# 病態生化学分野　Division of Pathogenic Biochemistry


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| 教　授 | 済木　育夫 | Professor | Ikuo Saiki (Ph.D. Med. Sci.) |
| 准教授 | 櫻井　宏明 | Associate Professor | Hiroaki Sakurai (Ph.D.) |
| 助　教 | 小泉　桂一（9月まで） | Assistant Professor | Keiichi Koizumi (Ph.D.) |
| 研究員 | 申　明淑 | Postdoctoral Fellow | Myoung-Sook Shin (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，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) Hayashi S., Sakurai H., Hayashi A., Tanaka Y., and Hatashita M.: Inhibition of NF-κB by combination therapy with parthenolide and hyperthermia and kinetics of apoptosis induction and cell cycle arrest in human lung adenocarcinoma cells. *Int. J. Mol. Med.,* 25: 81-87, 2010.**



**Abstract:** We investigated the mechanisms of thermosensitization related to combination therapy with sesquiterpene lactone parthenolide (PTL), a nuclear factor-κB (NF-κB) inhibitor, and hyperthermia using human lung adenocarcinoma cells A549. The kinetics of apoptosis induction and cell cycle of cells treated with PTL, heating, and combined treatment were examined by flow cytometric analysis. The flow cytometric distribution was calculated and expressed as a percentage. The ratios of the sub-G1 division, used to determine the induction of apoptosis, increased significantly with the combination therapy. Furthermore, the ratios of G2/M division increased and the ratios of G0/G1 division decreased, indicating cell cycle arrest in G2/M. The cell phase response to PTL by A549 cells synchronized in the G1/S border with hydroxyurea was also analyzed. PTL showed remarkable cytotoxicity at the S phase of the cell cycle

in A549 cells at all concentrations as well as with hyperthermia, thus PTL reduced the number of cells in the proliferation phase. Inhibition of intracellular transcription factor NF- κB activation in A549 cells with various incubation periods after treatments with PTL, heating and combined treatment was examined by Western blot analysis. Unexpectedly, PTL alone did not inhibit NF-κB activation in cells stimulated with TNF-α, while heating alone inhibited NF-κB early after treatment and that effect faded over time. In contrast, PTL combined with heating completely inhibited NF-κB activation. Our results demonstrated that PTL and heating in combination cause significant thermosensitization of A549 cells via induction of apoptosis or cell cycle arrest in G2/M by inhibiting NF-κB activation in a synergistic manner.

2) **Fujita M., Andoh T., Ohashi K., Akira A., Saiki I., and Kuraishi Y.: Roles of kinin B(1) and B(2) receptors in skin cancer pain produced by orthotopic melanoma inoculation in mice.** ***Eur. J. Pain.*** **14:588-594, 2010.**

**Abstract: BACKGROUND:** Although bradykinin is a potent algogenic peptide, the roles of this peptide and kinin receptors in cancer pain are unclear.
**AIMS:** The present study was conducted to clarify whether kinin B(1) and B(2) receptors would be involved in pain using a mouse model of skin cancer pain.
**METHODS:** B16-BL6 melanoma cells were inoculated into the hind paw of C57BL/6 mice. Licking, an index of spontaneous pain, allodynia and hyperalgesia were observed. Expression of kinin receptor mRNAs was analyzed with reverse transcription and polymerase chain reaction. The contents of kininogen and bradykinin-related peptides were assayed with Western blotting and enzyme immunoassay, respectively.
**RESULTS:** Melanoma inoculation induced spontaneous licking of the melanoma-bearing paw from day 18 post-inoculation, which was inhibited by local injections of B(1) and B(2) receptor antagonists. Allodynia was briefly attenuated by B(2), but not B(1) antagonist and hyperalgesia was not inhibited by either B(1) or B(2) antagonist. Local injections of B(1) and B(2) receptor agonists increased licking behavior in melanoma-bearing, but not healthy, paw. The expression of kinin B(1), but not B(2), receptor mRNA was markedly increased in the L4/5 dorsal root ganglia on the melanoma-bearing side. Melanoma cells expressed B(1) and B(2) receptors and kininogen. The content of bradykinin and related peptides was increased in the melanoma mass as compared with healthy skin.
**CONCLUSIONS:** Bradykinin and related peptides released from melanoma cells may cause spontaneous pain and allodynia in the melanoma-bearing paw, in which B(1) and B(2) receptors on primary afferent and melanoma cells may have different roles.

3) **Suzuki S., Zhou Y., Refaat A., Takasaki I., Koizumi K., Yamaoka S., Tabuchi Y., Saiki I., and Sakurai H.: HTLV-1 manipulates interferon regulatory signals by controlling TAK1-IRF3 and IRF4.** ***J. Biol. Chem.*** **285: 4441-4446, 2010.**

**Abstract:** We previously reported that human T cell lymphotropic virus 1 (HTLV-1) Tax oncoprotein constitutively activates transforming growth factor-β-activated kinase 1 (TAK1). Here, we established Tax-positive HuT-102 cells stably transfected with a short hairpin RNA vector (HuT-shTAK1 cells) and investigated the physiological function of TAK1. Microarray analysis demonstrated that several interferon (IFN)-inducible genes, including chemokines such as CXCL10 and CCL5, were significantly down-regulated in HuT-shTAK1 cells. In contrast, Tax-mediated constitutive activation of nuclear factor-κB (NF-κB) was intact in HuT-shTAK1 cells. IFN-regulatory factor 3 (IRF3), a critical transcription factor in innate immunity to viral infection, was constitutively activated in a Tax-dependent manner. Activation of IRF3 and IRF3-dependent gene expressions was dependent on TAK1 and TANK-binding kinase 1 (TBK1). On the other hand, IRF4, another member in the IRF family of transcription factors overexpressed in a Tax-independent manner, negatively regulated TAK1-dependent IRF3 transcriptional activity. Together, HTLV-1 manipulates IFN signaling by regulating both positive and negative IRFs.

4) **Andoh T., Akira A., Saiki I., and Kuraishi Y.: Bradykinin increases the secretion and expression of endothelin-1 through kinin B(2) receptors in melanoma cells.** ***Peptides*****, 31: 238-341, 2010.**

**Abstract:** The present study was conducted to determine whether bradykinin would affect the secretion and expression of endothelin-1 (ET-1) in B16-BL6 melanoma cells. Bradykinin administered to cultured

melanoma cells increased preproET-1 mRNA level and the secretion of ET-1. Although kinin B(1) and B(2) receptor mRNAs are expressed in the melanoma cells, the increase of preproET-1 mRNA expression and the secretion of ET-1 were inhibited by kinin B(2), but not by B(1), receptor antagonist. These results suggest that bradykinin regulates the secretion and biosynthesis of ET-1 through kinin B(2) receptor in tumor cells, especially melanoma cells.

5) **Miyanaga S., Sakurai H., Saiki I., Onaka H., and Igarashi Y.: Anti-invasive and anti-angiogenic activities of naturally occurring dibenzodiazepine BU-4664L and its derivatives.** ***Bioorg. Med. Chem. Lett.,*** **20: 963-965, 2010.**

**Abstract:** In the screening for antitumor leads from microbial secondary metabolites, BU-4664L (1), a naturally occurring dibenzodiazepine, was found to inhibit tumor invasion and angiogenesis in vitro. Compound 1 inhibited the gelatinase activities of MMP-2 and MMP-9 and the cellular motility. Four derivatives (2-5) were synthesized from 1 and their antitumor activities were evaluated. Compounds 3 and 4 exhibited potent anti-angiogenic effects on HUVEC, together with remarkable inhibition of cell migration at nanomolar concentrations, and showed much lower cytotoxicity.

6) **Prangsaengtong O., Koizumi K., Urano T., Nagata A., Sakurai H., Tohda C., and Saiki I.: Methanol extract of polygonati rhizoma enhances the tube formation of rat lymphatic endothelial cells.** ***J. Trad. Med.,*** **27: 59-65, 2010.**

7) **Fujita M., Andoh T., Sasaki A., Saiki I., and Kuraishi Y.: Involvement of peripheral adenosine 5'-triphosphate and P2X purinoceptor in pain-related behavior produced by orthotopic melanoma inoculation in mice.** ***Eur. J. Neurosci.*****, 31: 1629-1636, 2010.**

**Abstract:** Adenosine 5'-triphosphate (ATP) plays an important role in nociceptive processing. We used a mouse model of skin cancer pain to investigate the role of ATP in cancer pain. Orthotopic inoculation of B16-BL6 melanoma cells into the hind paw produced spontaneous licking of the tumor-bearing paw. Intraperitoneal injection of the P2 purinoceptor antagonist suramin suppressed spontaneous licking dose-dependently. Two P2X purinoceptor antagonists also suppressed spontaneous licking. An intraplantar injection of ATP, which did not induce licking in the healthy paw, increased licking of the tumor-bearing paw. Spontaneous firing of the tibial nerve was significantly increased in tumor-bearing mice and was inhibited by suramin. Extracellular concentration of ATP was significantly increased in the tumor-bearing paw than in the normal paw. ATP is concentrated in the culture medium of melanoma, lung cancer and breast cancer cells, but not fibroblasts. The P2X(3) receptor was expressed in about 40% of peripherin-positive small and medium-sized neurons in the dorsal root ganglia. P2X(3)-positive neurons were significantly increased in melanoma-bearing mice. These results suggest that ATP and P2X, especially P2X(3), receptors are involved in skin cancer pain, due to the increased release of ATP and increased expression of P2X(3) receptors in the sensory neurons.

8) **Lirdprapamongkol K., Sakurai H., Suzuki S., Koizumi K., Prangsaengtong O., Viriyaroj A., Ruchirawat S., Svasti J., and Saiki I.: Vanillin enhances TRAIL-induced apoptosis in cancer cells through inhibition of NF-κB activation.** ***In Vivo,*** **24: 501-506, 2010.**

**Abstract: BACKGROUND:** Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising anticancer agent which selectively kills cancer cells with little effect on normal cells. However, TRAIL resistance is widely found in cancer cells. We have previously reported antimetatstatic and antiangiogenic effects of vanillin, a flavoring agent from vanilla. Here we have evaluated the sensitizing effect of vanillin on a TRAIL-resistant human cervical cancer cell line, HeLa.
**MATERIALS AND METHODS:** Cell viability after treatments was determined by the WST-1 cell counting kit. Apoptosis was demonstrated by detection of caspase-3 activation and cleavage of poly (ADP-ribose) polymerase using immunoblot analysis. Effect of treatments on TRAIL signaling pathway and nuclear factor κB (NF-κB) activation was studied using immunoblot analysis and luciferase reporter assay.
**RESULTS:** Pretreatment of HeLa cells with vanillin enhanced TRAIL-induced cell death through the apoptosis pathway. Vanillin pretreatment inhibited TRAIL-induced phosphorylation of p65 and transcriptional activity of NF-κB.

**CONCLUSION:** Vanillin sensitizes HeLa cells to TRAIL-induced apoptosis by inhibiting NF-κB activation.

9) **Igarashi Y., Shimasaki R., Miyanaga S., Oku N., Onaka H., Sakurai H., Saiki I., Kitani S., Nihira T., Wimonsiravude W., Panbangred W.: Rakicidin D, an inhibitor of tumor cell invasion from marine-derived *Streptomyces sp. J. Antibiot.*, 63: 563-565, 2010.**

10) **Igarashi Y., Yu L., Miyanaga S., Fukuda T., Saitoh N., Sakurai H., Saiki I., Alonso-Vega P., Trujillo M.E.: Abyssomicin I, a Modified Polycyclic Polyketide from Streptomyces sp. CHI39. *J. Nat. Prod.*, 73: 1943-1946, 2010.**

**Abstract:** Abyssomicin I (1), a new modified polycyclic polyketide, was isolated from the culture extract of a soil-derived Streptomyces sp. The structure of 1 was elucidated by interpretation of NMR and other spectroscopic data. The stereochemistry of the new compound was assigned by NOE analysis, chemical derivatization, and application of the modified Mosher method. While 1 was inactive against bacteria and yeasts, the oxidized derivative 7 showed weak activities against gram-positive bacteria. Compounds 1 and 7 exhibited inhibitory effects on tumor cell invasion with IC(50) values of 11 and 0.21 μM, respectively.

11) **Sayama K., Yamamoto M., Shirakata Y., Hanakawa Y., Hirakawa S., Dai X., Tohyama M., Tokumaru S., Shin M.S., Sakurai H., Akira S., and Hashimoto K.: E2 polyubiquitin-conjugating enzyme Ubc13 in keratinocytes is essential for epidermal integrity. *J. Biol. Chem.*, 285: 30042-30049, 2010.**

**Abstract:** The E2 polyubiquitin-conjugating enzyme Ubc13 is a mediator of innate immune reactions. Ubc13 mediates the conjugation of keratin (K)63-linked polyubiquitin chains onto TNF receptor-associated factor 6 and IKKγ during NF-κB activation. In contrast to K48-linked polyubiquitin chains, K63-linked polyubiquitin chains function in nonproteasomal biological processes. Although Ubc13 has been shown to be critical for Toll-like receptor (TLR) and IL-1 receptor signaling, the function of Ubc13 in the epidermis has not been studied. We generated keratinocyte-specific Ubc13-deficient mice (Ubc13(flox/flox)K5-Cre). At birth, the skin of the Ubc13(flox/flox)K5-Cre mice was abnormally shiny and smooth; in addition, the mice did not grow and died by postnatal day 2. Histological analysis showed atrophy of the epidermis with keratinocyte apoptosis. Immunohistochemical analyses revealed reduced proliferation, abnormal differentiation, and apoptosis of keratinocytes in the Ubc13(flox/flox)K5-Cre mouse epidermis. In culture, Ubc13(flox/flox)K5-Cre keratinocyte growth was impaired, and spontaneous cell death occurred. Moreover, the deletion of Ubc13 from cultured Ubc13(flox/flox) keratinocytes by means of an adenoviral vector carrying Cre recombinase also resulted in spontaneous cell death. Therefore, Ubc13 is essential for keratinocyte growth, differentiation, and survival. Analyses of intracellular signaling revealed that the IL-1 and TNF-induced activation of JNK, p38, and NF-κB pathways was impaired in Ubc13(flox/flox)K5-Cre keratinocytes. In conclusion, Ubc13 appears to be essential for epidermal integrity in mice.

12) **Kato S., Koizumi K., Yamada M., Inujima A., Takeno N., Sakurai H., Nakanishi T., Nakagawa S., and Saiki I.: A phagocytotic inducer from herbal constituent, pentagalloylglucose (PGG) enhances lipoplex-mediated gene transfection in dendritic cells. *Biol. Pharm. Bull.*, 33: 1878-1885, 2010.**

**Abstract:** Antigen-presenting cells are key vehicles for delivering antigens in tumor immunotherapy, and the most potent of them are dendritic cells (DCs). Recent studies have demonstrated the usefulness of DCs genetically modified by lipofection in tumor immune therapy, although sufficient gene transduction into DCs is quite difficult. Here, we show that Paeoniae radix, herbal medicine, and the constituent, 1,2,3,4,6-penta-O-galloyl-β-D-glucose (PGG), have an attractive function to enhance phagocytosis in murine dendritic cell lines, DC2.4 cells. In particular, PGG in combination with lipofectin (LPF) enhanced phagocytic activity. Furthermore, PGG enhanced lipofection efficacy in DC2.4 cells, but not in colorectal carcinoma cell lines, Colon26. In other words, PGG synergistically enhanced the effect of lipofectin-dependent phagocytosis on phagocytic cells. Hence, according to our data, PGG could be an effective aid in lipofection using dendritic cells. Furthermore, these findings provide an expectation that constituents from herbal plant enhance lipofection efficacy.

## ◇著　書

1) 櫻井宏明，小泉桂一，済木育夫：「TNF-α は転移になぜ必要か，がん転移−臨床と研究の羅針盤−」監修：丸義朗，細胞工学　別冊 pp139-143，学研メディカル 秀潤社，2010.

## ◇総　説

1) 松本欣三，済木育夫：話題：JSPS（日本学術振興会）支援による拠点大学交流事業，ファルマシア，**46** (8): 770-774，2010.
2) 佐藤佳奈絵：実は存在していた！ErbB3 受容体のチロシンキナーゼ活性，ファルマシア，**46** (11): 1076-1077，2010
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4) 済木育夫：特別講演：癌転移と漢方，脳神経外科と漢方　講演記録集，63-76，2010.
5) 済木育夫：特別講演：漢方薬による癌転移阻害のメカニズム，産婦人科漢方研究のあゆみ No.28　講演記録集，63-76，2010.

## ◇学会報告　（*：特別講演，シンポジウム，ワークショップ等）

1) 鄭ダミ，渡公佑，白水隆喜，小野真弓，小泉桂一，済木育夫，金ユンチュル，樋口隆一，宮本智文：天然由来新規リンパ管新生阻害剤の探索　第 1 報，日本薬学会第 130 回年会，2010, 3, 28-30，岡山.
2) 渡邊貴信，長野一也，山下琢矢，岡村賢孝，金崎聡一郎，阿部康弘，吉川友晃，吉岡靖雄，鎌田春彦，伊藤徳夫，小泉桂一，角田慎一，堤康央：プロテオームミクスによる非アルコール性脂肪性肝疾患（NAFLD/NASH）のバイオマーカー探索，日本薬学会第 130 回年会，2010, 3, 28-30，岡山.
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6) 長野一也，山下琢矢，岡村賢孝，小泉桂一，済木育夫，堤康央，角田慎一：新規乳がん関連蛋白質 EphA10 および RREB-1 の転移との連関解析，第 19 回がん転移学会，2010, 6, 16-17，金沢.
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* 10) 櫻井宏明：第 13 回天然薬物研究方法論アカデミー 覚王山シンポジウム「漢方研究再考」「和漢薬データベースによる天然薬物研究の活性化」2010, 8, 21，名古屋.
* 11) Saiki I.: Juzentaihoto-induced inhibition of cancer metastasis – Establishment of molecular basis for Kampo medicine –, Sympojium 8: Strategies and problem of Asian traditional medicine in cancer treatment, 9th International Conference of the Asian Clinical Oncology Society “Talk to the world wide from Asia” -Multidisciplinary treatment for Asian cancer patients-, 2010, 8, 25-27,

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12) Waiwut P., Shin M.S., Inujima A., Koizumi K., Saiki I., and Sakurai H.: Gomisin N enhances TNF-α-induced apoptosis via inhibition of NF-κB and EGFR survival pathways. 第 27 回和漢医薬学会学術総会，2010, 8, 28-29，京都.

13) 櫻井宏明，Waiwut P.，犬嶌明子，申明淑，田中謙，小泉桂一，済木育夫：Kampo-Kinome 解析：十全大補湯構成生薬のプロテインキナーゼ阻害活性．第 27 回和漢医薬学会学術総会，2010, 8, 28-29，京都.

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* 15) Saiki I., Choo M.K., Kim D.H. and Sakurai H.: A ginseng saponin metabolite sppresses TNF-α-promoted metastasis by suppressing NF-κB signaling. The 10th International Symposium on Ginseng. – Ginseng, the Root of HumanWell-being – 2010, 9, 13-16, Seoul.

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17) Refaat A., Zhou Y., Suzuki S., Koizumi K., Saiki I., and Sakurai H.: Suppression of IRF4 induces IFN-γ production through IRF1 in IL-17-producing HTLV-1-infected T cells. 第 69 回日本癌学会総会，2010, 9, 22-24，大阪.

* 18) Saiki I.: Curcumin and cancer metastasis. Konkuk University Chungju 30th Anniversary. 2010 International Symposium on Biomedical and Helth Science & 4th Annual Symposium of Collage Biomedical and Health Science, 2010, 10, 26-27, Chungju.

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## ◇受賞

1) 加藤真一郎：第 9 回 NRCT-JSPS Joint Seminar The Outstanding Poster Award（2010, 12, 8-9）

## ◇その他

1) 済木育夫：特別講演 I 漢方薬のアレルギー性皮膚疾患への応用，アトピー性皮膚炎治療研究会第 15 回シンポジウム，2010, 2, 6，大阪.
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## ◇非常勤講師

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## ◇研究費取得状況

1) 平成 22 年度 厚生労働省科学研究費医薬技術実用化総合研究事業（代表：済木育夫）「漢方薬によるワクチンアジュバント効果の検討と臨床応用」
2) 平成 22 年度 厚生労働省科学研究費創薬基盤推進研究事業（代表：小泉桂一）「粘膜免疫機能を増強する漢方薬の探索とその有効成分の同定」
3) 平成 22 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）「Kampo-Kinome 解析によるケミカルバイオロジーの展開」
4) 平成 22 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」
5) 平成 22 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：櫻井宏明）900 万円 「和漢薬による免疫の賦活化に関する研究 −自然免疫系刺激およびタバコ煙によるマウス気道炎症モデルの確立と漢方方剤の影響−」
6) 平成 22 年度 文部科学省科学研究費補助金基盤研究（C）（代表：小泉桂一）「ケモカイン機能を利用したがん細胞呼び込み型 DDS 型剤の開発と腹膜播種治療への応用」
7) 平成 22 年度 文部科学省科学研究費補助金基盤研究（C）（分担：済木育夫）「オキサリプラチンの末梢神経障害に対する人参養栄湯の臨床効果とその分子機構」
8) 平成 22 年度 富山第一銀行奨学財団研究助成（代表：櫻井宏明）700 千円「Kampo-Kinome 解析：和漢薬のケミカルバイオロジー研究」

## ◇研究室在籍者

学 部 3 年 生：金諒英，兼頭直希
学 部 4 年 生：大江未来広
大学院修士 1 年：伊東彩 (2010, 9, 6 漢方診断学分野へ転出)，河西美保
大学院修士 2 年：加藤真一郎，周越，佐藤佳奈絵，保科瑛子
大学院博士 1 年：奇知藝 ( 2010, 4, 1~, 韓国 )
大学院博士 2 年：Pornthip Waiwut ( 2009, 4, 1~, Thailand )
大学院博士 3 年：Orawin Prangsaengtong ( 2008, 4, 1~, Thailand )
Alaa Eldin Tawfik Refaat ( 2008, 10, 1~, Egypt )
研 究 員：申明淑 ( 2010, 4, 1〜)
技 術 補 佐 員：犬嶌明子 ( 2010, 4, 1〜)
事 務 補 佐 員：岡田純子 ( 2008, 7, 1〜)

学 内 研 究 生：岡洋志（富山大学医学部・和漢診療学，2007, 2〜）
井上博喜（富山大学医学部・和漢診療学，2007, 10〜）
齋藤聖子（富山大学医学部・第三内科学，2009, 4〜）
和田暁法（富山大学医学部・第三内科学，2010, 7〜）
外国人客員研究員：Bui The Vinh (Research Center of Ginseng and Medicinal Materials,Vietnam)
2010, 1, 11〜2010, 3, 8
Managit Chittima (Srinakharinwirot University, Thailand)
2010, 8, 2〜2010, 9, 30
Kriengsak Lirdprapamongkol (Chulabhorn Research Institute, Thailand)
2010, 8, 2〜2010, 9, 30
Oranuch Thanaketpaisarn (Ubon Rtcathani University, Thailand)
2010, 9, 30〜2010, 11, 28
Habibie (Hasanuddin University, Indonesia)
2010, 9, 30〜2010, 11, 30
Abdelhamed Sherif Mohamed Diaa Eldin (National Research Center, Eygpt)
2010, 10, 6〜2011, 3, 31

## ◇学位（修士，博士）取得者

修士論文：
周越：HTLV-1 Tax 発現細胞における TAK1 を介するインターフェロン応答遺伝子の発現制御機構
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保科瑛子：黄耆建中湯の経口ワクチンのアジュバントとしての可能性に関する基礎的研究

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## ◇人事異動

小泉桂一：富山大学和漢医薬学総合研究所　漢方診断学分野准教授に昇任（2010, 10, 1）