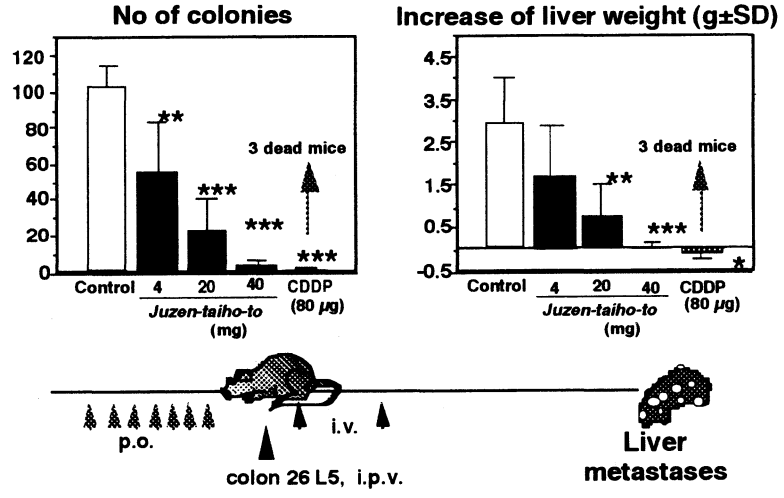
2）**Fujii H., Nishikawa N., Komazawa H., Suzuki M., Kojima M., Itoh I., Obata A., Ayukawa K., Azuma I and Saiki I.: A new pseudo-peptide of Arg-Gly-Asp (RGD) with inhibitory effect on tumor metastasis and enzymatic degradation of extracellular matrix. Clin. Exp. Metastasis, 16 : 94–104, 1998.**

Abstract: A series of pseudo-peptide analogs of the Arg-Gly-Asp (RGD) sequence of fibronectin have been synthesized, and their anti-metastatic effects in mice and inhibitory effects on tumor cell invasion *in vitro* have been examined. The partially modified retro pseudo-peptide of RGD, Rrev-COCH2CO-D (FC-63), was more effective in inhibiting tumor metastasis than the original RGDS peptide. Replacement of the malonyl moiety of FC-63 with a carboxy-ethylene linkage (Rrev-COCH$_2$ CH$_2$-D, FC-303) achieved more potent inhibi-

tion of lung metastasis of melanoma cells than FC-63. Among the analogs, FC-336, a p-xylylendiamine derivative having two FC-303 moieties, showed the most potent inhibitory effect on experimental lung metastasis produced by i.v. co-injection with B16-BL6 melanoma or colon 26 M3.1 cells in a dose-dependent manner. Multiple administrations of FC-336 after tumor inoculation also showed efficient therapeutic potency against spontaneous lung metastasis of B16-BL6 melanoma in mice. Furthermore, FC-336 effectively inhibited the invasion, migration and adhesion of tumor cells *in vitro*, but its inhibitory effects were not more than those of RGDS peptide. Zymography analysis revealed that FC-336 inhibited the degradation of gelatin substrate by matrix metalloproteinases (MMPs) produced by tumor cells, while the RGDS peptide did not affect the enzymatic degradation. These findings indicate that the pseudo-peptides of the RGD sequence, possessing the inhibitory property of the degradation by MMPs differently from original RGD-containing peptides, may be advantageous and useful in preventing tumor metastasis.

3) **Ohnishi Y., Fujii H., Hayakawa Y., Sakukawa R., Yamaura T., Nunome S., Komatsu Y. and Saiki I: Oral administration of a Kampo medicine Juzen-taiho-to inhibits liver metastasis of colon 26-L5 carcinoma cells. Jpn.J. Cancer Res., 89 : 206–213, 1998.**

Abstract : We have investigated the inhibitory effect of oral administration of *Juzen-taiho-to*, a Kampo Japanese herbal medicine, on liver metastasis by the inoculation of a liver-metastatic variant (L5) of murine colon 26 carcinoma cells into the portal vein. Oral administration of *Juzen-taiho-to* for 7 days before tumor inoculation resulted in dose-dependent inhibition of liver tumor colonies and significant enhancement of survival rate as compared with the untreated control, without side effects.



We also found that liver metastasis of L5 cells was enhanced in BALB/c mice pretreated with anti-asialo GM1 serum or 2-chloroadenosine, and in BALB/c nu/nu mice, compared to normal mice. This indicates that NK cells, macrophages, and T- cells play important roles in the prevention of metastasis of tumor cells. *Juzen-taiho-to* significantly inhibited the experi-

mental liver metastasis of colon 26-L5 cells in mice pretreated with anti-asialo GM1 serum and untreated normal mice, whereas it did not inhibit metastasis in 2-chloroadenosine-pretreated mice or T cell-deficient nude mice. Oral administration of *Juzen-taiho-to* activated peritoneal exudate macrophages (PEM) to become cytostatic against the tumor cells. These results show that oral administration of *Juzen-taiho-to* inhibited liver metastasis of colon 26-L5 cells, possibly through a mechanism mediated by the activation of macrophages and/or T-cells in the host immune system. Thus, *Juzen-taiho-to* may be efficacious for the prevention of cancer metastasis.

4) **Xu Q., Jiang J., Cao J., Wu F., Fujii H. and Saiki I.: LFA-1/ICAM-1 interaction is essentially involved in the pathogenesis of delayed-type hypersensitivity-induced liver injury to picryl chloride. Life Science, 62 : 1281–1292, 1998.**

Abstract : The kinetics of lymphocyte function associated antigen 1 (LFA-1) expression on spleen cells (SPC) and liver non-parenchymal cells (NPC), and intercellular adhesion molecule 1 (ICAM-1) expression on hepatocytes (HC) was examined in acute liver injury mice induced by a DTH reaction to picryl chloride (PCl). The peak expression of LFA-1 on SPC was seen at 6 hr after eliciting liver injury, and then that of LFA-1 on NPC and ICAM-1 on HC appeared at 12 hr. Thereafter, the serum ALT elevation reached to a peak at 18 hr. A splenectomy before the PCl elicitation significantly reduced the ALT elevation. Both SPC and NPC from liver injury mice induced a remarkable release of ALT from HC *in vitro*, in parallel with their LFA-1 expression. The pre-treatment of NPC or SPC with anti-LFA-1 mAb, irrespective of the presence of complement, completely blocked the ALT release. Also, when HC was prebound with anti-ICAM-1 mAb neither NPC nor SPC showed a cytotoxicity against the HC. Furthermore, the treatment of NPC with either anti-Thy1.2 or anti-CD4 mAb in the presence but not absence of complement, showed a complete abolishment of ALT release. Anti-CD8 mAb plus complement also tended to inhibit ALT release. The twofold increase in $CD4^+$ $LFA\text{-}1^+$ and mild increase in $CD8^+$ $LFA\text{-}1^+$ populations were also confirmed in NPC at 12 hr. These results suggest that PCl elicitation in liver may trigger an increased expression of LFA-1 on SPC and NPC and ICAM-1 on HC. LFA-1/ICAM-1 interaction between liver-infiltrating NPC, mainly including $CD4^+$ and $CD8^+$ T cells, and HC may be an essential step for the hepatocyte damage in PCl-DTH liver injury.

5) **Watanabe C., Hase K., Oku T., Koizumi F., Kadota S., Nagai H., Namba T. and Saiki I.: Effect of spikelets of *Miscanthus sinensis* on IgE-mediated biphasic cutanious reaction in mice. Planta Medica., 64 : 12–17, 1998.**

Abstract : The effect of spikelets of *Miscanthus sinensis* Andersson (*M. sinensis*) on IgE-mediated biphasic cutaneous reactions was investigated in BALB/c mice. Mice were passively sensitized by an intravenous (i.v.) injection of monoclonal antidinitrophenol IgE antibody (anti-DNP IgE mAb), or actively by an intraperitoneal (i.p.) injection of DNP-derivatized ovalbumin (DNP-OVA) plus alumin-ium hydroxide gel (Alum) as an adjuvant. Skin reac-

tions were elicited by and epicutaneous challenge of dinitrofluorobenzene (DNFB) and occurred biphasically with peak responses at 1 and 24 h in both animal models. The administrations of a nondialysable water extract of M. sinensis within 2 h before or after DNFB challenge via oral or i.p. route significantly inhibited the biphasic cutaneous reactions in passively and actively sensitized mice. The inhibitory effect was much stronger than those of a glucocorticoid, prednisolone, and histamine release inhibitor, amlexanox, as positive controls. The active component(s) was predominantly located in the glycoprotein fraction by gel chromatography. In the ears of DNFB-challenged mice, this fraction suppressed the accumulation of inflammatory cells, including mast cells and neutrophils/ macrophages. In addition, the biphasic ear swelling was also improved by an administration of the glycoprotein fraction 24 h before active sensitization. These findings that the glycoprotein fraction of M. sinensis was able to inhibit not only the IgE-mediated allergic inflammatory reaction but also the IgE formation. Thus, this fraction may be a useful antiallergic therapy.

6) **Fujii H., Inobe M., Hayakawa Y., Kimura F., Murakami M., Ohnishi Y., Azuma I., Ueda T. and Saiki I.: Vaccination with B7-1$^+$ tumor and anti-adhesion therapy with RGD pseudo-peptide (FC-336) efficiently induce anti-metastatic effect. Clin. Exp. Metastasis, 16 : 141–148, 1998.**

Abstract : We have previously shown that expression of costimulatory ligand B7-1 on MHC class I$^+$ tumor cells (B16-BL6 melanoma) resulted in marked reduction of lung metastasis caused by i.v. injection into immunocompetent syngeneic mice and led to induction of immunity to the challenge by the parental B7-1 negative tumor. Here we investigated the effectiveness of irradiated B7-1 transfected tumor cells as a vaccine on established tumor metastasis and whether or not expression of B7-1 molecule on tumor cells in combination with administration of anti-adhesion peptide FC-336 can augment the antimetastatic efficacy. Immunization with X-irradiated B7-1 transfectants after i.v. injection of B7-1$^-$ parental B16-BL6 cells was effective in inhibiting lung metastasis. We also found that vaccination with irradiated B7-1 transfectants after excision of primary tumor on day 21 resulted in significant inhibition of spontaneous lung metastasis by intrafootpad injection of viable B16-BL6 melanoma, as compared with the untreated control. However, immunizing twice with mock transfectants did not affect inhibition of spontaneous lung metastasis of wild-type tumors. On the other hand, multiple administration of a pseudo-peptide of RGD sequence (FC-336) after tumor inoculation inhibited spontaneous lung metastasis through the interference of tumor invasion, migration and adhesion. Combined treatment of B7-1 transfected tumor vaccine and anti-adhesive therapy with FC-336 led to the augmentation of the antimetastatic effect in both experimental and spontaneous metastasis models, as compared with either treatment alone. B7-1- and FC-336-mediated inhibition of tumor metastasis may be mediated by different mechanisms at various steps of metastasis, based on the regulation (promotion or inhibition) of tumor interaction with host cells and components.

7) **Ohnishi Y., Fujii H., Sakamoto T., Fujimaki M., Kojima M. and Saiki I: A new pseudo- peptide analogue of Arg-Gly-Asp (RGD) sequence inhibits liver metastasis of colon 26-L5 carcinoma cells. Cancer Letts., 124 : 157–163, 1998.**

Abstract : We have investigated the effect of the pseudo-peptide analogue (FC-336) of the Arg-Gly-Asp (RGD) sequence in a liver metastasis model by the inoculation of a highly liver- metastatic cell line of colon 26 carcinoma (colon 26-L5) into the portal vein of BALB/c mice. The intraportal injection of colon 26-L5 cells with FC-336 resulted in a marked suppression of liver metastatic colonies in a dose-dependent manner and it reduced the liver weights to a normal level. However, the co-injection of tumor cells with a high dose of RGDS tetrapeptide led to a slight inhibition of liver metastasis. The multiple i.v. administration of FC-336 after tumor inoculation as well as the injection of FC-336 with tumor cells caused significant inhibition of experimental metastasis in the liver. The multiple i.v. administration of the RGDS peptide did not show any inhibitory activity. FC-336 significantly enhanced the survival rate of mice compared with untreated controls when injected intraportally with tumor cells or when intravenously administered after tumor inoculation. Zymography analysis showed that FC-336 inhibited the degradation of gelatin substrate by matrix metalloproteinases (MMPs) produced by colon 26-L5 cells, while RGDS peptide did not affect the enzymatic degradation. These findings clearly indicate that the pseudo-peptides of the RGD sequence (FC-336) have a potent inhibitory activity on liver metastasis of colon 26-L5 carcinoma cells.

8) **大西康晴，藤猪英樹，村田　純，坂本　隆，田沢賢次，藤巻雅夫，塚田一博，済木育夫：「癌細胞と間質との相互関係からみた転移，浸潤の諸問題」細胞接着阻害擬似ペプチドによる抗接着療法の癌転移におよぼす効果，日本消化器外科学会誌，31 : 1004–1009, 1998.**

9) **Hasegawa H., Suzuki R., Wakabayashi C., Murata J., Tezuka Y., Saiki I. and Kadota S.: Synthesis of a biological active fluorescent derivative of GM1, a main ginseng saponin metabolite formed by intestinal bacteria. Biol. Pharm. Bull., 21 : 513–516, 1998.**

Abstsract : A fluorescent derivative of GM1 [20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol], a main Ginseng saponin metabolite formed by intestinal bacteria, was obtained from the condensation of its trisnor-aldehyde derivative with dansyl hydrazine. The dansylated GM1 fluoresced strongly and showed almost the same properties as its parent compound In lipophilicity and biological activities, so this fluorescent compound might provide an insight into the mechanism of pharmacological activities of GM1.

10) **Matsuoka T., Hirakawa K., Chung Y-S., Yashiro M., Nishimura S., Sawada T., Saiki I. and Sowa M.: Adhesion polypeptides are useful for the prevention of peritoneal dissemination of gastric cancer. Clin. Exp. Metastasis, 16 : 381–388, 1998.**

Abstract : We examined the effect of adhesion polypeptides on the adhesion and invasive-

ness of gastric cancer cell lines. We previously reported the establishment of an extensively peritoneal-seeding cell line, OCUM-2MD3, from a poorly seeding human scirrhous gastric carcinoma cell line, OCUM-2M. Both alpha2beta1 and alpha3beta1 integrin expression was markedly increased on OCUM-2MD3 cells compared with OCUM-2M cells, and the ability of OCUM-2MD3 cells to bind to the extracellular matrix (ECM) was also significantly higher than that of OCUM-2M cells. The adhesion polypeptides, YIGSR and RGD, and two RGD derivatives significantly inhibited the adhesion of OCUM-2MD3 cells to the submesothelial ECM, while not inhibiting the adhesiveness of OCUM-2M cells and two well differentiated human gastric cell lines, MKN-28 and MKN-74. The YIGSR and RGD peptides also significantly inhibited the invasiveness of OCUM-2MD3 cells. The survival of nude mice with peritoneal dissemination given YIGSR sequence intraperitoneally was obviously longer than that of untreated mice. The survival of mice treated with RGD was also improved, and this effect was increased using the RGD derivatives, poly(CEMA-RGDS) and CM-chitin RGDS. These polypeptides appear to block the binding of integrins, which are expressed on OCUM-2MD3 cells, to the submesothelial ECM, and consequently inhibit peritoneal implantation. The peritoneal of adhesion polypeptides may be a new therapy against the dissemination of scirrhous gastric cancer, and may be useful for the prevention of dissemination in high-risk patients.

11) **Wakabayashi C., Murakami K., Hasegawa H., Murata J. and Saiki I.: An intestinal metabolite of ginseng protopanaxadiol saponins has the ability to induce apoptosis in tumor cells. Biochem. Biophys. Res. Commun., 246 : 725–730, 1998.**

Abstract : Our previous study demonstrated that the *in vivo* anti-metastaticeffect induced by oral administration of ginseng protopanaxadiolsaponins was mediated by their metabolic component M1, and that the growth, invasion and migration of tumor cells were inhibited by M1 butnot by ginsenosides. Here we investigated the inhibitory mechanism of M1 on the growth of tumor cells. M1 inhibited the proliferation of B16-BL6 mouse melanoma cells in a time- and dose-dependent manner, with accompanying morphological changes at the concentration of 20 μM. In addition, at 40 μM M1 induced apoptotic cell death within 24 h. Fluorescence microscopy revealed that dansyl M1 entered the cytosol and quickly reached the nuclei (approximately 15 min). Western blot analysis revealed that M1 rapidly up-regulated the expression of $p27^{Kip1}$, but down-regulated the expression of c-Myc and cyclin D1 in a time-dependent manner. Thus, the regulation of apoptosis-related proteins by M1 is responsible for theinduction of apoptotic cell death, and this probably leads to the anti-metastatic activity *in vivo*.

12) **Ohnishi Y., Yamaura T., Tauchi K., Sakamoto T., Tsukada K., Nunome S., Komatsu Y. and Saiki I: Expression of anti-metastatic effects by *Juzen-taiho-to* is based on the content of Shimotsu-to constituents. Biol. Pharm. Bull., 21 : 761–765, 1998.**

Abstsract: We investigated the inhibitory effect of oral administration of *Juzen-taiho-to*, a Kampo Japanese herbal medicine, and its related formulations on the experimental liver and lung metastasis of tumor cells *in vivo*. Oral administration of *Juzen-taiho-to* for 7 d before tumor inoculation significantly reduced the number of liver metastatic colonies of colon 26-L5 carcinoma cells and attenuated the increase of liver weight in a dose-dependent manner ranging from 4 to 40 mg/d. Its oral administration for this same period before tumor inoculation also significantly inhibited lung metastasis of B16-BL6 melanoma cells. *Juzen-taiho-to* originally consisted of 8 crude drugs derived from *Shimotsu-to* and *Shikunshi-to* prescriptions together with two crude drugs (Cinnamomi Cortex and Astragali Radix). Oral administration of *Shimotsu-to* as well as *Juzen-taiho-to* for 7 d before tumor inoculation resulted in a significant reduction in the number of metastatic colonies and the liver weight as compared with the control, whereas *Shikunshi-to* did not exhibit such an inhibitory effect. *Unsei-in* containing four *Shimotsu-to* constituents was also active in inhibiting liver metastasis. *Toki-shakuyaku-san* and *Ninjin-yoei-to*, which include all *Shimotsu-to* constituents except Rehmanniae Radix and Cnidii Rhizoma, respectively, did not show a significant anti-metastatic effect. Rikkunshi-to and *Ninjin-yoei-to*, which contain *Shikunshi-to* constituents, did not affect the inhibition of liver metastasis. *Hochu-ekki-to* treatment before tumor inoculation also led to a significant inhibition of liver metastasis, probably through an inhibitory mechanism different from *Juzen-taiho-to*. These results suggest that the anti-metastatic effect of *Juzen-taiho-to* is partly associated with its *Shimotsu-to*-derived constituents.

13) **Tahara E., Satoh T., Watanabe C., Nagai H., Shimada Y., Terasawa K. and Saiki I.: Effect of Kampo medicines on IgE-mediated biphasic cutaneous reaction in mice. J. Traditional Med., 15 : 100–108, 1998.**

Abstract: The effect of 20 Kampo formulations on murine IgE-mediated biphasic cutaneous reaction was investigated in BALB/c mice. Mice were passively sensitized by an intravenous injection of monoclonal anti-dinitrophenol IgE antibody. Skin reactions were elicited by an epicutaneous challenge of dinitrofluorobenzene and occurred biphasically with immediate phase response (IPR) and late phase response (LPR) at 1 and 24 h, respectively. The inhibitory effect of 20 Kampo formulations on the biphasic cutaneous reaction was divided into three groups, expressed according to the inhibition rate of ear swelling. The first group included Sho-seiryu-to (小青竜湯), Toki-shakuyaku-san (当帰芍薬散), Byakko-kaninjin-to (白虎加人参湯) and Tokaku-joki-to (桃核承気湯), and significantly inhibited both IPR and LPR (IPR/LPR, +/+ group), similarly to the effect by prednisolone. The second group inhibited mainly LPR, but not IPR (-/+ group), and included Gorei-san (五苓散), Unsei-in (温清飲), Shimotsu-to (四物湯), and Ogi-kenchu-to (黄耆建中湯). The third group did not result in any inhibition of IPR and LPR (-/- group), and comprised Oren-gedoku-to (黄連解毒湯), Yoku-kan-san (抑肝散), Rokumi-gan (六味丸) and Inchinko-to (茵蔯蒿湯). These findings may be useful for the determination of treatment modality using Kampo medicines in some of the allergic disease.

14) **Banskota A.H., Tezuka Y., Prasain J.K., Matsushige K., Saiki I. and Kadota S.: Chemical constituents of Brazilian propolis and their cytotoxic activities. J. Nat. Prod., 61 : 896–900, 1998.**

Abstsract : The EtOAc-soluble fraction of the MeOH extract of propolis afforded a new prenylated chromane derivative, 3-hydroxy-2, 2-dimethyl-8-prenylchromane-6-propenoic acid (1), along with 22 known compounds, 2-23. Of the known compounds, 4, 7, 12-19, and 22 were isolated for the first time from propolis, and the absolute configuration of 23 was established as (2S,3R). Investigation suggested that *Baccharis* spp. are a significant source of tropical Brazilian propolis, in addition to *Clusia minor, Clusia major,* and *Araucaria heterophylla.* All the compounds were tested for their cytotoxicity toward human HT-1080 fibrosarcoma and murine colon 26-L5 carcinoma cells. Among these compounds, 9 and 19-21 showed potent cytotoxicity, having ED_{50} values equal to or less than 10 μg/mL.

15) **Viroonchatapan E., Sato H., Ueno M., Adachi I., Murata J., Saiki I., Tazawa K. and Horikoshi I.: Microdialysis assessment of 5-fluorouracil release from thermosensitive magnetoliposomes induced by an electromagnetic field in tumor-bearing mice. J. Drug Targeting, 5 : 379–390, 1998.**

Abstsract : The current study was designed to evaluate the properties of thermosensitive magnetoliposomes (TMs), a new drug carrier proposed by the authors, in an electromagnetic field pertaining to their selective heating and drug release under an *in vivo* condition. TMs containing 5-fluorouracil (5-FU) were prepared by reverse-phase evaporation, injected into the tumor mass of B16-BL6 melanoma in mice, and selectively heated by a 500-kHz electromagnetic field. The release profile of 5-FU from TMs was examined by using a microdialysis technique. The temperature of TMs in the tumor was effectively elevated to 42 degrees C and maintained at this temperature, overcoming the "cooling effect" of blood flow and surrounding tissues. The release kinetics of 5-FU from TMs was successfully analyzed by physiological modeling, which allows the prediction of intratumor drug concentrations during electromagnetic field exposure under various conditions. In conclusion, this study first demonstrated an *in vivo* evidence for the electromagnetic field-induced thermosensitive release of a drug from TMs in a tumor with the use of microdialysis.

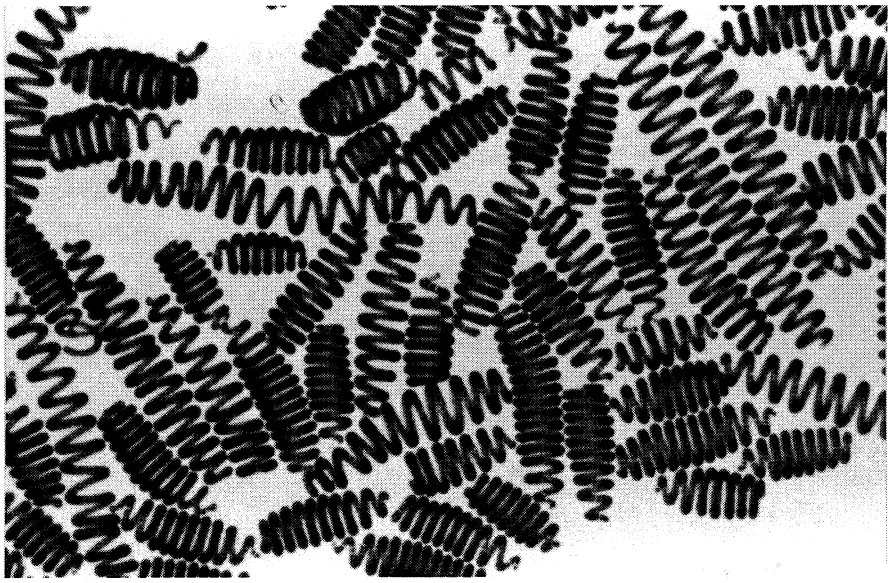
16) **Hayakawa Y., Fujii H., Hase K., Ohnishi Y., Sakukawa R., Kadota S., Namba T. and Saiki I.: Anti-metastatic and immunomodulating properties of the water extract from *Celosia argentea* seeds. Biol. Pharm. Bull., 21 : 1154–1159, 1998.**

Abstsract : We have investigated the anti-metastatic effect of *Celosia argentea* seed extracts (CAE), which have traditionally been used as a therapeutic drug for eye and hepatic diseases in China and Japan. Intraperitoneal (i.p.) administration of CAE for 7 d before tumor inoculation significantly inhibited liver metastasis caused by intraportal injection of colon 26-L5 carcinoma cells in a dose-dependent manner. CAE also showed concentration dependent mitogenic activity on BALB/c whole splenocytes, whereas incubation of the non-

adherent fraction of splenocytes with CAE did not induce this activity. CAE has the ability to induce interleukin (IL)-12 production from macrophages *in vitro*. Following i.p. administration of CAE the maximal levels of IL-12 and interferon (IFN)-gamma production in serum were achieved at 2-3 and 6 h, respectively. Experiments using macrophage- or NK cell-deficient mice revealed that CAE-induced IL-12 in serum was not mediated by macrophages and that IFN-gamma production was mainly dependent on natural killer (NK) cells. Since CAE was inactive when the contributions of macrophages were removed in our system, its inhibitory mechanism is likely to be mainly associated with the activation of macrophages to an anti-metastatic state rather than NK cells. CAE administration resulted in increased production of IL-2, IFN-gamma and decreased production of a Th2 cytokine (IL-4) from splenocytes stimulated by PMA an A23187. Thus, the anti-metastatic effect by CAE is based on its immunomodulating properties including induction of cytokines such as IL-12, IL-2 and IFN-gamma leading to a Th1 dominant immune state and activating macrophages to the tumoricidal state. This may provide a basis for the inhibition of cancer metastasis.

17) **Mishima T., Murata J., Toyoshima M., Fujii H., Nakajima M., Hayashi T., Kato T. and Saiki I: Inhibition of tumor invasion and metastasis by Calcium spirulan (Ca-SP), a novel sulfated polysaccharide derived from a blue-green alga *Spirulina platensis*. Clin. Exp. Metaastasis, 16 : 541–550, 1998.**

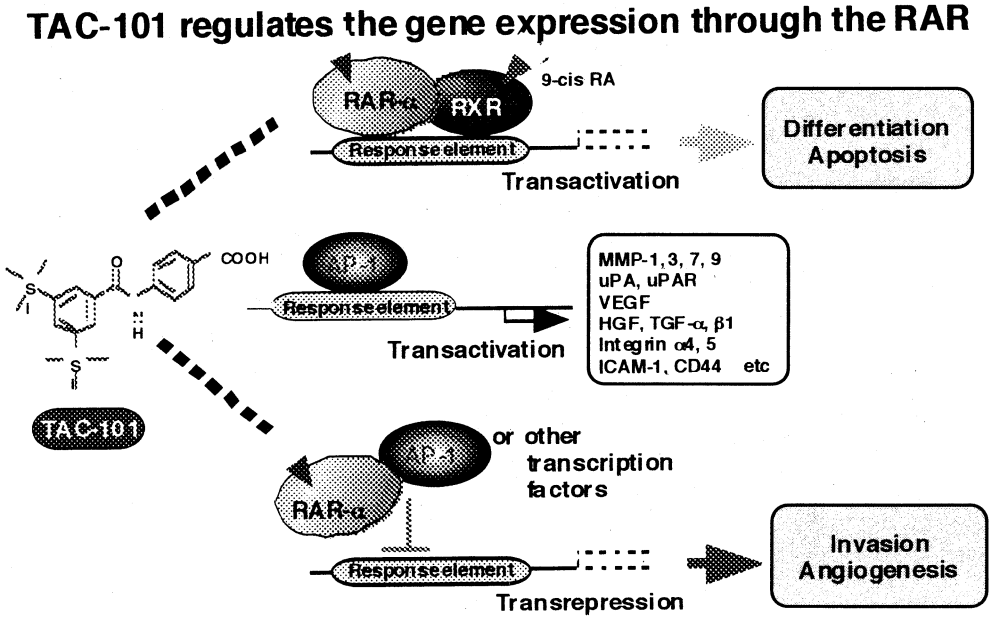
Abstsract : We have investigated the effect of calcium spirulan (Ca-SP) isolated from a blue-green alga, *Spirulina platensis*, which is a sulfated polysaccharide chelating calcium and mainly composed of rhamnose, on invasion of B16-BL6 melanoma, Colon 26 M3.1 carcinoma and HT-1080 fibrosarcoma cells through reconstituted basement membrane (Matrigel). Ca-SP significantly inhibited the invasion of these tumor cells through Matrigel/fibronectin-coated filters. Ca-SP also inhibited the haptotactic migration of tumor cells to laminin, but it had no effect on that to fibronectin. Ca-SP prevented the adhesion of B16-BL6 cells to Matrigel and laminin substrates but did not affect the adhesion to fibronectin. The pretreatment of tumor cells with Ca-SP inhibited the adhesion to laminin, while the pretreatment of laminin substrates did not. Ca-SP had no effect on the production and activation of type IV collagenase in gelatin zymography. In contrast, Ca-SP significantly inhibited degradation of heparan sulfate by purified heparanase. The experimental lung metastasis was significantly reduced by co-injection of B16-BL6 cells with Ca-SP. Seven intermittent i.v. injections of 100 μg of Ca-SP caused a marked decrease of lung tumor colonization of B16-BL6 cells in a spontaneous lung metastasis model. These results suggest that Ca-SP, a novel sulfated polysaccharide, could reduce the lung metastasis of B16-BL6 melanoma cells, by inhibiting the tumor invasion of basement membrane probably through the prevention of the adhesion and migration of tumor cells to laminin substrate and of the heparanase activity.



Spirulina platensis (x200)

18) **Sakukawa R., Murakami K., Ikeda T., Yamada Y. and Saiki I.: Effect of 4-[3,5-bis (trimethylsilyl) benzoamide] benzoic acid (TAC-101) on liver metastasis of colon 26-L5 carcinoma cells. Oncol. Res., 10 : 287–293, 1998.**

Abstract : We found that oral administration of the benzoic acid derivative, TAC-101 (4-[3,5-bis (trimethylsilyl)benzamido] benzoic acid) significantly inhibited experimental liver metastasis of murine colon 26-L5 carcinoma cells, while all-trans retinoic acid (ATRA) did not show any inhibitory effect. Treatment with more than 10 μM TAC-101 for 24 h showed direct cytotoxicity against tumor cells *in vitro*. In contrast, ATRA did not have any direct cytotoxicity. TAC-101 also inhibited the tumor cell invasion enhanced by TPA (12-O-tetradecanoylphorbol-13-acetate; AP-1 activator) in a concentration-dependent manner, while ATRA did not. Furthermore, zymographic analysis revealed that non-cytotoxic concentrations (<10 μM) of TAC-101 inhibited TPA-induced production of urokinase-type plasminogen activator (u-PA) and matrix metalloproteinase (MMP) -9 from tumor cells, which is considered to be associated with their invasive and metastatic potentials. These results suggest that such an inhibitory effect is partly due to the ability of TAC-101 to bind a retinoic acid receptor (RAR)-a and consequently inhibit metastasis-related gene transcription by interfering with AP-1/DNA binding, as we showed previously. On the other hand, TAC-101 also inhibited the production of MMP-2 which is not affected by TPA. Therefore, the anti-metastatic effect of TAC-101 includes an alternative regulatory mechanism for MMPs-production. These results indicate that the *in vivo* anti-metastatic effect of TAC-101 is partly due to the cytotoxicity against tumor cells which may be caused by the induction of apoptosis, and inhibition of the production of invasion-associated proteolytic enzymes.



19) **Banskota A.H., Tezuka Y., Phung L.K., Tran K.Q., Saiki I., Miwa Y., Taga T. and Kadota S.: Cytotoxic cycloartane-type triterpenes from *Combretum quadrangulare*. Bioorg. Med. Chem. Letts., 8 : 3519–3524, 1998.**

Abstract: Seven novel cycloartne-type triterpenes were isolated from *combretum quadrangulare*, and their structures were elucidated on the basis of spectral analysis. All these compounds were tested for their cytotoxicity against murine colon 26-L5 carcinoma cells. Methyl quadrangularate B (2) and methyl quadrangularate D (4) exhibited potent cytotoxicity having ED_{50} values 9.54 and 5.42 μM, respectively.

20) **Nishikawa N., Mori H., Saiki I.and Oku N. : Design of the functionalized liposomes using the molecules having saturated isoprenoid chains derived from archaebacterial lipids. Recemt Res. Devel. In Pure & Applied Chem., 2 : 239–245, 1998.**

Abstract: In this review, we would like to report the preparation of the functionalized liposomes based on a unique property of the saturated isoprenoid chain, derived from archaebacterial lipids. The emphasis is placed on the developments of a novel stabilizer of the liposomal membranes, a pH-sensitive liposome which releases its contents at the basic condition, and liposome having an anti tumor metastatic efficacy.

21) **Murakami K., Matsuura T., Sano M., Hashimoto A., Yonekura K., Sakukawa R., Yamada Y. and Saiki I.: 4-[3,5-bis(trimethylsilyl) benzoamide] benzoic acid (TAC-101) inhibits intrahepatic spread of hepatocellular carcinoma and prolongs lifespan of tumor bearing animals. Clin. Exp. Metastasis, 16 : 4633–644, 1998.**

Abstract: We examined the *in vivo* anti-tumor activity of the benzoic acid derivative, TAC-101 (4-[3,5-bis(trimethylsilyl)benzamido] benzoic acid) for intrahepatic spread of JHH-7 human carcinoma (HCC) cells and its mechanism of action. Oral administration of TAC-101

markedly inhibited liver tumor of JHH-7 cells and prolonged the life-span of tumor bearing mice without affecting the body weight. The life-prolonging effect of TAC-101 was more effective than that of other anti-cancer agents including CDDP, 5-FU, and CPT-11 (T/C (%) of life span ; 181 to 219, 128, 133, and 142%, respectively). *In vitro*, TAC-101 at the concentration of more than 10 μM, showed direct cytotoxicity against JHH-7 cells caused by induction of apoptosis. Hepatocyte growth factor (HGF) enhanced the invasive ability of JHH-7 cells without affecting the cell viability. Non-cytotoxic concentrations of TAC-101 inhibited the JHH-7 invasion induced by HGF and down-regulated the expression of c-MET protein in a concentration-dependent manner. In summary, these results suggest that TAC-101 would be useful for a new class of therapeutic agents and that it may improve prognosis of patients with liver-tumors including metastasizing tumor and HCC.

22) **Ikeda T., Murakami K., Hayakawa Y., Fujii H., Ohkoshi M. and Saiki I.: Anti-invasive activities of synthetic serine protease inhibitors and the combined effect with a matrix metalloproteinase inhibitor. Anticancer Res., 18 : 4259–4265, 1998.**

Abstract : Tumor invasion into the extracellular matrix (ECM) and basement membrane (BM) is a crucial step of tumor metastasis. In order to investigate the possible therapeutic procedure for the tumor invasion, we investigated anti-invasive activities of several synthetic serine protease inhibitors. FOY-305, a serine protease inhibitor, showed no cytotoxic activity against human HT-1080 firosarcoma cells at the concentrations ranging from 0.1 to 100 μg/ml, while its analogs ONO-3403 and FO-349 showed slight cytotoxic activities at the concentration of 100 μg/ml. These compounds inhibited the activity of urokinase-type plasminogen activator (u-PA) which is one of serine proteases and considered to be associated with tumor invasion and metastasis in the fibrin zymography. FOY-305 potently inhibited the invasion of HT-1080 cells into the reconstituted BM Matrigel as well as the u-PA activity compared with ONO-3403 and FO-349. These results suggest that anti-invasive activity of these compounds is well consistent with their anti-fibrinolytic activities. In addition, the combined treatment of FOY-305 with FC-336 with anti-invasive and anti-MMP properties resulted in marked enhancement of anti-invasive activity. In conclusion, FOY-305 inhibited the invasion of tumor cells through the interference with the u-PA activity in tumor cells, and such inhibitory activity was augmented by the combination with a MMP inhibitor.

23) **Ogasawara M., Murata J., Ayukawa K. and Saiki I.: Inhibitory effect of vasoactive intestinal polypeptide (VIP) on experimental liver metastasis by murine colon 26-L5 carcinoma cells. Oncol. Res., 10 : 361–370, 1998.**

Abstract : We previously reported that vasoactive intestinal polypeptide (VIP) significantly inhibited Matrigel invasion and haptotactic migration of murine Colon 26-L5 carcinoma *in vitro*. To extend our study, we investigated the inhibitory mechanisms of VIP on Matrigel invasion of Colon 26-L5 carcinoma, and the effect on metastatic properties of the tumor cells. VIP inhibited the invasion of the tumor cells in a concentration-dependent

manner without affecting their growth, and achieved approximately 50% reduction at 10^{-6} M. VIP also suppressed the cell motility with a similar inhibition rate to the invasion assay. Time course study revealed that the motility was reduced by 40% when the tumor cells were preincubated with 10^{-6} M VIP for 3 h. In contrast, 6 h-pretreatment with 10^{-6} M VIP caused the increased ability of the adhesion to both fibronectin and laminin with a 50% enhancement. A large amount of VIP1 receptor transcripts was expressed in the cells, whereas VIP2 receptor was undetectable, by RT-PCR and subsequent Southern blot hybridization. A specific antagonist for VIP1 receptor reversed the suppressed motility induced by VIP. Cryostat sections showed that the 3 h-pretreatment of tumor cells with VIP caused the reduction of the arrest in the livers at 6 h after the tumor inoculation into a portal vein of mice. VIP could prevent the experimental liver metastasis of the tumor cells in a dose-dependent manner. The cells pretreated with 10^{-6} M VIP for 3 h also showed the reduced ability of the liver metastasis. These results suggest that VIP could block the invasion and the metastasis of Colon 26-L5 carcinoma through the suppression of their motility.

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◇研究費取得状況

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◇研究室在籍者

学部4年生：黒崎いずみ，宮脇美帆
大学院前期1年：池田　敬，須田一仁，山浦　剛，山田智裕
大学院前期2年：作川理恵子，佐藤　卓，上谷幸男
大学院後期1年：早川芳弘，呉　文娟
大学院後期3年：小笠原　勝（日本学術振興会特別研究員，1998，4～）

研究機関研究員：藤猪英樹（1998，4～）
特別研究生：藤猪英樹（北海道大学大学院理学研究科博士3年，1997，4～1998，3）
受託研究員：長谷川秀夫（一都生命科学研究所，1996，4～1998，3）
　　村上孝司（大鵬薬品工業株式会社・創薬センター，1997，7～）

井下田勝広（富士薬品工業株式会社，1997，10～）
寺澤匡博（富士薬品工業株式会社，1998，10～）
萱垣　昇（第一薬産株式会社，1998，4～）

学内研究生：大西康晴（富山医科薬科大学医学部・第二外科，1995，4～1998，3）
永川　修（富山医科薬科大学医学部・泌尿器科，1996，9～1998，10）
土岐善紀（富山医科薬科大学医学部・第一外科学，1997，4～）
田原英一（富山医科薬科大学医学部・和漢診療学，1997，4～）
澤田成朗（富山医科薬科大学医学部・第二外科，1998，4～）
村石康博（富山医科薬科大学医学部・泌尿器科学教室，1998，4～）

外国人客員研究員：呉　文娟（上海医科大学薬学部，1997，10～1998，3）

出向者：早川芳弘（特別研究生，順天堂大学医学部免疫学，1998，4～1999，3）

◇学位（修士，博士）取得者

修士：

三嶋敬章：「藍藻スピルリナ由来の硫酸化多糖：Calcium spirulanによる癌転移の抑制とその作用機序の解析」

渡辺知恵：「アレルギー性皮膚炎の制御物質の探索とその作用機序の解析」

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若林千里：「薬用人参の腸内代謝産物による抗転移効果の作用機序解析」

博士：

大西康晴：「Oral administration of a Kampo (Japanese herbal) medicine *Juzen-taiho-to* inhibits liver metastasis of colon 26-L5 carcinoma cells」，
医学博士（富山医科薬科大学）

藤猪英樹：「B7-1遺伝子導入癌細胞を用いたワクチン療法とRGD擬似ペプチドを用いた抗接着療法による癌転移抑制とそれらの併用効果」，
理学博士（北海道大学）