[*Bioorg Med Chem.*, **16(2)**, 675-682 (2008)] [Lab. of Pharm. Chemistry]

Design, synthesis, and radiosensitizing activities of sugar-hybrid hypoxic cell radiosensitizers

Takashi NAKAE, Yoshihiro UTO, Motoko TANAKA, Haruna SHIBATA, Eiji NAKATA, Masahide TOMINAGA, Hiroshi MAEZAWA, Toshihiro HASHIMOTO, Kenneth L. KIRK, Hideko NAGASAWA*, Hitoshi HORI

We have designed sugar-hybrid TX-1877 derivatives conjugated with sugar moieties including beta-glucose (beta-Glc), beta-galactose (beta-Gal), alpha-mannose (alpha-Man) and N-acetyl-beta-galactosamine (beta-GalNAc). Compound 1 (TX-1877) was glycosylated with appropriate peracetylated sugars using BF(3)-OEt(2) to give acetylated sugar-hybrids, 5 (TX-2244), 6 (TX-2245), 7 (TX-2246), and 10 (TX-2243). Removal of the acetyl groups afforded the sugar-hybrids having free hydroxyl groups, 11 (TX-2141), 12 (TX-2218), 13 (TX-2217) and 14 (TX-2068). In the present study, we have succeeded in producing sugar-hybrid hypoxic cell radiosensitizers that have an increased radiosensitizing activity that does not depend on increased hydrophobicity.

[*Anticancer Res*, **27(6A)**, 3693-3700 (2007)] [Lab. of Pharm. Chemistry]

Effect of molecular chirality and side chain bulkiness on angiogenesis of haloacetylcarbamoyl-2-nitroimidazole compounds

Kazuto OHKURA, Yoshihiro UTO, Hideko NAGASAWA*, Hotoshi HORI

Angiogenesis is required for tumor growth and metastasis, and is an exciting target for cancer treatment. We designed and synthesized antiangiogenetic TX agent (TX-1898, -1900), and analyzed their structural features. TXs have a chiral center and S- and R-enantiomers. Conformation analysis and molecular dynamics simulation were undertaken. TX-1898 exhibited significant antiangiogenic activity. The order of antiangiogenic activity was as follows: TX-1898 (93% at 5 microg/pellet) > TX-1900 (82% at 5 microg/pellet) > TX-1897 (64% at 10 microg/pellet) > TX-1899 (58% at 10 microg/pellet). The chiral center has an important role for orienting the molecular characteristics.

[*Int J Hyperthermia*, **23(1)**, 29-35 (2007)] [Lab. of Pharm. Chemistry]

The usefulness of mild temperature hyperthermia combined with continuous tirapazamine administration under reduced dose-rate irradiation with gamma-rays

Shin-ichiro MASUNAGA, Hideko NAGASAWA*, Yoshihiro UTO, Hitoshi HORI, Kenji NAGATA, Minoru SUZUKI, Genro KASHINO, Yuko KINASHI, Koji ONO

We clarified the usefulness of mild temperature hyperthermia (MTH) in combination with the continuous administration of tirapazamine (TPZ) under reduced dose-rate irradiation (RDRI) using gamma-rays. TPZ increased the sensitivity of both populations, with a slightly more remarkable increase in Q cells. Further, MTH combined with TPZ raised the sensitivity of both the total and Q cell populations, especially the latter, under RDRI more markedly than under HDRI. From the viewpoint of solid tumour control as a whole, including intratumour Q-cell control, the use of TPZ, especially in combination with MTH, is useful for suppressing the reduction in the sensitivity of tumour cells caused by the decrease in irradiation dose rate in vivo.

[*Cancer Lett*, **252(2)**, 235-243 (2007)] [Lab. of Pharm. Chemistry]

Suppression of tumor-induced angiogenesis by Brazilian propolis: major component artepillin C inhibits in vitro tube formation and endothelial cell proliferation

Mok-Ryeon AHN, Kazuhiro KUNIMASA, Toshiro OHTA, Shigenori KUMAZAWA, Miya KAMIHIRA, Kazuhiko KAJI, Yoshihiro UTO, Hitoshi HORI, Hideko NAGASAWA*, Tsutomu NAKAYAMA

In this report, we examined an antiangiogenic effects of Brazilian propolis and investigated whether artepillin C was responsible for such effects. In an in vivo angiogenesis assay using ICR mice, we found that the ethanol extract of Brazilian propolis (EEBP) significantly reduced the number of newly formed vessels. EEBP also showed antiangiogenic effects in an in vitro tube formation assay. When compared with other constituents of EEBP, only artepillin C was found to significantly inhibit the tube formation of HUVECs in a concentration-dependent manner (3.13-50microg/ml). We concluded that artepillin C at least in part is responsible for the antiangiogenic activity of EEBP in vivo.

[*Chemical communications (Cambridge, England)*, **43**, 4516-4518 (2007)] [Lab. of Pharm. Chemistry]

One-pot synthesis of carbazoles by palladium-catalyzed N-arylation and oxidative coupling

Toshiaki WATANABE, Satoshi UEDA*, Shinsuke INUKI, Shinya OISHI, Nobutaka FUJII, Hiroaki OHNO

One-pot N-arylation and oxidative coupling can be promoted by a common palladium catalyst in the presence of appropriate additives: palladium-catalyzed N-arylation of anilines with aryl triflates under the standard conditions followed by addition of acetic acid under oxygen or air atmosphere afforded various types of functionalized carbazoles in good to excellent yields.

[*Chem. Eur. J.*, **13**(5), 1432-1441 (2007)] [Lab. of Medicinal Chemistry]

Mechanistic Study of a Pd/C-catalyzed Reduction of Aryl Sulfonates using the Mg-MeOH-NH_4OAc System

Akinori MORI, Tomoteru MIZUSAKI, Takashi IKAWA, Tomohiro MAEGAWA, Yasunari MONGUCHI, and Hironao SAJIKI*

A method for the deoxygenation of phenolic hydroxy groups via aryl triflates or mesylates has been established by using a combination of Pd/C-Mg-MeOH. The addition of NH_4OAc to the system markedly accelerated the reaction rate and expanded the scope of the reaction. Mechanistic studies suggested that a single-electron transfer process from the Pd(0) center to the benzene ring is involved in the reduction of aryl sulfonates and that NH_4OAc works as a solubilization reagent of the Mg salt and as an accelerator of the electron transfer, thus enhancing the reaction process. Our method was also applicable to the regioselective deuteration of benzene derivatives with CH_3OD as the solvent and deuterium source: the original hydroxy group could be efficiently replaced with a deuterium atom.

[*Chem. Eur. J.*, **13**(14), 4052-4063 (2007)] [Lab. of Medicinal Chemistry]

Efficient H/D Exchange Reactions of Alkyl-substituted Benzene Derivatives by Means of the Pd/C-H_2-D_2O System

Hiroyoshi ESAKI, Fumiyo AOKI, Miho UMEMURA, Masatsugu KATO, Tomohiro MAEGAWA, Yasunari MONGUCHI, and Hironao SAJIKI*

A method for efficient and extensive H/D exchange of substituted benzene derivatives which is catalyzed by heterogeneous Pd/C in D_2O as a deuterium source under hydrogen atmosphere is described. Multideuterium incorporation into unactivated linear or branched alkyl chains that bear a carboxyl, hydroxyl, ether, ester, or amide moiety and are connected with a benzene ring was achieved by using the Pd/C-H_2-D_2O system. The present method does not require expensive deuterium gas or any special equipment.

[*Chem. Eur. J.*, **13**(20), 5937-5943(2007)] [Lab. of Medicinal Chemistry]

Heterogeneous Pd/C-catalyzed Ligand-free, Room-temperature Suzuki-Miyaura Coupling Reactions in Aqueous Media

Tomohiro MAEGAWA, Yoshiaki KITAMURA, Satoko SAKO, Takahiro UDZU, Ai SAKURAI, Asami TANAKA, Yusuke KOBAYASHI, Koichi ENDO, Bora UTPAL, Takanori KURITA, Atsushi KOZAKI, Yasunari MONGUCHI, and Hironao SAJIKI*

A mild and efficient ligand-free Suzuki-Miyaura coupling reaction catalyzed by heterogeneous Pd/C was developed. Aryl bromides and triflates undergo the cross-coupling with aryl boronic acids in excellent yields without the presence of any additives in aq. media at room temperature Arylvinyl boronic acids are also applicable to this coupling reaction in high yields. The application of wet-type Pd/C to the coupling reaction was achieved without any loss of activity under aerobic conditions, and the reuse of Pd/C is feasible for a fifth run without significant loss of activity. Inductively coupled plasma (ICP) mass-spectrometric analysis of the filtrate from the reaction mixture demonstrated that the palladium metal hardly leached into the solution within the limits of the detector (< 1 ppm).

[*Chem. Commun.*, **47**, 5069-5071 (2007)] [Lab. of Medicinal Chemistry]

Ligand-free Pd/C-catalyzed Suzuki-Miyaura Coupling Reaction for the Synthesis of Heterobiaryl Derivatives

Yoshiaki KITAMURA, Satoko SAKO, Takahiro UDZU, Azusa TSUTSUI, Tomohiro MAEGAWA, Yasunari MONGUCHI, and Hironao SAJIKI*

We have developed a mild and efficient protocol for the ligand-free and heterogeneous Pd/C-catalyzed hetero Suzuki-Miyaura coupling reaction that allows for the synthesis of both heteroaryl-aryl and heteroaryl-heteroaryl derivatives in good to excellent yields.

[*J. Org. Chem.*, **72**(5), 1675-1680 (2007)] [Lab. of Medicinal Chemistry]

Design, Synthesis, and Validation of a Branched Flexible Linker for Bioactive Peptides

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Ethylene glycol-based branched flexible linker I that incorporates a fluorescent dansyl moiety was synthesized and used to connect two high affinity NDP-α-MSH (Ser-Tyr-Ser-Nle-Glu-His-D-Phe-Arg-Trp-Gly-Lys-Pro-Val) ligands or two low affinity MSH(4) (His-D-Phe-Arg-Trp) ligands. The linker was incorporated into the conjugate by solid-phase synthesis. In vitro biological evaluations showed that potency of binding to the human melanocortin 4 receptor was not diminished for linker-ligand combinations relative to the corresponding ligand alone.

[*J. Org. Chem.*, **72**(6), 2143-2150 (2007)] [Lab. of Medicinal Chemistry]

Novel Pd/C-Catalyzed Redox Reactions between Aliphatic Secondary Alcohols and Ketones under Hydrogenation Conditions: Application to H-D Exchange Reaction and the Mechanistic Study

Hiroyoshi ESAKI, Rumi OHTAKI, Tomohiro MAEGAWA, Yasunari MONGUCHI, and Hironao SAJIKI*

A liquid-phase redox system between secondary alcohols and ketones is described. Deuteration of either secondary alcohols or ketones using the Pd/C-H_2-D_2O system gave a mixture of deuterium-labeled secondary alcohols and ketones. The results indicated that the secondary alcohol was oxidized to the corresponding ketone without oxidants under the hydrogenation conditions and the hydrogenation of the aliphatic ketone to the corresponding secondary alcohol simultaneously proceeded. Detailed mechanistic studies on the redox system as well as the H-D exchange reaction are discussed.

[*Chem. Pharm. Bull.*, **55**(5), 837-839 (2007)] [Lab. of Medicinal Chemistry]

Pd/C(en) Catalyzed Chemoselective Hydrogenation in the Presence of Aryl Nitriles

Tomohiro MAEGAWA, Yuki FUJITA, Ai SAKURAI, Akira AKASHI, Mutsumi SATO, Kenji OONO, and Hironao SAJIKI*

The development of synthetic methods of aromatic nitriles were increasing in terms of its usefulness. Since aromatic nitriles are susceptible to the hydrogenation, it was desired for the development of chemoselective hydrogenation method with retention of nitrile groups. Although Pd/C is one of the most popular catalysts for hydrogenation, it is very difficult to achieve the chemoselective hydrogenation of substrates containing two or more reducible functional groups. A Pd/C formed an isolable complex with ethylenediamine (en) employed as catalytic poison, and [Pd/C(en)] catalyzed chemoselective hydrogenation of a variety of reducible functionalities distinguishing *O*-benzyl, *N*-Cbz and *O*-TBDMS protective groups, benzyl alcohols and epoxides. In these studies, the authors found the aryl nitriles could survive under the Pd/C(en)-catalyzed hydrogenation conditions in THF whose choice is important for the effective suppression. This methodology could be applied to the selective hydrogenation of alkene and alkyne functionalities in the presence of aromatic nitrile.

[*Synth. Commun.*, **37**(24), 4381-4388 (2007)] [Lab. of Medicinal Chemistry]

Development of a Practical and Scalable Preparation using Sonication of Pd/Fibroin Catalyst for Chemoselective Hydrogenation

Yoshiaki KITAMURA, Asami TANAKA, Mutsumi SATO, Keiji OONO, Takashi IKAWA, Tomohiro MAEGAWA, Yasunari MONGUCHI, and Hironao SAJIKI*

A practical and efficient preparation method of palladium-fibroin (Pd/Fib), silk-fibroin-supported Pd(0) by means of sonication, has been developed. The Pd/Fib catalyst could be prepared within 12 h at room temperature starting from commercial silk-fibroin and $Pd(OAc)_2$ in MeOH, whereas our previous preparation method required at least 4 days. The present improved process is applicable to a large-scale preparation of Pd/Fib. The Pd/Fib prepared by the present method also catalyzed chemoselective hydrogenation of acetylenes, olefins, and azides in the presence of aromatic ketones, aldehydes, and halides; N-Cbz protective groups; and benzyl esters, which are readily hydrogenated under the Pd/C- or Pd/C(en)-catalyzed hydrogenation conditions.

[*Tetrahedron*, **63**(5), 1270-1280. (2007)] [Lab. of Medicinal Chemistry]

Palladium on carbon-diethylamine-mediated hydrodeoxygenation of phenols under mild conditions

Akinori MORI, Tomoteru MIZUSAKI, Takashi Ikawa, Tomohiro MAEGAWA, Yasunari MONGUCHI, and Hironao SAJIKI*

Phenolic hydroxyl groups were readily deoxygenated via aryl sulfonate under the Pd/C-catalyzed hydrogenation conditions in the presence of diethylamine and the method could also be applicable to the hydrodeoxygenation of morphine to afford 3-deoxy-7,8-dihydromorphine. Diethylamine was not only a scavenger of the corresponding methanesulfonic acid derivative, which was produced during the reaction progress, but also a strong promoter of the Pd/C-catalyzed reduction of aryl sulfonates. This catalyst system could provide a general method for the deoxygenation of various phenol derivatives because of its mild reaction conditions, ease of handling, and no need of particular appratus.

[*Tetrahedron*, **63**(16), 6621-6631 (2007)] [Lab. of Medicinal Chemistry]

Heterogeneous Pd/C-catalyzed Ligand-free Suzuki-Miyaura Coupling Reaction Using Aryl Boronic Esters

Yoshiaki KITAMURA, Ai SAKURAI, Takahiro UDZU, Tomohiro MAEGAWA, Yasunari MONGUCHI, and Hironao SAJIKI*

Heterogeneous Pd/C-catalyzed Suzuki-Miyaura cross-coupling reaction of aryl boronic esters with aryl bromides was successfully carried out in aq. media at room temperature without the use of a ligand such as phosphine derivatives.

[*Synlett*, 2521-2524 (2007)] [Lab. of Medicinal Chemistry]

Ligand- and Base-free Synthesis of 1,3-Diynes Catalyzed by Low Loading of Heterogeneous Pd/C and CuI

Takanori KURITA, Masami ABE, Tomohiro MAEGAWA, Yasunari MONGUCHI, and Hironao SAJIKI*

A facile and environmentally friendly synthetic method for a variety of symetrical 1,3-diyne derivatives based on the Pd/C-CuI-catalyzed homocoupling reaction of terminal alkynes has been developed. The reaction was efficiently catalyzed by the extremely low loading (0.01-0.03 mol%) of Pd/C and CuI (3 mol%) in the presence of molecular oxygen (O_2) as an oxidant without any phosphine ligands and bases.

[*Inorg. Chem.*, **46**(24), 4381-4388 (2007)] [Lab. of Medicinal Chemistry]

Structural, Kinetic, and Thermodynamic Characterization of the Interconverting Isomers of MS-325, a Gadolinium(III)-Based Magnetic Resonance Angiography Contrast Agent

Zoltan TYEKLAR, Stephen U. DUNHAM, Katarina MIDELFORT, Daniel M. SCOTT, Hironao SAJIKI*, Karen ONG,Randall B. LAUFFER, Peter CARAVAN, and Thomas J. MCMURRY

The amphiphilic gadolinium complex MS-325 is a contrast agent for magnetic resonance angiography. MS-325 comprises a GdDTPA core with an appended phosphodiester moiety linked to a diphenylcyclohexyl group to facilitate noncovalent binding to serum albumin and extension of the plasma half-life in vivo. The chiral DTPA ligand (*R*) was derived from L-serine, and upon complexation with gadolinium, forms two interconvertible diastereomers, denoted herein as isomers **A** and **B**. The isomer interconversion is an acid-catalyzed process and is first orderin the metal complex. Solutions of MS-325 equilibrate at a 1.81:1 mixture of isomer **A**/isomer **B**. It is noteworthy that the biophysical properties of the two isomers are very similaras discussed in the accompanying manuscript.

[*Tetrahedron Lett.*, **48**, 1131—1133 (2007)] [Lab. of Pharm. Synthetic Chemistry]

Facile Synthesis of Phenacyl Iodides from Styrenes under Visible Light Irradiation with Fluorescent Lamps

Hiroki Nakayama, Akichika Itoh*

Phenacyl iodides were easily synthesized from styrenes with iodine under irradn. of visible light from a fluorescent lamp.

[*Chem. Pharm. Bull.*, **55**, 156—158 (2007)] [Lab. of Pharm. Synthetic Chemistry]

Photooxidation of Aldehydes with Molecular Oxygen in the Presence of Catalytic Bromine or Hydrobromic Acid

Shin-ichi Hirashima, Akichika Itoh*

Aldehydes were found to be oxidized with mol. oxygen to the corresponding carboxylic acid in the presence of catalytic hydrobromic acid or bromine under photoirradn.

[*Tetrahedron Lett.*, **48**, 2931—2934 (2007)] [Lab. of Pharm. Synthetic Chemistry]

Aerobic Photo-Oxidation in the Presence of Catalytic Allyl Bromide

Taichi Sugai, Akichika Itoh*

Alkyl groups at arom. nucleus and alcs. were found to be photo-oxidized to the corresponding carboxylic acid in the presence of catalytic allyl bromide.

[*Green Chem.*, **9**, 318-320 (2007)] [Lab. of Pharm. Synthetic Chemistry]

Aerobic Oxidation of Alcohols under Visible Light Irradiation of Fluorescent Lamp

Shin-ichi Hirashima, Akichika Itoh*

A catalytic amt. of magnesium bromide diethyletherate ($MgBr_2 \cdot Et_2O$) enabled us to carry out the aerobic photooxidn. of alcs. under irradn. of VIS from a general-purpose fluorescent lamp. Aliph. primary alcs., secondary alcs. and benzyl alcs. generally afforded the carboxylic acids directly in good to high yield. The bromine radical was generated in situ by continuous aerobic photooxidn. of the bromo anion from $MgBr_2.Et_2O$, and effected this oxidn. reaction.

[*Photochem. Photobiol. Sci.* **6**, 521-524 (2007)] [Lab. of Pharm. Synthetic Chemistry]

Aerobic Visible Light-Oxidation of Aromatic Methyl Groups to Carboxylic Acids

Shin-ichi Hirashima, Akichika Itoh*

A catalytic amt. of magnesium bromide diethyletherate ($MgBr_2 \cdot Et_2O$) enabled us to carry out the aerobic photo-oxidn. of a Me group at the arom. nucleus to the corresponding carboxylic acid in high yield under irradn. of VIS from a general-purpose fluorescent lamp. The bromine radical was generated in situ by continuous aerobic photo-oxidn. of the bromine anion from $MgBr_2 \cdot Et_2O$, and to effect this oxidn. reaction.

[*Chem. Pharm. Bull.*, **55**, 861-864 (2007)] [Lab. of Pharm. Synthetic Chemistry]

Deprotection of A Silyl Group with Mesoporous Silica

Akichika Itoh,* Tomohiro Kodama, Yukio Masaki

The triethylsilyl (TES) group of silyl ethers of several types is selectively and easily removed in the presence of a t-butyldimethylsilyl (TBDMS) group with a mesoporous silica MCM-41/MeOH heterogeneous system. Comparison of the efficiency was carried out among several solvents, and among such promoters as common zeolites and ion-exchange resins. Furthermore, FSM-16, another mesoporous silica, was examd. for the possibility of recycling by re-calcination at 400 °C after the reaction.

[*Tetrahedron Lett.*, **48**, 9096—9099 (2007)] [Lab. of Pharm. Synthetic Chemistry]

Aerobic Oxidation under Visible Light Irradiation of A Fluorescent Lamp with A Combination of Carbon Tetrabromide and Triphenyl Phosphine

Taichi Sugai, Akichika Itoh*

A combination of CBr_4-Ph_3P, a non-metal method, enables us to carry out aerobic photo-oxidn. of alcs. and arom. Me groups to the corresponding carboxylic acids under irradn. of vis from a general-purpose fluorescent lamp. Aliph. primary- and secondary alcs., benzyl alcs., and Me groups at the arom. nucleus generally afforded the carboxylic acids directly in good to high yield.

[*J. Photopolym. Sci. Techol.*, **20**, 197-200 (2007)] [Lab. of Pharm. Physical Chemistry]

Surface Engineering of Polymer Sheet by Plasma Techniques and Atom Transfer Radical Polymerization for Covalent Immobilization of Biomolecules.

Yasushi SASAI*, Michinori OIKAWA, Shin-ichi KONDO, and Masayuki KUZUYA

Well-defined polyglycidylmethacrylate (pGMA) brushes were fabricated on low-density polyethylene (LDPE) surface by plasma techniques and atom-transfer radical polymerization (ATRP). The fibrinolytic enzyme, urokinase, was covalently immobilized through a ring-opening coupling reaction of epoxy groups of pGMA chains with the nucleophilic groups of urokinase. The activity of immobilized urokinase was strongly affected by the thickness of pGMA brushes which can be controlled by ATRP condition. The stability of immobilized urokinase on pGMA grafted LDPE surface was really improved, indicating that the pGMA brushes worked as an efficient biointerface for immobilization of urokinase.

[*Chem. Pharm. Bull.*, **55**, 389-392 (2007)] [Lab. of Pharm. Physical Chemistry]

Conventional Synthesis of Amphiphilic Block Copolymer Utilized for Polymeric Micelle by Mechanochemical Solid-State Polymerization.

Shin-ichi KONDO*, Hisato MORI, Yasushi SASAI, and Masayuki KUZUYA

The first example is presented here of an amphiphilic block copolymer synthesized by mechanochemical solid-state polymerization and used to form polymeric micelles. Polymeric micelle formation was carried out by a dialysis method with the block copolymer possessing galactose as a hydrophilic side chain and theophylline as a hydrophobic side chain. A narrow distribution of diameters was observed in the polymeric micelle solution. It was suggested that the block copolymer synthesized by mechanochemical solid-state polymerization was suitable for the preparation of polymeric micelles as materials obtained by living polymerization.

[*Thin Solid Films*, **515**, 4136-14140 (2007)] [Lab. of Pharm. Physical Chemistry]

Development of biomaterial using durable surface wettability fabricated by plasma-assisted immobilization of hydrophilic polymer.

Shin-ichi KONDO*, Yasushi SASAI, Masayuki KUZUYA

As a series of plasma-assisted immobilization of bio-molecule for bio application, 12-mer oligo-DNA was immobilized on the surface of LDPE-VEMAC sheet, which was prepared by plasma-assisted method and possessed a lot of carboxyl groups on the surface. A larger amount of oligo-DNA could be immobilized by the present technique compared with other methods reported. The sheet immobilizing oligo-DNA detected the complementary oligo-DNA and was reusable for several times at least under present experimental condition. This method would be useful for the fabrication of the analytical instrument such as DNA chip, protein chip and affinity chromatography.

[*Asian.J. Pharm.Sci.*, **2**, 220-226 (2007)] [Lab. of Pharm.Engineering]

Evaluation of the interaction of polyethylene glycol coated PLGA nanospheres with macrophage cells using flow cytometry

Koji NAKANO, Yohei BANDO, Yuichi TOZUKA, Hirofumi TAKEUCHI*

To assess the interaction between nanospheres composed with *D,L*-lactide/glycolide copolymer (PLGA) and J774 cells using different particulate formulations and determine suitable formulations for polymeric nanospheres having reduced uptake by macrophage cells. The polymeric nanospheres were prepared by the emulsion solvent diffusion method with PLGA and polyethylene glycol (PEG) conjugated PLGA (PEGylated PLGA). The interaction of polymeric nanospheres with J774 cells was evaluated with flow cytometry. When PEGylated PLGA nanospheres were incubated with J744 cells, a signifi cantly lower fluorescence emission intensity from 1,1'-Dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate (DiI) incorporated in the particle was detected than was the case for non-coated nanospheres.

[*Microvasucular Research*, **73**, 39-47 (2007)] [Lab. of Pharm.Engineering]

Interaction between liposomes and RBC in microvessels in vivo

Jae Hong JEONG, Yasuhiko SUGII, Motomu MINAMIYAMA, Hirofumi TAKEUCHI*, Koji OKAMOTO

Liposomes are phospholipid vesicles that can serve as carriers of biologically active agents in vitro and in vivo. Here, we describe the movement of liposomes suspended with blood flowing in capillaries. Liposomes were coated with a polymer to extend their lifespan in rat mesenteric blood vessels and detected by fluorescent staining. Liposome activity was observed by intravital microscopy using a high-speed camera system at 5 and 60 min after liposome administration. Liposome velocity was determined using two-dimensional cross-correlation, and blood flow was measured by high-resolution PIV (particle image velocimetry). The results showed that the motion of polymer-coated liposome followed the phase averaged velocity distribution of heartbeats while flowing with red blood cells in microvessels. Liposome particles tend to move toward the near blood vessel wall in the low velocity of blood flow.

[*Int. J. Pharm.*, **331**, 38–45 (2007)] [Lab. of Pharm. Engineering]

Application of Ascorbic Acid 2-glucoside as a Solubilizing Agent for Clarithromycin: Solubilization and Nanoparticle Formation.

Yutaka INOUE, Sachi YOSHIMURA, Yuichi TOZUKA*, Kunikazu MORIBE, Takuya KUMAMOTO, Tsutomu ISHIKAWA and Keiji YAMAMOTO.

Clarithromycin (CAM) was co-ground with L-ascorbic acid 2-glucoside (AA-2G), a newly developed food additive, to improve the solubility characteristics. The complete solubilizing effect of AA-2G was observed for the ground mixture with 1:1 molar ratio. When ground mixtures of CAM and AA-2G (2:1) were dispersed into water, not only the solubilization of CAM was observed but also nanoparticle formation with a mean particle diameter of 280 nm. The formation of nanoparticles was only observed when CAM was co-ground with AA-2G in the molar ratio of 2:1, which might be attributable to a grinding-induced interaction in the solid-state via the ketone group in lactone ring of CAM.

[*J. Incl. Phenom. Macrocyc. Chem.*, **57**, 289–295 (2007)] [Lab. of Pharm. Engineering]

Solubility-dependent Complexation of Active Pharmaceutical Ingredients with Trimethyl-β-cyclodextrin under Supercritical Fluid Condition.

Kunikazu MORIBE, Takayuki FUJITO, Yuichi TOZUKA* and Keiji YAMAMOTO.

The effect of the solubility of active pharmaceutical ingredients (APIs) in supercritical carbon dioxide (SC-CO_2) on their complexation behavior with trimethyl-β-cyclodextrin (TM-β-CD) has been investigated. Drug complexation depended both on SC-CO_2 treatment time and on drug solubility in SC-CO_2. The inclusion complex formation of flurbiprofen with TM-β-CD proceeded slowly compared with the case of ibuprofen. The slower complexation behavior was also observed when naproxen was used as the guest molecule. These results indicate that dissolution of drug molecules in SC-CO_2 is a rate-determining step for the inclusion complex formation with TM-β-CD and that complexation proceeds after dissolving the both components in SC-CO_2.

[*Chem. Pharm. Bull.*, **55**, 359–363 (2007)] [Lab. of Pharm. Engineering]

Preparation of Drug Nanoparticles by Co-grinding with Cyclodextrins: Formation Mechanism and Factors Affecting Nanoparticle Formation.

Arpansiree WONGMEKIA, Yuichi TOZUKA*, Kunikazu MORIBE and Keiji YAMAMOTO.

The aim of this study was to investigate the factors affecting the formation of pranlukast nanoparticle prepared by co-grinding with β-cyclodextrin (β-CD) and to elucidate the mechanism of nanoparticle formation. High-resolution scanning electron microscopy demonstrated that primary drug nanoparticles having a particle size around 50 nm were observed in the ground mixture. The grinding time, the moisture content, and the CD content had significant influences on the formation of drug nanoparticles. The CD matrix may form and stabilize primary particles by its interaction with the particle surface through water molecules.

[*Int. J. Pharm.*, **338**, 1–6 (2007)] [Lab. of Pharm. Engineering]

Stabilization Mechanism of Limaprost in Solid Dosage Form.

Kunikazu MORIBE, Noboru SEKIYA, Takayuki FUJITO,Chihiro YOKOHAMA, Yuichi TOZUKA* and Keiji YAMAMOTO.

The effect of polymeric pharmaceutical excipients on the degradation of limaprost by hydrolysiswas assessed by near infrared (NIR) spectroscopy and spin–spin relaxation time (T_2) measurements of proton NMR. Freeze-dried limaprost-alfadex formulated with various polymeric pharmaceutical excipientswas exposed under humidified condition at 25°C and 75% relative humidity. The proton NMR spin–spin relaxation time measurements indicated that the structural relaxation of a polymeric excipient changed upon humidification. The polysaccharides showed only Gaussian relaxations, but the cellulose derivatives showed Lorentzian relaxations and Gaussian relaxations. The T_2 values of the Gaussian relaxation in HPMC and HPC-L were higher than those in dextran40, dextrin, and pullulan throughout the humidifying period. The higher molecular mobility of HPMC and HPC-L is related to the mobility of water, which may accelerate limaprost degradation.

[*Anticancer Res.*, **27**, 927-932 (2007)] [Lab. of Pharmaceutics]

Incadronate Induces Cell Detachment and Apoptosis in Prostatic PC-3 Cells.

Shinji MATSUNAGA, Kazuhiro IGUCHI, Shigeyuki USUI, and Kazuyuki HIRANO*.

Bisphosphonates are widely used for the treatment and prevention of osteoporosis and are also effective in the treatment of bone metastasis of prostatic cancer. Several mechanisms underlaying the antitumor effect of bisphosphonates have been proposed, including direct effects on tumor cells, such as induction of apoptosis and inhibition of invation. It was found that incadronate induced cell detachment with dephosphorylation of focal adhension kinase (FAK). The induction of cell detachment by incadronate was prevented by coincubation with geranylgeraniol. The activation of caspase-3 was observed in incadronate-treated floating cells, but not in adherent cells. A caspase inhibitor did not inhibit cell detachment by incadronate but it markedly prevented cell death. These results suggest that incadronate induces cell detachment, followed by caspase-dependent apoptosis.

[*J. Androl.*, **28**, 670-678 (2007)] [Lab. of Pharmaceutics]

Isolation and Characterization of LNCaP Sublines Differing in Hormone Sensitivity.

Kazuhiro IGUCHI, Kenichiro ISHII, Toru NAKANO, Takashi OTSUKA, Shigeyuki USUI, Yoshiki SUGIYAMA, and Kazuyuki HIRANO*.

Prostate cancer is a heterogeneous disease with varying degree of androgen sensitivity. In this study, we performed a limiting dilution of human prostate LNCaP cells, and isolated two sublines, LNCaP-E9 and LNCaP-G4, with differential hormone-sensitivity. The growth of E9 cells was decreased in the presense of androgens, while that of androgen-treated G4 cells was biphasic. Although the androgen receptor expression level in E9 cells was similar to that seen in G4 cells, the expression of PSA mRNA and protein was significantly lower in the E9 cells. Moreover, the androgen-based stimulation of PSA mRNA expression was less sensitive in E9 cells than G4 cells. LNCaP-E9 cells show lower androgen sensitivity than LNCaP-G4 cells. E9 and G4 cells would be helpful for understanding the biology of hormone-refractory prostate cancer.

[*J. Cell. Biochem.*, **102**, 1051-1058 (2007)] [Lab. of Pharmaceutics]

Transcriptional Regulation of Aquaporin 3 by Insulin.

Shota HIGUCHI, Masafumi KUBOTA, Kazuhiro IGUCHI, Shigeyuki USUI, Tadashi KIHO, and Kazuyuki HIRANO*.

We constructed a luciferase reporter vector containing promoter region of the AQP3 gene for a reporter gene assay and observed that luciferase activity in transfectants with the plasmid decreased on treatment with insulin. Serial deletion constructs revealed two regions responsible for the insulin-mediated repression, one between bps -1382 and -780, and the other between bps -404 and -82. mRNA expression of forkhead box a2 (Foxa2), the binding site of which was located between bps -1382 and –780, was found to decrease on treatment with insulin. A mutant reporter plasmid with an altered Foxa2-binding site and siRNA for the Foxa2 sequence counteracted the insulin-mediated repression of AQP3 transcription. These results suggest that Foxa2 is one of the transcriptional regulators for AQP3 gene expression regulated by insulin.

[*Anticancer Res.*, **27**, 3843-3848 (2007)] [Lab. of Pharmaceutics]

Pamidronate Down-regulates Urokinase-type Plasminogen Activator Expression in PC-3 Prostate Cancer Cells.

Kazuhiro IGUCHI, Yoshiki TATSUDA, Shigeyuki USUI, and Kazuyuki HIRANO*.

Bisphosphonates are considered to be effective in preventing tumor metastasis to bone. Urokinase-type plasminogen activator (uPA) is thought to be critically involved in the metastatis phenotype of prostate cancer. In this study, we examined the effect of pamidronate on uPA expression in PC-3 prostate cancer cells. Pamidronate inhibited uPA mRNA expression by about 90% at 24 h. The inhibition of uPA mRNA expression was prevented in part by cotreatment with geranylgeranyl diphosphonate. Moreover, GGTI-286, a selective inhibitor of geranylgeranyl transferase , also inhibited uPA mRNA expression. These results indicate that the decrease in uPA expression brought about by pamidronate is dependent on the inhibition of geranylgeranylation of proteins and occurs at the transcriptional level.

[*Mol .Cancer Ther.*, **6**, 2310-2318 (2007)] [Lab. of Pharmaceutics]

Alteration of dihydropyrimidine dehydrogenase expression by IFN-alpha affects the antiproliferative effects of 5-fluorouracil in human hepatocellular carcinoma cells.

Shinji OIE, Mayumi ONO, Hiroto FUKUSHIMA, Fumihito HOSOI, Hirohisa YANO, Yuuichiro MARUYAMA, Masamichi KOJIRO, Tadafumi TERADA, Kazuyuki HIRANO*, Michihiko KUWANO, and Yuji YAMADA.

This study examines the role of DPD in the antiproliferative effects of 5-FU combined with IFN-alpha on hepatocellular carcinoma (HCC) cells in culture. Coadministration of IFN-alpha and 5-FU showed synergistic effects against HAK-1A and KYN-2 but antagonistic effects against KYN-3. Coadministration of a selective DPD inhibitor, 5-chloro-2,4-dihydroxypyridine (CDHP), enhanced the antiproliferative effect of 5-FU and IFN-alpha on KYN-3 approximately 4-fold. Inhibition of DPD activity by CDHP may enhance the efficacy of IFN-alpha and 5-FU combination therapy in patients with HCC showing resistance to this therapy.

[*Biomed. Pharmacothe.*, **61**, 113-119 (2007)] [Lab. of Hygienics]

Suppressive Effect of Post- or Pre-treatment of Aspirin Metabolite on Mitomycin C-induced Genotoxicity Using the Somatic Mutation and Recombination Test in *Drosophila melanogaster*.

Miki NIIKAWA, Seizai SHIN and Hisamitsu NAGASE*.

To reveal the mechanism of bio-antimutagenicity and/or preventive effect of aspirin, we evaluated the suppressive ability of each aspirin metabolite, such as salicylic acid (SA), salicyluric acid (SUA), gentisic acid (GA), gentisuric acid (GUA) and 2,3-dihydroxybenzoic acid (DHBA), in SMART in *Drosophila melanogaster* using post- and pre-treatment. As for the post-treatment, SA reduced the numbers of large single and twin spots. GA reduced the small single and large single spots, and GUA reduced the single spots, large single and twin spots. The inhibition of GUA is slightly stronger than that of any other metabolites. As for the pre-treatment, aspirin, SUA, GA and DHBA reduced the numbers of small single spots. SUA, GE and DHBA reduced the number of large single spots. Aspirin and its metabolites did not reduce the number of twin spots. The results of the present study suggest that SA, GA and GUA repair or replicate DNA-damage by MMC and SUA, GA, GUA and DHBA prevent DNA-damage by MMC.

[*Biomed. Pharmacother.*, **61**, 250-253(2007)] [Lab. of Hygienics]

Effect of Aspirin on DNA Damage Induced by MMC in *Drosophila*

Miki NIIKAWA and Hisamitsu NAGASE*

To reveal the mechanism of antigenotoxicity of aspirin, we evaluated the protective effects of aspirin against the genotoxicity of MMC with the DNA repair test in *Drosophila melanogaster*. Three types of treatment of aspirin were performed as co-, post- and pre-treatment. Aspirin co-treatment suppressed effectively the genotoxicity of MMC in a dose-dependent manner and the sex ratio at a dose of aspirin 10 mg/bottle elevated from 0.01 (without aspirin) to 0.65 at *sc* z^1 $w^{+(TE)}$ *mei-9*^{a} *mei-41*^{D5} / *-C(1)DX, y f* [mei-9 mei-41, Rec^- male・Rec^+ female] consists of DNA repair-deficient (Rec^-) males and –proficient (Rec^+) females. The antigenotoxic effect of aspirin on [mei-41, Rec- male・Rec^+ female] was similar to that on [mei-9, Rec- male・Rec^+ female]. But post- and pre-treatment by aspirin did not affect the genotoxicity of MMC on [mei-9 mei-41, Rec^- male・Rec^+ female].

[*Biol. Pharm. Bull.*, **30**, 1265-1270 (2007)] [Lab. of Herbal Garden]

DNA Authentication of Plantago Herb Based on Nucleotide Sequences of 18S-28S rRNA Internal Transcribed Spacer Region

Fatma Pinar SAHIN, Hiromi YAMASHITA, Yahong GUO, Kazuyoshi TERASKA, Toshiya KONDO, Yutaka YAMAMOTO, Hiroshi SHIMADA, Masao FUJITA, Takeshi KAWASAKI, Eiji SAKAI, Toshihiro TANAKA, Yukihiro GODA and Hajime MIZUKAMI*.

Internal transcribed spacer (ITS) regions of nuclear ribosomal RAN gene were amplified from 23 plant- and herbarium specimens belonging to eight *Plantago* species (*P. asiatica, P. depressa, P. major, P. erosa, P. hostifolia, P. camtschatica, P. virginica* and *P. lanceolata*). Sequence comparison indication that these *Plantao* species could be identified based on the sequence type of the ITS locus. Sequence analysis of the ITS regions amplified from the crude drug Plantago Herb obtained in the markets indicated that all the drugs from Japan were derived from P. asiatica whereas the samples obtained in China were originated from various *Plantago* species including *P. asiatica, P. depressa, P. major* and *P. erosa.*

[*Heterocycles*, **71**, 1779-1785 (2007)] [Lab. of Herbal Garden]

New Constituents From the Roots of *ERYTHRINA* x *Bidwillii*

Hitoshi TANAKA, * Hisanori HATTORI, Masaru SATO, Ryozo YAMAGUCHI, Toshio FUKAI, Toshihiro TANAKA and Eiji SAKAI.

Three new compounds, erythbidins C-E (1-3), together with five known compounds 4-8 were isolated from the roots of *Erythrina* x *bidwillii*. Their structures were established on the basis of spectroscopic evidence. Among the isolated compounds, erythbidin E (3) showed a potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA).

[*Allergology Int.*, **56**, 293-301 (2007)] [Lab. of Clinical Pharmacology]

Lactobacillus Acidophilus Strain L-92 Regulates the Production of Th1 Cytokine as well as Th2 Cytokines.

Akiko TORII, Shinpei TORII, Shigeru FUJIWARA, Hiroyuki TANAKA, Naoki INAGAKI and Hiroichi NAGAI*.

L-92 singnificantly suppressed serum OVA-specific IgE levels for a long period. Cytokines such as interferon (IFN)-γ, interleukin (IL)-4 and IL-10 and Igs such as total IgE and OVA-specific IgE were produced at singnificantly lower levels by splenocytes of L-92-treated mice, compared with those of control mice. In contrast, transforming growth factor (TGF)-β and IgA levels produced by PPs from L-92-treated mice were significantly higher than in those from control mice.

[*Eur. J. Pharmacol.*, **563**, 233-239 (2007)] [Lab. of Pharmacology]

Pharmacological Characterization of a Chronic Pruritus Model Induced by Multiple Application of 2,4,6-Trinitrochlorobenzene in NC Mice.

Hirotaka YAMASHITA*, Toshiaki MAKINO, Hajime MIZUKAMI and Mitsuhiko NOSE

Female NC/Jic mice were sensitized and challenged repeatedly at 48 h intervals for 10 and 30 days by painting 1% 2,4,6-trinitrochlorobenzene (TNCB) on both ears. Mice challenged with TNCB for 30 days developed an inflammatory dermatitis with high immunoglobulin E (IgE) titer. Histological analysis with acidic Toluidine Blue staining revealed that dermal mast cells markedly differentiated and intensely degranulated, consistent with a dramatic increase in scratching behavior. Terfenadine and cyproheptadine attenuated the chronic scratching behavior. Tacrolimus and dexamethasone were less effective and cromolyn showed no effect. In addition, terfenadine and tacrolimus suppressed the degranulation of mast cells. The present chronic scratching model could be suitable to evaluate drugs effective for suppression of mast cell differentiation and degranulation by irritation.

[*Arch. Biochem. Biophys.*, **464**, 122–129 (2007)] [Lab. of Biochemistry]

Rat NAD$^+$-dependent 3α-Hydroxysteroid Dehydrogenase (AKR1C17): A Member of the Aldo-Keto Reductase Family Highly Expressed in Kidney Cytosol.

Masaharu SANAI, Satoshi ENDO, Toshiyuki MATSUNAGA, Shuhei ISHIKURA, Kazuo TAJIMA, Ossama EL-KABBANI and Akira HARA*

The recombinant AKR1C17 efficiently oxidized 3α-hydroxysteroids and bile acids using NAD$^+$ as the preferred coenzyme, and was inhibited by ketamine and organic anions. The mRNA for AKR1C17 was detected specifically in rat kidney, where the enzyme was more highly expressed as a cytosolic protein than NADP(H)-dependent 3α-HSD (AKR1C9). Thus, AKR1C17 represents a novel NAD$^+$-dependent type of cytosolic 3α-HSD with unique inhibitor sensitivity and tissue distribution. In addition, the replacement of Gln270 and Glu276 of AKR1C17 with the corresponding residues of AKR1C9 resulted in a switch in favor of NADP$^+$ specificity, suggesting their key roles in coenzyme specificity.

[*Arch. Biochem. Biophys.*, **465**, 136-147 (2007)] [Lab. of Biochemistry]

Enzymatic Characteristics of an Aldo-Keto Reductase Family Protein (AKR1C15) and its Localization in Rat Tissues.

Satoshi ENDO*, Toshiyuki MATSUNAGA, Kenji HORIE, Kazuo TAJIMA, Yasuo BUNAI, Vincenzo CARBONE, Ossama El-KABBANI and Akira HARA

We show that recombinant AKR1C15 is an NADPH-dependent reductase with broad substrate specificity for various carbonyl compounds. Especially, all-*trans*-retinal, α-diketones and lipid-derived aldehydes were excellent substrates showing low K_m values. Immunohistochemical and RT-PCR analyses revealed that AKR1C15 is highly expressed in rat bronchiolar Clara cells, type II alveolar cells, gastric parietal cells, the epithelial cells of the stomach and colon and the brown adipocytes. Moreover, the enzyme was consistently expressed in the vascular endothelial cells. These results suggest that AKR1C15 plays a role in retinoid, steroid, isoprenoid and carbohydrate metabolism, as well as a defense system, protecting against reactive carbonyl compounds.

[*Arch. Biochem. Biophys.*, **467**, 76-86 (2007)] [Lab. of Biochemistry]

Characterization of Rat and Mouse NAD$^+$-dependent 3α/17β/20α-Hydroxysteroid Dehydrogenases and Identification of Substrate Specificity Determinants by Site-Directed Mutagenesis.

Satoshi ENDO*, Masaharu SANAI, Kenji HORIE, Toshiyuki MATSUNAGA, Shuhei ISHIKURA, Kazuo TAJIMA, Ossama El-KABBANI and Akira HARA

We characterized rat and mouse aldo-keto reductases (AKR1C16 and AKR1C13, respectively). The enzymes oxidized non-steroidal alcohols and showed low 3α/17β/20α-hydroxysteroid dehydrogenase (HSD) activities. On the other hand, AKR1C17 that shares 95% sequence identity with AKR1C16 showed 3α-HSD activity. We examined roles of Tyr24, Asp128 and Phe129 by site-directed mutagenesis. As a result, the importance of the residue 24 for substrate recognition was verified. AKR1C16 is also 92% identical with rat NAD$^+$-dependent 17β-HSD (AKR1C24), which possesses Tyr24. The replacement of Asp128, Phe129 and Ser137 of AKR1C16 with the corresponding residues of AKR1C24 increased the catalytic efficiency for 17β- and 20α-hydroxysteroids.

[*Med. Chem.*, **3**, 546-50 (2007)] [Lab. of Biochemistry]

A Salicylic Acid-Based Analogue Discovered from Virtual Screening as a Potent Inhibitor of Human 20α-Hydroxysteroid Dehydrogenase.

Urmi DHAGAT, Vincenzo CARBONE, Roland P.-T. CHUNG, Toshiyuki MATSUNAGA, Satoshi ENDO, Akira HARA* and Ossama El-KABBANI

20α-HSD (AKR1C1) plays a key role in the metabolism of progesterone and other steroid hormones. Increased activity of AKR1C1 is associated with termination of pregnancy and the development of breast cancer, endometriosis and endometrial cancer. Inhibition of the undesired activity of AKR1C1 will help reduce risks of premature birth, neurological disorders and the development of cancer. In order to identify new inhibitors of AKR1C1 we adopted a virtual screening-based approach using the automated DOCK program. Kinetic analysis revealed 3,5-diiodosalicylic acid as a potent competitive inhibitor (K_i=9 nM). This is the first report to show aspirin (IC_{50}=21 μM) and its metabolite salicylic acid (IC_{50}=7.8 μM) as inhibitors of AKR1C1.

[*Acta Crystallogr. Sect. F Struct. Biol. Cryst. Commun.*, **63**, 825-30 (2007)] [Lab. of Biochemistry]

Structure of 3(17)α-Hydroxysteroid Dehydrogenase (AKR1C21) Holoenzyme from an Orthorhombic Crystal Form: An Insight into the Bifunctionality of the Enzyme.

Urmi DHAGAT, Vincenzo CARBONE, Roland P.-T. CHUNG, Clemens Schulze-BRIESE, Satoshi ENDO, Akira HARA* and Ossama EL-KABBANI.

Mouse 3(17)α-hydroxysteroid dehydrogenase (AKR1C21) is a bifunctional enzyme that catalyses the oxidoreduction of the 3- and 17-hydroxy/keto groups of steroid substrates such as oestrogens, androgens and neurosteroids. The structure of the AKR1C21-NADPH binary complex was determined from an orthorhombic crystal belonging to space group P2(1)2(1)2(1) at a resolution of 1.8 A. In order to identify the factors responsible for the bifunctionality of AKR1C21, three steroid substrates including a 17-keto steroid, a 3-keto steroid and a 3α-hydroxysteroid were docked into the substrate-binding cavity. These models suggest that Lys31, Gly225 and Gly226 are important for ligand recognition and orientation in the active site.

[*Life Sci.*, **80**, 554-558 (2007)] [Lab. of Biochemistry]

Stereoselective Reduction of 4-Benzoylpyridine in the Heart of Vertebrates.

Hideaki SHIMADA, Koji IMAISHI, Takaomi HIRASHIMA, Takeshi KITANO, Shuhei ISHIKURA, Akira HARA* and Yorishige IMAMURA.

4-Benzoylpyridine (4-BP) was stereoselectively reduced to S(-)-α-phenyl-4-pyridylmethanol [S(-)-PPOL] in the cytosolic fractions from the heart of pig, rabbit and guinea pig. However, only rat heart cytosol had little ability to reduce stereoselectively 4-BP. To elucidate this reason, amino acid sequence of rat heart carbonyl reductase (RatHCR) was compared with that of pig heart carbonyl reductase (PigHCR). RatHCR showed a high identity with PigHCR in amino acid sequence. Furthermore, recombinant RatHCR was confirmed to reduce stereoselectively 4-BP to S(-)-PPOL with a high optical purity comparable to recombinant PigHCR. It is possible that in the cytosolic fraction from the heart of rat, constitutive reductase other than RatHCR counteracts the stereoselective reduction of 4-BP to S(-)-PPOL, by catalyzing the reduction of 4-BP to the R(+)-enantiomer.

[*Biol. Pharm. Bull.*, **30**, 1787-1791 (2007)] [Lab. of Biochemistry]

Characterization of an Oligomeric Carbonyl Reductase of Dog Liver: Its Identity with Peroxisomal Tetrameric Carbonyl Reductase.

Satoshi ENDO*, Toshiyuki MATSUNAGA, Makoto NAGANO, Hiroko ABE, Shuhei ISHIKURA, Yorishige IMAMURA and Akira HARA

Dog liver contains an oligomeric NADPH-dependent carbonyl reductase (CR) with substrate specificity for alkyl phenyl ketones. The enzyme is a ~100-kDa tetramer composing of 27-kDa subunit, and resembles pig PTCR in substrate specificity and inhibitor sensitivity. Furthermore, the amino acid sequence of dog CR was 84% identical to that of pig PTCR and had a C-terminal peroxisomal targeting signal type 1. The immunoprecipitation using the anti-pig PTCR antibody shows that the dog enzyme is a major form of soluble NADPH-dependent all-*trans*-retinal reductase in liver. Thus, dog oligomeric CR is identical to PTCR, and may play a role in retinoid metabolism as a retinal reductase.

[*Cell Tissue Res.*, **328**, 355-63 (2007)] [Lab. of Biochemistry]

Comparative Characterization of Pulmonary Surfactant Aggregates and Alkaline Phosphatase Isozymes in Human Lung Carcinoma Tissue.

Nozomi IINO, Toshiyuki MATSUNAGA*, Tsuyoshi HARADA, Seiji IGARASHI, Iwao KOYAMA and Tsugikazu KOMODA

Since several different AP isozymes have been detected in the pneumocytes of lung cancer patients, we have investigated contents of surfactant-associated protein A (SP-A) and alkaline phosphatase (AP) isozymes in subtype of surfactant aggregates. Liver AP, Bone type AP and SP-A were different among tissues from patients with non-carcinoma, squamous cell carcinoma and adenocarcinoma. These proteins were identified immunohistochemically in type II pneumocytes from non-carcinoma and adenocarcinoma tissues, but SP-A was observed in squamous cell carcinoma tissues. The present study has thus revealed several differences in pulmonary surfactant aggregates and AP isozymes between adenocarcinoma and squamous cell carcinoma tissues.

[*J. Autoimmun.*, **28**, 7–18 (2007)] [Lab. of Biochemistry]

Autoantibody Response to Microsomal Epoxide Hydrolase in Hepatitis C and A.

Toshitaka AKATSUKA, Nobuharu KOBAYASHI, Takashi ISHIKAWA, Takafumi SAITO, Michiko SHINDO, Masayoshi YAMAUCHI, Kazutaka KUROKOHCHI, Hitoshi MIYAZAWA, Hongying DUAN, Toshiyuki MATSUNAGA*, Tsugikazu KOMODA, Christophe MORISSEAU and Bruce D. HAMMOCK

The AN6520 antigen (AN-Ag) is a normal cellular protein mainly expressed in liver that was found associated with non-A, non-B hepatitis. IgM capture assay using purified AN-Ag confirmed that the antibody response to AN-Ag is associated almost exclusively with hepatitis C cases (29%). Screening of a human liver expression library revealed that AN-Ag is mainly the microsomal epoxide hydrolase. Study using the recombinant human AN-Ag found that antibodies against this protein are associated with nearly 82% of hepatitis C virus infections and surprisingly with 46% of patients with hepatitis A. The appearance of AN-Ag in hepatitis C patients and the antibody responses indicate AN-Ag to be a marker for pathology associated with hepatitis C and A.

[*Jpn. J. Pharm. Health Care Sci.*, **33**, 925-931 (2007)] [Lab. of Clinical Pharmacy]

Analysis of Dispensing Errors Made by Fourth Year Students during Pharmacy Practice at Gifu Pharmaceutical University.

Hitomi TERAMACHI*, Aya SHINODA, Eiji TAKASHIMA, Masafumi KUBOTA and Teruo TSUCHIYA

We conducted a survey of fourth year students at Gifu Pharmaceutical University during practical training in the pharmacy department. The rate of dispensing errors was a high 7.8%, and errors relating to names and specifications of drugs accounted for 42.1% of them. Dispensing errors were most frequent on the 1st (Mon.) and 4th (Thu.) days of practice. These results indicate that dispensing practice should be shortened on the 1st day to allow time for an orientation lecture and on the fourth day, students need to pay more attention to avoiding careless mistakes. On a daily basis, the rate of dispensing errors was highest between the early morning and 11 a.m., and 2 p.m. to 3 p.m. From this we inferred that, regardless of the workload, errors often occur soon after the start of pharmacy practice, both in the morning and afternoon, so students need to be more alert in the morning and after lunch.

[*J. Jpn. Soc. Hosp. Pharma.*, **43**, 1680-1683 (2007)] [Lab. of Clinical Pharmacy]

Introduction and Evaluation of the Simple Suspension Method.

Hitomi TERAMACHI*, Minako YASUDA, Michiyo OKADA, Eiji TAKASHIMA, Yoshihiro ITO and Teruo TSUCHIYA

Many elderly patients are fed by tube in Nishimino Kousei Hospital. Therefore the work of crushing practice for medication using feeding tubes has been increasing steadily. The purpose of this study was to investigate the current crushing practice and to improve pharmacy practice efficiency through the introduction of simple suspension method that enables tablets and capsules to be administrated after dissolving or collapsing in hot water without crushing. The current crushing practice hours was compared with predicted hours using simple suspension method between May and December 2004. We predicted that the simple suspension method would reduce the weekly dispensing time from 5.1 hours required for crushing to 1.5 hours. These results suggest that the introduction of simple suspension method enable to conduct more efficient and effective pharmacy practice.

[*Pediatr. Emerg. Care*, **23**, 472-473 (2007)] [Lab. of Drug Informatics]

Accidental Etizolam Ingestion in an Infant.

Zenichiro KATO, Mitsuhiro NAKAMURA*, Michinori FUNATO, Hideaki KUWABARA and Naomi KONDO.

Etizolam is an antidepressive tianozepine drug that is used worldwide. The most frequent adverse effects in adults are drowsiness and muscle weakness, and paradoxical excitation can be caused rarely, however, no information exists on intoxication in children. We present a case of a child who accidentally took a single dose of etizolam, approximately the same as a therapeutic dose for adults, and who showed paradoxical excitation and muscle weakness. The case suggests that pediatricians and emergency physicians should be aware of the possible therapeutic approaches such as flumazenil against intoxication of etizolam and necessity of further investigations on a specific therapeutic guideline for overdose management especially in children.

[*Jpn. J. Ther. Drug Monit.*, **24**, 104-112 (2007)] [Lab. of Drug Informatics]

Development of TDM Management System using Paperless Electronic Medical Records.

Mitsuhiro NAKAMURA*, Katsuhiko MATSUURA, Teruo TSUCHIYA and Tadashi SUGIYAMA.

In order to improve efficiency and efficacy of therapeutic drug monitoring (TDM) services, we designed a new TDM management system based on an advanced paperless electrical medical recording system (SystemGIFU). Our TDM system can create TDM reports for doctors. The reports standardized with eXtensible Markup Language (XML), and stored in the database placed in SystemGIFU and can be viewed on-line through a unified user interface and visualization. The number of TDM order running on this TDM system were 2491 from April 1, 2005 to May 31, 2006. TDM system satisfy "the Notification on the Electronic Storage of Clinical Records" issued by the Ministry of Health and Welfare. This system can contribute to clinical supporting by TDM.

[*Jpn. J. Drug Inform.*, **8**, 315-319 (2007)] [Lab. of Drug Informatics]

Development and Evaluation of an Admixing Support System for Injectable Anticancer Drugs.

Mitsuhiro NAKAMURA*, Kana FUKAWA, Chika IWATA, Akemi MURAOKA, Reiko MAMIYA and Tadashi SUGIYAMA.

Preparation and dispensing of cancer drugs are often complicated. We developed an admixing support program for injectable anticancer drugs. Database program, which facilitates calculation of the admixing liquid volume and the number of vials from prescribed amount of cancer drugs, has been developed with FileMaker Pro (FileMaker Inc.). This program also indicates proper dosage, infusion liquid volume and/or drip infusion rate based on the individual patient's information (i. e. age, weight, body surface area). Using check sheets prepared by the program, pharmacists and nurses involved with admixing procedudres in pediatric ward of our hosital. The program was applied to 433 calculataions for injectable anticancer drugs. In response to a questionnaire, nurses estimated the value of this program. Using this program, the admixing procedures have been performed more precisely and improved medical safety practices.

[*Jpn. J. Pharm. Health Care Sci.*, **33**, 191-199 (2007)] [Lab. of Drug Informatics]

Development of Preparation Checking System for Injections using Order Entry System Information and Newly Designed Clean Bench and Safety Cabinet.

Shinji OKAYASU, Mitsuhiro NAKAMURA*, Koichi CHIGUSA, Kiyoshi SAKURAI and Tadashi SUGIYAMA.

Clinical pharmacists are deeply involved with dispensing of injectable anticancer drugs and TPN. Checking prescription and dispensing of injectable drugs are often complicated and time consuming. In order to improve efficiency and efficacy of these procedures, we newly designed an aseptic preparation support system. We developed the clean bench and safty cabinet, which were incorporated an embedded 15" LCD monitor and a three-button footswitch. The clean bench and safty cabinet were equipped with a weighing machine that records measured weights on a PC in real-time. They allowed us to have hands-free control under aseptic condition. A newly developed PC program also indicates proper dosage, infusion liquid volume and/or drip infusion rate based on the individual patient's information. All this information available is displayed on LCD monitor. The admixing procedures have been performed more precisely with this system,

[*Bioorg. Med. Chem.*, **15**, 4897-4902 (2007)] [Lab. of Pharmacognosy]

Mechanism of the melanogenesis stimulation activity of (-)-cubebin in murine B16 melanoma cells.

Noriko HIRATA, Shunsuke NARUTO, Kenji OHGUCHI, Yukihiro AKAO, Yoshinori NOZAWA, Munekazu IINUMA* and Hideaki MATSUDA

(-)-Cubebin showed a melanogenesis stimulation activity in murine B16 melanoma cells. Tyrosinase activity was increased at 24-72 h after addn. of cubebin to B16 cells, and then intracellular melanin amt. was increased at 48-96 h after the treatment. The expression levels of tyrosinase were time-dependently enhanced after the treatment with cubebin. At the same time, the expression levels of tyrosinase mRNA were also increased after addn. of cubebin. Furthermore Western blot anal. revealed that cubebin elevated the level of phosphorylation of p38 MAPK. SB203580, a selective inhibitor of p38 MAPK, completely blocked cubebin-induced expression of tyrosinase mRNA in B16 cells. These results suggested that cubebin increased melanogenesis in B16 cells through the enhancement of tyrosinase expression mediated by activation of p38 MAPK

[*Biol. Pharm. Bull.*, **30**, 2402-2405 (2007)] [Lab. of Pharmacognosy]

Testosterone 5alpha-reductase inhibitory active constituents of *Piper nigrum* leaf.

Noriko HIRATA, Masashi TOKUNAGA, Shunsuke NARUTO, Munekazu IINUMA* and Hideaki MATSUDA

Testosterone 5alpha-reductase inhibitory activity of aqueous ethanolic extracts obtained from several different parts of six *Piper* species, namely *Piper nigrum*, *P. methysticum*, *P. betle*, *P. kadsura*, *P. longum*, and *P. cubeba*, were examined. Among them, the extracts of *P. nigrum* leaf, *P. nigrum* fruit and *P. cubeba* fruit showed potent inhibitory activity. Activity-guided fractionation of *P. nigrum* leaf extract led to the isolation of (-)-cubebin and (-)-3,4-dimethoxy-3,4-desmethylenedioxycubebin. The 5alpha-reductase inhibitory activities of (-)-cubebin and piperine were found for the first time. In addition, the P. nigrum leaf extract showed in vivo anti-androgenic activity using the hair regrowth assay in testosterone sensitive male C57Black/6CrSlc strain mice.

[*Chem. Pharm. Bull.*, **55**, 1535-1539 (2007)] [Lab. of Pharmacognosy]

Resveratrol tetramers with a C_6-C_3 or a C_1 unit from *Upuna borneensis*.

Tetsuro ITO, Naohito ABE, Zulfiqar ALI, Masayoshi OYAMA, Toshiyuki TANAKA, Jin MURATA, Dedy DARNAEDI and Munekazu IINUMA*

Investigation of the chemical constituents in the stem of *Upuna borneensis* (Dipterocarpaceae) resulted in the isolation of three new resveratrol derivatives, upunaphenols L, M (resveratrol tetramers with a C_6-C_3 unit) and N (resveratrol tetramer with a C_1 unit). The structures have the same partial structure as vaticanol B. Upunaphenols L and M are new complex polyphenol compounds, lignostilbene. Their structures were determined by spectroscopic analyses including two dimensional NMR. Upunaphenol M was found to be an artifact generated by silica gel catalyzed methanolysis of upunaphenol L.

[*Nat. Prod. Res., Part A*, **21**, 156-160 (2007)] [Lab. of Pharmacognosy]

A new germacranolide-type sesquiterpene lactone from *Tanacetum santolinoides*.

Ahmed A. MAHMOUD, Mohammed A. Al-OMAIR and Munekazu IINUMA*

A new germacranolide-type sesquiterpene lactone, 1alpha -hydroxy-3-oxo-7alpha ,11beta H-germacra-4Z,9Z-dien-12,6alpha -olide, was isolated from the CH_2Cl_2-MeOH ext. of the aerial parts of *T. santolinoides*. Its structure was detd. by spectroscopic techniques including, IR, high-resoln.-EIMS, and extensive 400 MHz one- and two-dimensional NMR-anal. (^{1}H, ^{13}C-NMR, DEPT, ^{1}H-^{1}H COSY, HMQC, HMBC, and NOE expts.).

[*Bioorg. Med. Chem.*, **15**, 5620-5628 (2007)] [Lab. of Pharmacognosy]

Characterized mechanism of alpha -mangostin-induced cell death: Caspase-independent apoptosis with release of endonuclease-G from mitochondria and increased miR-143 expression in human colorectal cancer DLD-1 cells.

Yoshihito NAKAGAWA, Munekazu IINUMA*, Tomoki NAOE, Yoshinori NOZAWA and Yukihiro AKAO

alpha -Mangostin, a xanthone from the pericarps of mangosteen was evaluated for in vitro cytotoxicity against human colon cancer DLD-1 cells. The cytotoxic effect of 20 micro M alpha -mangostin was found to be mainly due to apoptosis, as indicated by morphol. findings. Western blotting, the results of an apoptosis inhibition assay using caspase inhibitors, and the examn. of caspase activity did not demonstrate the activation of any of the caspases tested. However, endonuclease-G released from mitochondria with the decreased mitochondrial membrane potential was shown. The co-treatment with alpha -mangostin and 5-FU, both at 2.5 micro M, augmented growth inhibition compared with the treatment with 5 micro M of alpha -mangostin or 5 micro M 5-FU alone. These findings indicate unique mechanisms of alpha -mangostin-induced apoptosis and its action as an effective chemosensitizer.

[*Tetrahedron Lett.*, **48**, 8290-8292 (2007)] [Lab. of Pharmacognosy]

Pauferrol A, a novel chalcone trimer with a cyclobutane ring from *Caesalpinia ferrea* Mart exhibiting DNA topoisomerase II inhibition and apoptosis-inducing activity.

NOZAKI, Ken-ichiro HAYASHI, Masahiro KIDO, Kazuyuki KAKUMOTO, Shogo IKEDA, Nobuyasu MATSUURA, Hiroyuki TANI, Daisuke TAKAOKA, Munekazu IINUMA* and Yukihiro AKAO

Pauferrol A, a unique chalcone deriv. was isolated from the stems of *Caesalpinia ferrea*, and the structure was detd. on the basis of 2D-NMR spectroscopy to be a chalcone trimer fused by a cyclobutane ring. This new chalcone trimer showed potent inhibitory activity against human topoisomerase II, with an IC_{50} value of 2.1 micro M, and cell proliferation inhibitory activity through the induction of apoptosis in human leukemia HL60 cells, with an IC_{50} value of 5.2 micro M. To our knowledge, this is the first report of the isolation and structure of this chalcone trimer and its biological activity

[*Chem. Pharm. Bull.*, **55**, 675-678 (2007)] [Lab. of Pharmacognosy]

Allergy-preventive flavonoids from *Xanthorrhoea hastilis*.

Yuko OGAWA, Hisae OKU, Emiko IWAOKA, Munekazu IINUMA* and Kyoko ISHIGURO

Allergy-preventive activity was demonstrated for an ext. of resins from *Xanthorrhoea hastilis* R. BR. in a search for allergy-preventive substances from natural sources. By bioassay-directed fractionation of this plant ext., a new flavanone, 3',5'-dihydroxy-7,4'-dimethoxyflavanone, and two new chalcones, 3,5,2'-trihydroxy-4,4'-dimethoxychalcone and 5,2'-dihydroxy-3,4,4'-trimethoxychalcone, were isolated together with five known compounds, 5'-hydroxy-7,3',4'-trimethoxyflavanone, 3'-hydroxy-7,4'-dimethoxyflavanone, liquiritigenin 7-Me ether, 4,2'-dihydroxy-4'-methoxychalcone and sakuranetin. The structures were elucidated by spectroscopic methods. All of these compounds showed allergy-preventive effects.

[*Helv. Chim. Acta*, **90**, 63-71 (2007)] [Lab. of Pharmacognosy]

Five new steroidal glycosides from *Caralluma dalzielii*.

Masayoshi OYAMA, Ibrahim ILIYA, Toshiyuki TANAKA and Munekazu IINUMA*

Five new pregnane glycosides, caradalzielosides A-E, were isolated from the aerial parts of *Caralluma dalzielii*. Their structures were elucidated by extensive 1D- and 2D-NMR spectroscopic anal. as well as by HR-FAB-MS expts.

[*Biocontrol Sci.*, **12**, 7-14 (2007)] [Lab. of Pharmacognosy]

Antibacterial activity of stilbene oligomers against vancomycin-resistant *Enterococci* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) and their synergism with antibiotics.

Yoshikazu SAKAGAMI, Akiyoshi SAWABE, Sadao KOMEMUSHI, Zulfiqar ALI, Toshiyuki TANAKA, Ibrahim ILIYA and Munekazu IINUMA*

Two resveratrol trimers, gnemonol B isolated from *Gnetum gnemon* and gnetin E obtained from the *Gnetum* species, were found to exhibit strong antibacterial activities against vancomycin-resistant Enterococci (VRE) and methicillin-resistant Staphylococcus aureus (MRSA). The MIC values of gnemonol B against five strains of VRE and nine strains of MRSA were 12.5 and 6.25 micro g/mL, resp. The MIC values of gnetin E against five strains of VRE and nine strains of MRSA ranged from 12.5 to 25 micro g/mL. These compounds also showed synergistic effects when used in combination with com. available antibiotics according to the evaluation method using FIC indexes. These findings suggested that the application of the test compounds alone or in combination with antibiotics might be useful in controlling and treating VRE and MRSA infections.

[*Cancer Chemother.*, **60**, 681-691 (2007)] [Lab. of Pharmacognosy]

Vaticanol C, a novel resveratrol tetramer, reduces lymph node and lung metastases of mouse mammary carcinoma carrying p53 mutation.

Masa-Aki SHIBATA, Yukihiro AKAO, Eiko SHIBATA, Yoshinori NOZAWA, Tetsuro ITO*, Satoshi MISHIMA, Junji MORIMOTO and Yoshinori OTSUKI

The effects of vaticanol C (Vat-C), a novel resveratrol tetramer, were studied in a mouse metastatic mammary cancer model carrying mutations in p53 that produce a metastatic spectrum similar to that seen in human breast cancers. Mammary tumors, induced by inoculation of syngeneic BALB/c mice with BJMC3879 cells, were subsequently treated with Vat-C at 0, 100 and 200 ppm in their diet. The results suggest that the observed antimetastatic activity of Vat-C may be of clinical significance as an adjuvant therapy in metastatic human breast cancer having p53 mutations, and may also be useful as a chemopreventative of breast cancer development.

[*Am. J. Physiol.*, **293**, C411-C418 (2007)] [Lab. of Pharmacognosy]

Vaticanol B, a resveratrol tetramer, regulates endoplasmic reticulum stress and inflammation.

Yoshiyuki TABATA, Katsura TAKANO, Tetsuro ITO, Munekazu IINUMA*, Tanihiro YOSHIMOTO, Hikari MIURA, Yasuko KITAO, Satoshi OGAWA and Osamu HORI

Vaticanol B, a tetramer of resveratrol, as an agent that protects against ER stress-induced cell death. Vaticanol B suppressed the induction of unfolded protein response-targeted genes such as glucose-regulated protein 78 and C/EBP-homologous protein after cells were treated with ER stressors. Analysis in the mouse macrophage cell line RAW 264.7 revealed that vaticanol B also possesses a strong anti-inflammatory activity. Production of a variety of inflammatory modulators such as tumor necrosis factor-alpha , nitric oxide, and prostaglandin E2 was inhibited by vaticanol B to a much greater extent than by monomeric or dimeric resveratrol after exposure of cells to lipopolysaccharide. These results suggest that vaticanol B is a novel anti-inflammatory agent that improves the ER environment by reducing the protein load on the ER and by maintaining the membrane integrity of the ER.

[*Am. J. Physiol*, **293**, C1884-C1894 (2007)] [Lab. of Pharmacognosy]

A dibenzoylmethane derivative protects dopaminergic neurons against both oxidative stress and endoplasmic reticulum stress.

Katsura TAKANO, Yasuko KITAO, Yoshiyuki TABATA, Hikari MIURA, Kosuke SATO, Kazuhiro TAKUMA, Kiyofumi YAMADA, Satoshi HIBINO, Tominari CHOSHI, Munekazu IINUMA*, Hiroto SUZUKI, Rika MURAKAMI, Masashi YAMADA, Satoshi OGAWA and Osamu HORI

A dibenzoylmethane deriv. 14-26 (2,2'-dimethoxydibenzoylmethane) was identified as a novel neuroprotective agent. Anal. in SH-SY5Y cells and in PC12 cells revealed that the regulation of ER stress by 14-26 was associated with its anti-oxidative property. 14-26 prevented the production of reactive oxygen species (ROS) when the cells were exposed to oxidants such as hydrogen peroxide and 6-hydroxydopamine or an ER stressor brefeldin A. 14-26 also prevented ROS-induced damage in both the ER and the mitochondria, including the protein carbonylation in the microsome and the redn. of the mitochondrial membrane potential. The results suggest that 14-26 is an antioxidant that protects dopaminergic neurons against both oxidative stress and ER stress and could be a therapeutic candidate for the treatment of PD.

[*Am. J. Physiol.*, **292**, C353-C361 (2007)] [Lab. of Pharmacognosy]

Methoxyflavones protect cells against endoplasmic reticulum stress and neurotoxin.

Katsura TAKANO, Yoshiyuki TABATA, Yasuko KITAO, Rika MURAKAMI, Hiroto SUZUKI, Masashi YAMADA, Munekazu IINUMA*, Yukio YONEDA, Satoshi OGAWA and Osamu HORI

ER stress leads to cell death in various pathophysiol. situations. During a search for compounds that regulate ER stress, we identified methoxyflavones, a group of flavonoids, as strong protective agents against ER stress. Consistent with the results in cultured cells, pretreatment of mice with tangeretin, a methoxyflavone, enhanced expression of GRP78 and HO-1 without causing ER stress in renal tubular epithelium and prevented tunicamycin-induced cell death. Furthermore, preadministration of tangeretin in mice enhanced expression of GRP78 in the substantia nigra pars compacta and protected dopaminergic neurons against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a neurotoxin that induces both oxidative and ER stress.

[*Nat. Prod. Commun.*, **2**, 55-59 (2007)] [Lab. of Pharmacognosy]

Phenolic constituents of leaves of *Diospyros montana*.

Toshiyuki TANAKA, Miyuki FURUSAWA, Tetsuro ITO, Ibrahim ILIYA, Masayoshi OYAMA, Munekazu IINUMA*, Nobuyuki TANAKA and Jin MURATA

Five flavonol glycosides and two naphthalene dimer glycosides, including three new compounds, were isolated from the leaves of *D. montana*. The structures of the isolated compounds were detd. by spectroscopic anal. One of the isolated compounds showed DPPH radical scavenging activity.

[*Biochem Biophys Res Commun.*, **352**, 360-365 (2007)] [Lab. of Mol. Biology]

Selenazoles (selenium compounds) facilitate survival of cultured rat pheochromocytoma PC12 cells after serum-deprivation and stimulate their neuronal differentiation via activation of Akt and mitogen-activated protein kinase, respectively.

Atsuyoshi NISHINA, Akihiro SEKIGUCHI, Ryo-hei FUKUMOTO, Mamoru KOKETSU and Shoei FURUKAWA.*

Selenium-containing compounds three selenazoles, CS1, CS2, and CS3 were found to activate the mitogen-activated protein kinase (MAPK) signal pathway of cultured PC12 cell. These compounds enhanced the phosphorylation of Akt, induced neurite outgrowth and facilitated the expression of neurofilament-Ms. The activation of some receptor tyrosine kinase(s) is involved in the mechanism of action of CSs 1–3. The activation of MAPK by CSs 1–3 was suppressed by a MEK inhibitor, but not by an inhibitor of TrkA; an antagonist of epidermal growth factor receptor; or by pertussis toxin. These results demonstrate that the activation was responsible for suppressed apoptosis and facilitated neuronal differentiation. Our results suggest that CSs are promising candidates as neuroprotective agents against various neurodegenerative neurological disorders.

[*Biochem Biophys Res Commun.*, **353**, 1056-1062 (2007)] [Lab. of Mol. Biology]

Processing of nerve growth factor: the role of basic amino acid clusters in the pro-region.

Akihiro MOURI, Hiroshi NOMOTO* and Shoei FURUKAWA.

Neurotrophins are synthesized first as precursors called pro-neurotrophins, and their propeptides are then proteolytically removed to form mature neurotrophins. However, a significant proportion of total neurotrophins has been shown to be secreted as pro-neurotrophins. Furthermore, pro- and mature neurotrophins have been shown to elicit opposite effects on cell survival. Thus, the processing step of neurotrophins is very important. In order to understand the mechanism of neurotrophin processing, we focused on the two basic amino acid clusters in the pro-region of nerve growth factor (NGF). Various NGFs mutated at basic amino acids in the pro-region were introduced in COS7 and PC12 cells. The results indicated that these basic amino acid clusters were actually cleaved in the cells by furin, but that their cleavage contributed little to the production of mature NGF. However, one of the two sites was considered to contribute to mature NGF production depending on conditions used.

[*Biomed Res.*, **28**, 139-146 (2007)] [Lab. of Mol. Biology]

Royal jelly-induced neurite outgrowth from rat pheochromocytoma PC12 cells requires integrin signal independent of activation of extracellular signal-regulated kinases.

Noriko HATTORI, Hiroshi NOMOTO, Hidefumi FUKUMITSU, Satoshi MISHIMA and Shoei FURUKAWA*.

Neurite outgrowth of rat pheochromocytoma PC12 cells was stimulated by royal jelly extract (PERJ) or its unique component, AMP N_1-oxide. In this study, we found that the neurite outgrowth required serum. The pentapeptide GRGDS, which includes the RGD sequence shared by extracellular matrix (ECM) components, could attenuate the effect of serum, suggesting that integrin receptor signaling was essential for the neurite outgrowth. Mn^{2+} induces neurite outgrowth and activates ERK1/2 through integrin signals and activation of ERK1/2 is essential for Mn^{2+}-induced neurite outgrowth, a difference in the mechanism between Mn^{2+}-induced and PERJ- or AMP N_1-oxide-induced one. These results demonstrate that AMP N_1-oxide and its analogues were the only entities in PERJ with neurite outgrowth-inducing activity and that they required integrin signaling in addition to activation of A_{2A} receptors to induce neurite outgrowth.

[*Biochem Biophys Res Commun.*, **356**, 919-924 (2007)] [Lab. of Mol. Biology]

Pro-region of neurotrophins determines the processing efficiency.

Hiroshi NOMOTO*, Masatoshi TAKAIWA, Akihiro MOURI and Shoei FURUKAWA.

Neurotrophins are synthesized as precursors called pro-neurotrophins and then mature neurotrophins are formed proteolytically from them. Recent findings revealed that pro- and mature neurotrophins elicit opposite functional effects on cell survival, highlighting the importance of this processing step. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) belong to the neurotrophin family and are mutually homologous, but BDNF is less efficiently processed. In order to find the reason for this, we examined some possibilities by using PC12 cells, and found that the pro-region, especially the last half of it, affected very much the processing efficiency of these neurotrophins.

[*Biomed Res.*, **28**, 261-266 (2007)] [Lab. of Mol. Biology]

Royal jelly and its unique fatty acid, 10-hydroxy-trans-2-decenoic acid, promote neurogenesis by neural stem/progenitor cells *in vitro*.

Noriko HATTORI, Hiroshi NOMOTO, Hidefumi FUKUMITSU, Satoshi MISHIMA and Shoei FURUKAWA*.

Neural stem/progenitor cells (NSCs) proliferate vigorously as neurospheres in medium containing basic fibroblast growth factor (FGF-2), but start differentiating into neurons, astrocytes or oligodendrocytes in FGF-2-free medium. An extract of royal jelly (RJ) increased the percentage in the total cell population of not only neurons immunoreactive for Tuj1 but also astrocytes immunoreactive for GFAP, and oligodendrocytes immunoreactive for CNPase generated from NSCs, but decreased that of nestin-positive NSCs. These results highlight a novel and outstanding property of the RJ, *i.e.*, that it facilitates the differentiation of all types of brain cells. 10-Hydroxy-trans-2-decenoic acid (HDEA), an unsaturated fatty acid characteristic for RJ, increased the generation of neurons and decreased that of astrocytes. These suggest that RJ contains plural components that differently influence neuronal and/or glial lineages and that HDEA is one of such components of RJ that facilitates neurogenesis by NSCs.

[*Evid Based Complement Altern Med.*, Advance Access published online on October 29 (2007)] [Lab. of Mol. Biology]

AMP N_1-oxide, a unique compound of royal jelly, induces neurite outgrowth from PC12 cells via signaling by protein kinase A independent of that by mitogen-activated protein kinase.

Noriko HATTORI, Hiroshi NOMOTO, Hidefumi FUKUMITSU, Satoshi MISHIMA and Shoei FURUKAWA*.

Earlier we identified AMP N_1-oxide as a unique compound of royal jelly (RJ) that induces neurite outgrowth (neuritegenesis) from cultured PC12 cells. Now, we found that AMP N_1-oxide stimulated the phosphorylation of not only mitogen-activated protein kinase (MAPK) but also that of cAMP/calcium-response element-binding protein (CREB). Inhibition of MAPK activation by a MEK inhibitor did not influence the neuritegenesis, whereas that of protein kinase A, KT5720, by a selective inhibitor reduced neurite outgrowth. AMP N_1-oxide suppressed the growth of PC12 cells, which correlated well with the neurite outgrowth-promoting activity. KT5720 restored the growth of AMP N_1-oxide-treated PC12 cells. Thus, AMP N_1-oxide elicited neuronal differentiation of PC12 cells, as evidenced by generation of neurites, and inhibited cell growth through adenosine A_{2A} receptor-mediated PKA signaling, which may be responsible for characteristic actions of RJ.

[*Biomed Res.*, **28**, 295-299 (2007)] [Lab. of Mol. Biology]

AMP N_1-oxide potentiates astrogenesis by cultured neural stem/progenitor cells through STAT3 activation.

Noriko HATTORI, Hiroshi NOMOTO, Hidefumi FUKUMITSU, Satoshi MISHIMA and Shoei FURUKAWA*.

The effects of AMP N_1-oxide on the proliferation and/or differentiation of cultured neural stem/progenitor cells (NSCs) were examined. As for cell proliferation, low micromolar concentrations of AMP N_1-oxide or its parent compound, AMP, similarly enhanced the NSC proliferation-inducing activity of basic fibroblast growth factor (FGF-2), although neither compound tested alone affected cell proliferation. Conversely, AMP N_1-oxide (over 20 μM) suppressed cell growth even in the presence of FGF-2. However, this suppression was not observed with AMP. As for cell differentiation, AMP N_1-oxide, but not AMP, increased the generation of astrocytes in medium lacking FGF-2. The generation of neurons or oligodendrocytes was not influenced by AMP N_1-oxide. Furthermore, AMP N_1-oxide increased the phosphorylation of STAT3, a transcription factor that mediates the expression of astrocyte specific genes. These results suggest that AMP N_1-oxide facilitates astrogenesis by NSCs through activation of STAT3.

[*Microbiol. Immunol.*, **51**, 581-592 (2007)] [Lab. of Microbiology]

Neutralizing activity of polyvalent Gb_3, Gb_2 and galacto-trehalose models against Shiga toxins.

Paola NERI, Saori Itoh NAGANO, Shin-ichiro YOKOYAMA, Hirofumi DOHI, Kazukiyo KOBAYASHI, Tsuyoshi MIURA, Toshiyuki INAZU, Tsuyoshi SUGIYAMA, Yoshihiro NISHIDA, Hiroshi MORI*.

In this study, we examined linear copolymers of acrylamide conjugated with globotriaosyl (Gb_3), galabiosyl (Gb_2) or galacto-trehalose to find novel Shiga toxins (Stxs)-neutralizing agents with high toxin affinity. Gb_3 and Gb_2 are natural receptors for Stxs, whereas galacto-trehalose is designed as an unnatural receptor-analog, that is expected to be resistant to enymatic degradation *in vivo*. Gb_3 and Gb_2 copolymers neutralized both Stx-1 and Stx-2 in a cytotoxicity assay. Galacto-trehalose copolymers showed the activity against only Stx-1. We examined copolymers with different Gb_3 unit density and found that the copolymers with higer Gb_3 unit density showed stronger neutralizing activity against Stx-2 than those with lower density. The intravenous administration of Gb_3 copolymer prevented death in mice infected orally with *E. coli* O157:H7 producing Stx-1 and Stx-2.

[*Biol. Pharm. Bull.*, **30**, 1697-1701 (2007)] [Lab. of Microbiology]

Monovalent Gb_3-/Gb_2- derivatives conjugated with a phosphatidyl residue: a novel class of Shiga toxin-neutralizing agent.

Paola NERI, Shunji TOKORO, Shin-ichiro YOKOYAMA, Tsuyoshi MIURA, Takeomi MURATA, Yoshihiro NISHIDA, Tetsuya KAJIMOTO, Satoshi TSUJINO, Toshiyuki INAZU, Taiichi USUI, Hiroshi MORI*.

Shiga toxins (Stxs) exert toxic activity by binding to globotriaosyl (Gb_3) and galabiosyl (Gb_2) ceramide on the surface of target cells. In this study, we synthesized monovalent Gb_3- or Gb_2-derivatives conjugated with a phosphatidyl residue and examined them for the neutralizing activity against Stxs. The Gb_3- and Gb_2-phosphatidyl derivatives showed strong neutralizing activity against not only Stx-1 but also Stx-2 *in vitro*. We showed that monovalent Gb_3- or Gb_2-fluorescein had no neutralizing activity against Stxs. As a mechanism for Gb_3- and Gb_2-phosphatidyl derivatives to have strong neutralizing activity on Stxs, it is likely that these compounds form liposomes and make flexible clusters of sugar unit.

[*ChemBioChem*, **8**, 2117-2124 (2007)] [Lab. of Microbiology]

Glycochips from polyanionic glycopolymers as tools for detecting Shiga toxins.

Hirotaka UZAWA, Hiroki ITO, Paola NERI, Hiroshi MORI*, Yoshihiro NISHIDA.

Glycochips carrying globobioside (Gb_2), β-lactoside or α-D-mannoside residues were prepared and used as surface plasmon resonance (SPR) devices for detection of Shiga toxins (Stxs). Both Stx-1 and Stx-2 show binding specificity for the Gb_2 glycochip as well as a weak affinity for β-lactoside glycochip. The affinity constants of these toxins depended strongly on the sugar content of the Gb_2 polymer used to prepare the glycochip. Greater affinity was observed for chips with higher sugar content in the Gb_2 glycopolymer. A clear difference was observed between the two toxins when Gb_2 acrylamide copolymer was used as competitor in inhibitory experiments. The SPR response of Stx-1was suppressed in the presence of Gb_2 acrylamide copolymer. In the case of Stx-2, the suppression of SPR response was incomplete. In conclusion, the glycochips were found to be useful as SPR devices and enabled us to detect and discriminate between Stx-1 and Stx-2.

[*Carcinogenesis*, **28**, 2398-2403 (2007)] [Lab. of Radiochemistry]

Nrf2 and p53 cooperatively protect against BBN-induced urinary bladder carcinogenesis.

Katsuyuki IIDA, Ken ITOH, Jonathan M. MAHER, Yoshito KUMAGAI, Ryoichi OYASU, Yukio MORI*, Toru SHIMAZUI, Hideyuki AKAZA and Masayuki YAMAMOTO

To explore whether nuclear factor-erythroid 2-related factor 2 (Nrf2) and p53 cooperatively act in tumor prevention, we investigated the susceptibility of *Nrf2-/-::p53+/-* mice to *N*-nitrosobutyl(4-hydroxybutyl)amine (BBN)-induced urinary bladder carcinogenesis. The incidences of BBN-induced urinary bladder carcinoma, especially muscle invasive carcinoma, were higher in *Nrf2-/-::p53+/-* mice than either wild-type, *p53+/-* or *Nrf2-/-* mice. Furthermore, urinary concentrations of *N*-nitrosobutyl(3-carboxypropyl)amine, a proximate carcinogen of BBN, were increased in *Nrf2-/-* mice. BBN administration increased p21 and detoxifying enzymes expression in *Nrf2-/-* and *p53+/-* mice, respectively. These results indicate that tumor susceptibility is synergistically exacerbated in *Nrf2-/-::p53+/-* mice and both factors cooperatively contribute to tumor prevention.

[*Neurochem. Res.*, **32**, 489-495 (2007)] [Lab. of Clinical pharmaceutics]

Pyrroloquinoline quinone is a potent neuroprotective nutrient against 6-hydroxydopamine-induced neurotoxicity.

Hirokazu HARA*, Hideaki HIRAMATSU, Tetsuo ADACHI

In this study, we investigated the ability of PQQ to protect against 6-OHDA-induced neurotoxicity using human neuroblastoma SH-SY5Y. When SH-SY5Y cells were exposed to 6-hydroxydopamine (6-OHDA) in the presence of pyrroloquinoline quinone (PQQ), PQQ prevented 6-OHDA-induced cell death and DNA fragmentation. Flow cytometry analysis using the ROS-sensitive fluorescence probe, dihydroethidium, revealed that PQQ reduced elevation of 6-OHDA-induced intracellular ROS. In contrast to PQQ, antioxidant vitamins, ascorbic acid and α-tocopherol, had no protective effect. Moreover, we showed that PQQ effectively scavenged superoxide, compared to the antioxidant vitamins. Therefore, our results suggest the protective effect of PQQ on 6-OHDA-induced neurotoxicity is involved, at least in part, in its function as a scavenger of ROS, especially superoxide.

[*Atherosclerosis*, **191**, 147-152 (2007)] [Lab. of Clinical Pharmaceutics]

Decreased plasma extracellular superoxide dismutase level in patients with vasospastic angina.

Kazuhito YAMASHITA, Takahiro KUBARA, Fumihiko KAMEZAKI, Tetsuo ADACHI*, Hiromi TASAKI

We assigned 105 patients with normal or mildly stenotic coronary arteries into either a VSA or chest pain syndrome (CPS) groups. Plasma EC-SOD and other biochemical variables were measured, and major coronary risk factors were assessed. Results showed that apart from smoking status there were no significant differences in patient characteristics and biochemical variables between the two groups. In the VSA group, prevalence of smoking was significantly higher, and plasma EC-SOD level was significantly lower. Not only smoking but also plasma EC-SOD was an independent risk factor for VSA. In patients with VSA, plasma EC-SOD level was substantially reduced. Furthermore, plasma EC-SOD level followed by cigarette smoking was the most predictive risk factor for coronary spasms.

[*Hypertens. Res.*, **30**, 699-706 (2007)] [Lab. of Clinical Pharmaceutics]

Angiotensin receptor blocker improves coronary flow velocity reserve in hypertensive patients: Comparison with calcium channel blocker.

Fumihiko KAMEZAKI, Hiromi TASAKI, Kazuhito YAMASHITA, Kiyoko SHIBATA, Noriko HIRAKAWA, Masato TSUTSUI, Ryouji KOUZUMA, Toshihisa NAGATOMO, Tetsuo ADACHI*, Yutaka OTSUJI

We designed this study to compare the effects of an angiotensin receptor blockers (ARB) and a calcium channel blocker (CCB) on coronary flow velocity reserve (CFVR). Sixteen hypertensive patients were randomly allocated in a double-blind fashion to valsartan (n=8) or nifedipine (n=8) groups. Age- and gender-matched subjects without hypertension were enrolled as a control group (n=12). CFVR in the valsartan group was significantly higher than that in the nifedipine group, which was little changed at 6 months. This discrepancy was derived from the significant increase of hyperemic velocity in the valsartan group. We concluded that the ARB valsartan not only reduced high blood pressure but improved CFVR in hypertensive patients. However, these effects were not seen with the CCB nifedipine.

[*J. Immunol.*, **178**, 3316-3322 (2007)] [Lab. of Clinical pharmaceutics]

A critical role for allograft inflammatory factor-1 in the pathogenesis of rheumatoid arthritis.

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In the current work, we examined the expression of allograft inflammatory factor-1 (AIF-1) in synovial tissues and measured AIF-1 in synovial fluid (SF) derived from patients with either rheumatoid arthritis (RA) or osteoarthritis (OA). We also examined the proliferation of synovial cells and induction of IL-6 following AIF-1 stimulation. Synovial expression of AIF-1 in RA was significantly greater than the expression in OA. AIF-1 induced the proliferation of cultured synovial cells in a dose-dependent manner and increased the IL-6 production of synovial fibroblasts and PBMC. The levels of AIF-1 protein were higher in synovial fluid from patients with RA compared with patients with OA ($p < 0.05$).

[*Life Sci.*, **80**, 370-377(2007)] [Lab. of Molecular Pharmacology]

Water extract of propolis and its main constituents, caffeoylquinic acid derivatives, exert neuroprotective effects vis antioxidant actions.

Yoshimi NAKAJIMA, Masamitsu SHIMAZAWA, Satoshi MISHIMA and Hideaki HARA*

We investigated whether water extract of Brazilian green propolis (WEP) and its main constituents exert neuroprotective effects against the retinal damage induced by oxidative stress. WEP, 3,4-di-*O*-caffeoylquinic acid, 3,5-di-*O*-caffeoylquinic acid, chlorogenic acid, and *p*-coumaric acid inhibited oxidative stress-induced neurotoxicity in cultured retinal ganglion cells. At their effective concentrations against oxidative stress-induced retinal damage, WEP, 3,4-di-caffeoylquinic acid, 3,5-di-caffeoylquinic acid, and chlorogenic acid (but not cinnamic acid derivatives) inhibited lipid peroxidation in mouse forebrain homogenates. These findings indicate that WEP and caffeoylquinic acid derivatives have neuroprotective effects against retinal damage *in vitro*, and that these effects may be partly mediated *via* antioxidant effects.

[*Exp. Eye Res.*, **84**, 529-536(2007)] [Lab. of Molecular Pharmacology]

New quantitative analysis, using high-resolution images, of oxygen-induced retinal neovascularization in mice.

Yuichi CHIKARAISHI, Masamitsu SHIMAZAWA and Hideaki HARA*

We attempted quantification using new imaging software and high-resolution images taken with a high-resolution CCD camera. Neonatal mice were exposed to 75% oxygen from postnatal day 7 (P7) to P12, then returned to room air until P17. Total images of the retinal vasculature were collected and analyzed using the imaging software. P17 normal retinas showed increases in computerized total tube area, total tube length, number of segments, and number of branch points. These increases coincided with the development of the retinal vasculature between P7 and P17. P17 Oxygen-induced retinopathy (OIR) retinas similarly showed increases in those parameters, and the number of nodes and the node area were markedly increased (versus P17 normal retinas). Quantification using the present imaging software should be useful for evaluating physiological and pathological neovascularizations in this OIR model.

[*Mol. Vision*, **13**, 578-587(2007)] [Lab. of Molecular Pharmacology]

Involvememt of ER stress in retinal cell death.

Masamitsu SHIMAZAWA, Yuta INOKUCHI, Yasushi ITO, Hiroshi MURATA, Makoto AIHARA, Makoto ARAIE and Hideaki HARA*

The purpose was to clarify whether endoplasmic reticulum (ER) stress is involved in retinal cell death, using cultured retinal ganglion cells (RGC-5), and transgenic mice [ERAI (ER stress-activated indicator) mice] carrying a human XBP1 and venus fusion gene. Tunicamycin induced apoptotic cell death in RGC-5 and also productions of ER stress-related proteins [BiP, the phosphorylated form of eIF2α, and C/EBP-homologous (CHOP) protein]. In vivo, tunicamycin induced RGC loss and thinning of the inner plexiform layer at 7 days after intravitreal injection. In transverse cross-sections from ERAI mice, the fluorescence intensity was first increased in cells of the ganglion cell and inner plexiform layers at 12 and 24 h, respectively, after NMDA injection. In conclusion, these data indicate that ER-stress may play a pivotal role in RGC death, whether induced by NMDA or IOP elevation.

[*Mol. Cell. Biol.*, **27**, 1716-1729(2007)] [Lab. of Molecular Pharmacology]

BBF2H7, a novel transmembrane bZIP transcription factor, is a new type of ER stress transducer.

Shinichi KONDO, Atsushi SAITO, Shin-ichiro HINO, Tomohiko MURAKAMI, Maiko OGATA, Soshi KANEMOTO, Satoshi NARA, Akinori YAMASHITA, Kazuya YOSHINAGA, Hideaki HARA* and Kazunori IMAIZUMI

We report here that BBF2H7 (BBF2 human homolog on chromosome 7), an endoplasmic reticulum (ER)-resident transmembrane protein with the bZIP domain in the cytoplasmic portion and structurally homologous to OASIS (old astrocyte specifically induced substance), is cleaved at the membrane in response to ER stress. The cleaved fragments of BBF2H7 translocate into the nucleus and can bind directly to cyclic AMP-responsive element sites to activate transcription of target genes. Although BBF2H7 protein is not expressed under normal conditions, it is induced at the translational level during ER stress, suggesting that BBF2H7 might contribute to only the late phase of unfolded protein response signaling. Our results suggest that BBF2H7 is a novel ER stress transducer and could play important roles in preventing accumulation of unfolded proteins in damaged neurons.

[*Invest. Ophthalmol. Vis. Sci.*, **48**, 3729-3736(2007)] [Lab. of Molecular Pharmacology]

Involvement of double-stranded RNA-dependent protein kinase in ER stress-induced retinal neuron damage.

Masamitsu SHIMAZAWA, Yasushi ITO, Yuta INOKUCHI and Hideaki HARA*

The purpose was to clarify whether activation of a double stranded RNA-dependent protein kinase (PKR) participates in the cell death induced by endoplasmic reticulum (ER) stress using cultured retinal ganglion cells (RGC-5) and effect of a PKR inhibitor (an imidazolo-oxindole derivative) on *N*-methyl-D-aspartate (NMDA)-induced retinal damage in mice. Tunicamycin for 24 h increased the number of YO-PRO-1 and PI-positive cells. Immunoblotting analysis showed that tunicamycin a induced BiP, ATF4, and CHOP protein productions, and also PKR phosphorylation. Both the PKR inhibitor and PKR-knockdown (using siRNA) inhibited tunicamycin-induced RGC-5 cell death. Inhibiting PKR activation is neuroprotective against ER stress-induced retinal damage, suggesting that PKR activation may be involved in the mechanisms underlying ER stress-induced cell death.

[*Brain. Res.*, **1154**, 215-224(2007)] [Lab. of Molecular Pharmacology]

Fasudil, a Rho kinase (ROCK) inhibitor, protects against ischemic neuronal damage in vitro and in vivo by acting directly on neurons.

Kentaro YAMASHITA, Yoshinori KOTANI, Yoshimi NAKAJIMA, Masamitsu SHIMAZAWA, Shin-ichi YOSHIMURA, Shigeki NAKASHIMA, Toru IWAMA and Hideaki HARA*

Our purpose was to evaluate both the involvement of a Rho kinase (ROCK) activity in ischemic neuronal damage and any direct neuroprotective effect of fasudil against cerebral infarction. ROCK expression and activity increased in the sriatum, especially in axons, in the early phase of ischemia. Fasudil reduced this ROCK activity and protected against cerebral infarction in vivo. Hydroxyfasudil inhibited oxygen-glucose deprivation (OGD)-induced PC12 cell death, and fasudil and hydoxyfasudil each attenuated glutamate-induced neurotoxicity in vitro. ROCK plays a pivotal role in the mechanism underlying ischemic neuronal damage and that a direct effect of fasudil on neurons may be partly responsible for its protective effects against such damage.

[*Neuroscience*, **147**, 956-967(2007)] [Lab. of Molecular Pharmacology]

Involvement of endoplasmic reticulum stress after middle cerebral artery occlusion in mice.

Nobutaka MORIMOTO, Yasuhisa OIDA, Masamitsu SHIMAZAWA, Masayuki MIURA, Takashi KUDO, Kazunori IMAIZUMI and Hideaki HARA*

The endoplasmic reticulum (ER) stress-related markers [immunoglobulin binding protein (BiP)/glucose-regulated protein (GRP) 78, activating transcription factor-4 (ATF-4), and C/EBP-homologous protein (CHOP)] in the striatum and the cortex were investigated after permanent middle cerebral artery occlusion (MCAO) in mice. Using ER stress-activated indicator (ERAI) transgenic mice, we monitored the regional changes in fluorescence after MCAO. BiP mRNA was increased in the cortex at 6 h. The expressions of ER stress-related markers were increased in the infarct region, more strongly in the cortex than in the striatum. ERAI fluorescence was observed in the ischemic area starting from 6 h and 12 h, respectively, after MCAO. These findings suggest that permanent MCAO induces expression of ER-stress related genes mainly in the periphery of the MCA territory.

[*Neuroscience*, **148**, 105-114 (2007)] [Lab. of Molecular Pharmacology]

Neuroprotective effect of erythropoietin, and role of metallothionein-1 and -2, in permanent focal cerebral ischemia.

Kenji WAKIDA, Masamitsu SHIMAZAWA, Masahiko SATOH, Hisamitsu NAGASE, Kazunori IMAIZUMI and Hideaki HARA*

We investigated the role of metallothioneins (MT) -1 and -2 using MT-1,-2 knock-out (KO) mice. MT-1,-2 KO mice exhibited greater neuronal damage after permanent middle cerebral artery occlusion (MCAO) than wild-type mice. MT-2 mRNA was significantly increased at 6, 12, and 24 h after MCAO in the wild-type mouse brain, while MT-1 and MT-3 were decreased at 12 and 24 h. Since erythropoietin (EPO) has been reported to induce MT-1 and -2 gene expressions *in vitro*, we examined its effect after permanent MCAO, and explored the possible underlying mechanism by examining MT-1 and -2 induction *in vivo*. MTs may be neuroprotective against neuronal damage, after MCAO. Furthermore, EPO is neuroprotective *in vivo* during permanent MCAO.

[*Neuroscience*, **149**, 779-788(2007)] [Lab. of Molecular Pharmacology]

Prevention of in vitro and in vivo acute ischemic neuronal damage by (2S)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{4-[4-(4-fluorobenzyl) phenyl]-1-piperazinyl}-2-propanol dimethanesulfonate (SUN N8075), a novel neuroprotective agent with antioxidant properties.

Yoshinori KOTANI, Nobutaka MORIMOTO, Yasuhisa OIDA, Yoshiko TAMURA, Shigeki TAMURA, Teruyoshi INOUE, Masamitsu SHIMAZAWA, Shin-ichi YOSHIMURA, Toru IWAMA and Hideaki HARA*

We examined whether SUN N8075 inhibited the neuronal damage resulting from permanent focal cerebral ischemia, and examined its neuroprotective properties *in vivo* and *in vitro* mechanism. SUN N8075 reduced brain swelling when administered 10 min before, 1 h, or 3 h after occlusion. SUN N8075 inhibited lipid peroxidation, leakage of lactate dehydrogenase, caspase-3 activation induced by *in vitro* hypoxia, and the neuronal damage induced by *in vitro* $FeSO_4$ exposure. SUN N8075 has neuroprotective effects against acute ischemic neuronal damage in mice and may prove promising as a therapeutic drug for stroke.

[*Jpn. J. Pharm. Health. Care. Sci.*, **33**, 114-118 (2007)] [Lab. of Pharmacy Practice and Social Science]

Development and Evaluation of a Prescription Checking System Using Clinical Laboratory Data.

Chitoshi GOTO, Koji YASUDA and Tadashi SUGIYAMA*.

Clinical Laboratory Data are an importance basis for understanding the patient's condition when pharmacists examine the appropriateness of prescriptions. Since it is difficult for them to check patient clinical laboratory data at the time of dispensing, we developed a prescription checking system under which prescription data and clinical laboratory data are simultaneously transmitted to the pharmacy and any abnormal clinical laboratory data are marked on the prescription sheet and the prescription-checking list. Pharmacist can use these marks to check the patient's condition. Between December 2004 and November 2005, abnormal clinical laboratory data were marked 245 prescriptions under our system, and pharmacist advised doctors of 25 cases in which drugs were contraindicated, and corrections were made. We therefore conclude that our system is useful in promoting the proper use of drugs.

[*Jpn. J. Drug Inform.*, **8**, 315-319 (2007)] [Lab. of Pharmacy Practice and Social Science]

Development and Evaluation of an Admixing Support System for Injectable Anticancer Drugs.

Mitsuhiro NAKAMURA, Kana FUKAWA, Chika IWATA, Akemi MURAOKA, Reiko MAMIYA and Tadashi SUGIYAMA*.

We developed an admixing support program for injectable anticancer drugs. Database sets and operating programs have been developed using FileMaker Pro (FileMaker Inc.), which have facilitated calculation of the admixing liquid volume and the number of vials from the dosage of the drug and contents per vial automatically. The program also indicates proper dosage, infusion liquid volume and/or drip infusion rate based on the individual patient information (i.e.age, weight, body surface area). Using check sheets prepared by the program, pharmacists and nurses involved in the admixing procedure in the pediatric ward. Using this program, the admixing procedures have been performed more precisely and improved proper medical inspection and medical safety practices.

[*Jpn. J. TDM.*, **24**, 104-112 (2007)] [Lab. of Pharmacy Practice and Social Science]

Development of TDM Management System using Paperless Electronic Medical Records.

Mitsuhiro NAKAMURA, Katsuhiko MATSUURA, Teruo TSUCHIYA and Tadashi SUGIYAMA*.

In order to improve efficiency and efficacy of therapeutic drug monitoring (TDM) services, we designed a new TDM management system based on this paperless electronic medical recording system. The TDM system is a constituent of systemGIFU, and comprises of two parts of practice, one part for the drug assay ordering system on SystemGIFU, and another part for TDM management program utilized in our department of pharmacy. This program can create TDM reports for doctors, containing pharmacist's comment, patient's information, BMP and/or GIF images. The reports were standardized with eXtensible Markup Language (XML), and stored in the database placed in SystemGIFU. The reports can be viewed on-line through a unified user interface and visualization environment on every client of SystemGIFU. This system can contribute to clinical supporting.

[*Pharm Stage*, **7(6)**, 31-34 (2007)] [Lab. of Pharmacy Practice and Social Science]

An Evaluation of Oral Dried Jelly Preparations as a New Type of Medicine for Patient with Dysphagia.

Tadashi SUGIYAMA*, Katsuhiko MATSUURA, Misao NISHIMURA, Tadao TSUKIOKA and Yoshinori ITOH.

The quality of the Oral Jelly Coated Film (OJCF) type medicine for patients with difficulty for swallowing was evaluated. Study of the OJCF formula showed that by changing the concentration of each component of the formulation. The OJCF preparation showed superior characteristic in uniformity of the amount, dissolution profiles under pH 1.2 and water conditions, and stability under acceleration test condition (40℃/75%RH). Thus, the OJCF preparation is suggested as a new type of medicine for patient with dysphagia.

[*Jpn. J. Pharm. Health. Care. Sci.*, **33**, 191-199 (2007)] [Lab. of Pharmacy Practice and Social Science]

Development of Preparation Checking System for Injections Using Order Entry System Information and Newly Designed Clean Bench and Safety Cabinet.

Shinji OKAYASU, Mitsuhiro NAKAMURA, Koichi CHIGUSA, Kiyoshi SAKURAI and Tadashi SUGIYAMA*.

We developed an aseptic preparation support system to raise efficiency in making admixtures of injectable drugs and improve risk management. We redesigned the clean bench and safey cabinet, and incorporated an embedded 15"LCD monitor. It is equipped with a weighting machine that allows us to record weights on a PC in real-time. A three-button footswitch is connected to PC to allow us to have hands-free control of the system to maintain aseptic conditions. Liquid volumes and weights and number of vials are automatically calculated from the content per vial and the dosage of the drug in the injection order information. All of this information is displayed on the monitor and using it, we mix tne injectablr drugs. Differences between calculated and measured weights of vials are also recorded on PC. The new system has raised the efficiency of mixing injections and improved monitoring accuracy.

[*J. Jpn. Soc. Hosp. Pharm.*, **43**, 938-941 (2007)] [Lab. of Pharmacy Practice and Social Science]

Establishment of an Electronic Recording System for the Dispensing Process.

Kana FUKAWA,Chitoshi GOTO, Katsuhiko MATSUURA and Tadashi SUGIYAMA*.

Total medical information system named "SystemGIFU" is running at Gifu University Hospital. The concept of the SystemGIFU is that data on the hospital information are all accumulated on electronic medical recording system (EMRS) and utilized for medical examination and treatment. We developed the pharmacy department information system, which conformed to the concept of the SystemGIFU. For electronic storage of pharmacy services on EMRS, we recorded processes and reports of dispensing, pharmaceutical care practice electronically in conformity with the standard of "Authenticity", "Visual Readability" and "Storage Property". We conclude that our newly-developed system is useful in improving total pharmaceutical practices.

[*Jpn. J. Pharm. Health. Care. Sci.*, **33**, 937-941 (2007)] [Lab. of Pharmacy Practice and Social Science]

Survey on Prescription Changes in Patients Following Renal Transplantation.

Shiro YOSHIOKA, Katsuhiko MATSUURA, Tadashi SUGIYAMA* and Yoshinori ITOH.

Forty-two patients were surveyed regarding prescription changes and incidence of adverse events after undergoing renal transplantation at Gifu University Hospital. The immunosuppressive therapy, including methylpredonisolone, tacrolimus, mycophenolate mofetil and basiliximab was performed after renal transplantation. As there was a significant increase in plasma concentrations of total cholesterol were and a significant elevation of uric acid levels, we feel that it is important to check laboratory data and prescriptions for patients who have undergone renal transplantation in practice of pharmaceutical care.

[*Jpn. J. Pharm. Health. Care. Sci.*, **33**, 1007-1012 (2007)] [Lab. of Pharmacy Practice and Social Science]

Evaluation of Oral Dried Jelly Preparations - A New Type of Medicine for Patients with Dysphagia.

Misao NISHIMURA, Tadashi SUGIYAMA*, Katsuhiko MATSUURA, Tadao TSUKIOKA and Yoshinori ITOH.

We conducted a pharmaceutical study to evaluate the quality of oral dried jelly preparations, a new type of medicine for patient with dysphagia. Four kinds of acetaminophen-containing dried jelly preparations (A, B, C, D) consisting three layers of film were produced. We performed content uniformity test, stability test, initial dissolution test and dissolution test performed after storage. Among the 4 preparations, preparation D, which was composed of gelatin-based outer films containing hydroxypropyl methylcellulose and gelatin-based drug-containing film, had the best quality profile as regards stability and dissolution, and our overall suggest that oral dried jelly preparations are suitable for clinical use as a new type of medicine.

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