[*Redox Biology* **6**, 578-586 (2015)] [Lab. of Pharmaceutical & Medicinal Chemistry]

Ovarian Endometriosis-associated Stromal Cells Reveal Persistently High Affinity for Iron.

Masahiko Mori, Fumiya Ito, Lei Shi, Yue Wang, Chiharu Ishida, Yuka Hattori, Masato Niwa, Tasuku Hirayama*, Hideko Nagasawa*, Akira Iwase, Fumitaka Kikkawa and Shinya Toyokuni

Ovarian endometriosis is a recognized risk for infertility and epithelial ovarian cancer, presumably due to iron overload resulting from repeated hemorrhage. To find a clue for early detection and prevention of ovarian endometriosis-associated cancer, it is mandatory to evaluate catalytic (labile) ferrous iron (catalytic Fe(II)) and to study iron manipulation in ovarian endometriotic lesions. By the use of tissues from women of ovarian endometriosis as well as endometrial tissue from women with and without endometriosis, we for the first time performed histological analysis and cellular detection of catalytic Fe(II) with a specific fluorescent probe (HMRhoNox-M). The data suggest that ecESC play a protective role for cancer-target epithelial cells by collecting excess iron, and that these characteristics are retained in the immortalized ecESCs.

[*Acta Cryst.* **E71**, o694- o695 (2015)] [Lab. of Pharmaceutical & Medicinal Chemistry]

Crystal Structure of (2-{[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl](5-methyl-2*H*-pyrrol-2-ylidene)methyl}-5-methyl-1*H*-pyrrolido-κ^2 *N*,*N'*)difluoridoboron.

Yukio Morimoto, Keizo Ogawa, Yoshihiro Uto, Hideko Nagasawa* and Hitoshi Hori

The title compound, $C_{25}H_{31}BF_2N_2O$, is a potential boron tracedrug in boron neutron capture therapy (BNCT), in which the B atom adopts a distorted BN_2F_2 tetrahedral geometry: it is soluble in dimethyl sulfoxide, dimethylformamide and methanol. The pyrrolylidenemethylpyrrole triple fused ring system is almost planar (r.m.s. deviation = 0.031 Å) and subtends a dihedral angle of 47.09 (5)° with the plane of the pendant phenol ring. The phenol –OH group is blocked from forming hydrogen bonds by the adjacent bulky tert-butyl groups. In the crystal, inversion dimers linked by pairs of very weak C—H···F interactions generate $R^2_2(22)$ loops.

[*Biochem. Biophys. Res. Commun.* **463**, 881-887 (2015)] [Lab. of Pharmaceutical & Medicinal Chemistry]

A Highly Sensitive Assay of IRE1 Activity Using the Small Luciferase NanoLuc: Evaluation of ALS-related Genetic and Pathological Factors.

Takahiro Hikiji, Junpei Norisada, Yoko Hirata, Kensuke Okuda*, Hideko Nagasawa*, Shinsuke Ishigaki, Gen Sobue, Kazutoshi Kiuchi and Kentaro Oh-Hashi

In this study, we established a highly sensitive assay of IRE1 activity using a small luciferase, NanoLuc, which has approximately 100-fold higher activity than firefly luciferase. Using this technique, we evaluated the effects of several genetic and pathological factors associated with the onset and progression of amyotrophic lateral sclerosis (ALS) on NanoLuc reporter activity. Under our experimental conditions, inhibition of ER-Golgi transport by the overexpression of mutant Sar1 activated luciferase activity, whereas the co-expression of mutant SOD1 or the C-terminal fragment of TDP-43 (TDP-25) did not. Our analytical procedure is highly sensitive for screening compounds modulating IRE1-XBP1 signaling pathways and IRE1 activation.

[*Bio.Med. Research International* **2015**, (2015)] [Lab. of Pharmaceutical & Medicinal Chemistry]

Nordihydroguaiaretic Acid Disrupts the Antioxidant Ability of Helicobacter Pylori Through the Repression of SodB Activity *In Vitro*.

Hitoshi Tsugawa, Hideki Mori, Juntaro Matsuzaki, Tatsuhiro Masaoka, Tasuku Hirayama*, Hideko Nagasawa*, Yasubumi Sakakibara, Makoto Suematsu and Hidekazu Suzuki

Iron-cofactored superoxide dismutase (SodB) of Helicobacter pylori plays an indispensable role in the bacterium's colonization of the stomach. Previously, we demonstrated that FecA1, a Fe^{3+}-dicitrate transporter homolog, contributes to SodB activation by supplying ferrous iron (Fe^{2+}) to SodB, and *fecA1*-deletion mutant strains have reduced gastric mucosal-colonization ability in Mongolian gerbils, suggesting that FecA1 is a possible target for the development of a novel eradication therapy. The present study demonstrated that NDGA repressed SodB activity associated with the gastric mucosal-colonization via inhibition of intracellular Fe^{2+} uptake by FecA1, suggesting that NDGA might be effective for the development of a novel eradication therapy.

[*J. Clin. Biochem. Nutr.* **56**, 57-63 (2015)] [Lab. of Pharmaceutical & Medicinal Chemistry]

Catalytic Ferrous Iron in Amniotic Fluid as a Predictive Marker of Human Maternal-fetal Disorders.

Yuka Hattori, Takahiro Mukaide, Li Jiang, Tomomi Kotani, Hiroyuki Tsuda, Yukio Mano, Seiji Sumigama, Tasuku Hirayama*, Hideko Nagasawa*, Fumitaka Kikkawa and Shinya Toyokuni

Amniotic fluid contains numerous biomolecules derived from fetus and mother, thus providing precious information on pregnancy. Here, we evaluated oxidative stress of human amniotic fluid and measured the concentration of catalytic Fe(II). Levels of 8-OHdG and dityrosine were higher in the 3rd trimester compared with the 2nd trimester in normal subjects, and the abnormal groups generally showed lower levels than the controls, thus suggesting that they represent fetal metabolic activities. In contrast, catalytic Fe(II) was higher in the 2nd trimester than the 3rd trimester in the normal subjects, and overall the abnormal groups showed higher levels than the controls, suggesting that high catalytic Fe(II) at late gestation reflects fetal pathologic alterations. Notably, products of H_2O_2 and catalytic Fe(II) remained almost constant in amniotic fluid.

[*Biochem. Biophys. Res. Commun.* **457**, 706-711 (2015)] [Lab. of Pharmaceutical & Medicinal Chemistry]

The Inhibitory Effect of Hypoxic Cytotoxin on the Expansion of Cancer Stem Cells in Ovarian Cancer.

Noriko Nozawa-Suzuki, Hideko Nagasawa*, Ken Ohnishi and Ken-Ichirou Morishige

While an increase in progression free survival time is seen when an angiogenesis inhibitor is used in the treatment of high-relapse rate ovarian cancer, it has little effect on overall survival. A possible cause of treatment-resistance to angiogenesis inhibitors is the growth of stem cells in a hypoxic microenvironment built inside the tumor tissue by angiogenesis inhibition. In this study, we examined the possible suppression of stem cell and cancer stem cell (CSC) expansion by hypoxic cytotoxin, TX-402.

[*J. Heterocycl. Chem.* **52**, 880–887 (2015)] [Lab. of Pharmaceutical & Medicinal Chemistry]

Polycyclic *N*-Heterocyclic Compounds 84: Reaction of *N*-(pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4-yl)amidines or *N*-(pyrido[2',3':4,5]furo[3,2-*d*]pyrimidin-4-yl)amidines with Hydroxylamine Hydrochloride.

Kensuke Okuda*, Ryota Ide, Naoto Uramaru and Takashi Hirota

The reactions of nine *N*-(pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4-yl)amidines (**3**) with hydroxylamine hydrochloride produced new cyclization products. These were formed via ring cleavage of the pyrimidine component followed by a 1,2,4-oxadiazole-forming ring closure to give *N*-[2-([1,2,4]oxadiazol-5-yl)thieno[2,3-*b*]pyridin-3-yl]formamide oximes (**11**). Reaction of six *N*-(pyrido[2',3':4,5]furo[3,2-*d*]pyrimidin-4-yl)amidines (**12**) with hydroxylamine hydrochloride gave similar results. Effects of the newly synthesized compounds on pentosidine formation were also evaluated.

[*J. Heterocycl. Chem.* **52**, 888–895 (2015)] [Lab. of Pharmaceutical & Medicinal Chemistry]

Polycyclic *N*-Heterocyclic Compounds 85: Synthesis and Evaluation of Anti-platelet Aggregation Activity of 2,4-Disubstituted 5,6-Dihydro[1]benzazepino[5,4-*d*]pyrimidine and Related Compounds.

Kensuke Okuda*, Ying-Xue Zhang, Takashi Hirota and Kenji Sasaki

We have synthesized a large number of tricyclic 2-substituted 4-alkylamino-5,6-dihydro[1]benzazepino [5,4-*d*]pyrimidines as part of our research to develop new effective antiplatelet drugs. A variety of alkyl and aryl groups were used as substituents at the 2-position. Evaluation of the effects of the newly synthesized compounds on collagen-induced platelet aggregation revealed several promising antiplatelet candidates with potencies superior to aspirin.

[*J. Heterocycl. Chem.* **52**, 780–792 (2015)] [Lab. of Pharmaceutical & Medicinal Chemistry]

Polycyclic *N*-Heterocyclic Compounds 86: Synthesis and Evaluation of Anti-platelet Aggregation Activity of 2,4-Disubstituted 9-Chloro-5,6-Dihydro[1]benzazepino[5,4-*d*]pyrimidine and Related Compounds.

Kensuke Okuda*, Shigeki Takarada, Takashi Hirota and Kenji Sasaki

Libraries of tricyclic 2-substituted 4-alkylamino-9-chloro-5,6-dihydropyrimido[5,4-*d*]benzazepines and tetracyclic 12-substituted 8-chloro-1,2,5,6-tetrahydro-4*H*-imidazo[1',2':1,6]pyrimido[5,4-*d*]benzazepines were synthesized as part of our research to develop new effective antiplatelet drugs. Several alkyl and aryl groups were used as substituents at the 2-position. Evaluation of the effects of the newly synthesized compounds on collagen-induced platelet aggregation revealed several promising antiplatelet candidates with potencies superior to aspirin.

[*ChemSusChem* **8**, 3773-3776 (2015)] [Lab. of Organic Chemistry]

Stainless-Steel Ball-Milling Method for Hydro-/Deutero-genation using H_2O/D_2O as a Hydrogen/Deuterium Source.

Yoshinari SAWAMA,* Takahiro KAWAJIRI, Miki NIIKAWA, Ryota GOTO, Yuki YABE, Tohru TAKAHASHI, Takahisa MARUMOTO, Miki ITOH, Yuuichi KIMURA, Yasunari MONGUCHI, Shin-ichi KONDO and Hironao SAJIKI*

A one-pot continuous-flow method for hydrogen (deuterium) generation and subsequent hydrogenation (deuterogenation) was developed using a stainless-steel (SUS304)-mediated ball-milling approach. SUS304, especially zero-valent Cr and Ni as constituents of the SUS304, and mechanochemical processing played crucial roles in the development of the reactions.

[*J. Org. Chem.* **80**, 5556-5565 (2015)] [Lab. of Organic Chemistry]

Biarylmethane and Fused Heterocyclic Arene Synthesis via *in situ*-Generated *ortho*- and/or *para*-NaphthoquinoneMethides.

Yoshinari SAWAMA,* Takahiro KAWAJIRI, Shota ASAI, Naoki YASUKAWA, Yuko SHISHIDO, Yasunari MONGUCHI and Hironao SAJIKI*

The 4-alkyl- or silyl-substituted 1-(siloxymethyl)-1,4-epoxy-1,4-dihydronaphthalene was transformed to *o*-NQM (1-naphthoquinone-2-methide), which underwent Friedel–Crafts 1,4-addition of the α,β-unsaturated carbonyl moiety to provide the 2-benzyl-1-naphthol as the biarylmethane and [4 + 2]-cycloaddition with a dienophile to give the fused heterocyclic arene. Meanwhile, the 4-unsubstituted 1-(siloxymethyl)-1,4-epoxy-1,4-dihydronaphthalene could be converted to the corresponding 4-benzyl-1-naphthol by the Friedel–Crafts 1,6-addition of *p*-NQM (1-naphthoquinone-4-methide) generated by the site-selective ring opening of the 1,4-epoxy moiety.

[*Adv. Synth. Catal.* **357**, 3667-3670 (2015)] [Lab. of Organic Chemistry]

Hydrogen Self-Sufficient Arene Reduction to Cyclohexane Derivatives Using a Combination of Platinum on Carbonand 2-Propanol.

Yoshinari SAWAMA,* Misato MORI, Tsuyoshi YAMADA, Yasunari MONGUCHI and Hironao SAJIKI*

Various arenes have been hydrogenated using platinum on carbon in a 2-propanol-aqueous mixed solvent at 100 °C without the addition of flammable hydrogen gas to give the corresponding cyclohexane derivatives. 2-Propanol plays a role as an efficient hydrogen source based on the platinum on carbon-catalyzed dehydrogenation.

[*Eur. J. Org. Chem.* 2492-2497 (2015)] [Lab. of Organic Chemistry]

Facile Arene Hydrogenation under Flow Conditions Catalyzed by Rhodium or Ruthenium on Carbon.

Tomohiro HATTORI, Takashi IDA, Aya TSUBONE, Yoshinari SAWAMA, Yasunari MONGUCHI* and Hironao SAJIKI*

An efficient and practical protocol for the flow hydrogenation of aromatic rings was developed. The hydrogenation of a variety of aromatic compounds, such as benzene, furan, and pyridine derivatives, could be completed within only 20 s during a single pass through a catalyst cartridge containing 10 % rhodium on carbon (Rh/C) or 10 % ruthenium on carbon (Ru/C) under neutral conditions. The protocol was successfully applied to a 10 mmol scale reaction. Furthermore, the 10 % Rh/C and 10 % Ru/C did not deteriorate during the entire study.

[*Synlett* **26**, 2014-2018 (2015)] [Lab. of Organic Chemistry]

Tertiary-Amino-Functionalized Resin-Supported Palladium Catalyst for the Heterogeneous Suzuki–Miyaura Reaction of Aryl Chlorides.

Yasunari MONGUCHI,* Tomohiro ICHIKAWA, Moeko NETSU, Tomohiro HATTORI, Tomoteru MIZUSAKI, Yoshinari SAWAMA and Hironao SAJIKI*

A palladium catalyst supported on a tertiary-amino-functionalized resin bearing N,N-dimethylamino substituents on the polystyrene-divinylbenzene-based resin was developed. The catalyst was effectively used for the ligand-free Suzuki–Miyaura reactions of less-reactive chloroarenes with arylboronic acids. No leached palladium species were detected in the reaction media after the reaction.

[*Chem Pharm. Bull.* **63**, 757-761 (2015)] [Lab. of Organic Chemistry]

Gold-Catalyzed Benzylic Azidation of Phthalans and Isochromans and Subsequent $FeCl_3$-Catalyzed Nucleophilic Substitutions.

Shota ASAI, Yuki YABE, Ryota GOTO, Saori NAGATA, Yasunari MONGUCHI, Yasuyuki KITA, Hironao SAJIKI* and Yoshinari SAWAMA*

The benzylic positions of the phthalan and isochroman derivatives as benzene-fused cyclic ethers effectively underwent gold-catalyzed direct azidation using trimethylsilylazide ($TMSN_3$) to give the corresponding 1-azidated products possessing the *N*,*O*-acetal partial structure. The azido group of the *N*,*O*-acetal behaved as a leaving group in the presence of catalytic iron(III) chloride, and 1-aryl or allyl phthalan and isochroman derivatives were obtained by nucleophilic arylation or allylation, respectively.

[*RSC Adv.* **5**, 92954-92957 (2015)] [Lab. of Organic Chemistry]

Mild Deuteration Method of Terminal Alkynes in Heavy Water using Reusable Basic Resin.

Tsuyoshi YAMADA, Kwihwan PARK, Yasunari MONGUCHI, Yoshinari SAWAMA* and Hironao SAJIKI*

The mild and efficient deuteration of terminal alkynes (mono-substituted alkynes) proceeded in the presence of a basic anion exchange resin, WA30, which is a polystyrene polymer bearing a tertiary amine residue on the aromatic nuclei, in heavy water (D_2O) at room temperature. WA30 could be easily removed by a simple filtration and repeatedly reused.

[*ChemCatChem* **7**, 2155-2160 (2015)] [Lab. of Organic Chemistry]

Unique Chemoselective Hydrogenation Using Palladium Catalyst Immobilized on Ceramic.

Yasunari MONGUCHI,* Takahisa MARUMOTO, Tomohiro ICHIKAWA, Yutaka MIYAKE, Yoshiyuki NAGAE, Michiyuki YOSHIDA, Yasunori OUMI, Yoshinari SAWAMA, Hironao SAJIKI*

A heterogeneous palladium catalyst supported on a ceramic (5 % Pd/ceramic) was developed. The catalyst exhibited a specific chemoselectivity for hydrogenation that has never been achieved by other palladium-catalyzed methods. Either aliphatic or aromatic *N*-Cbz groups could be deprotected to the corresponding free-amines, while the hydrogenolysis of benzyl esters and ethers did not proceed. Furthermore, aryl chlorides and epoxides were tolerant under the Pd/ceramic-catalyzed hydrogenation conditions. 5 % Pd/ceramic could be reused without any loss of catalyst activity, as no palladium leaching was detected in the reaction media.

[*ACS Sustainable Chem.* **3**,683-689 (2015)] [Lab. of Organic Chemistry]

Stainless-Steel-Mediated Quantitative Hydrogen Generation from Water under Ball Milling Conditions.

Yoshinari SAWAMA,* Miki NIIKAWA, Yuki YABE, Ryota GOTO, Takahiro KAWAJIRI, Takahisa MARUMOTO, Tohru TAKAHASHI, Miki ITOH, Yuuichi KIMURA, Yasushi SASAI, Yukinori YAMAUCHI, Shin-ichi KONDO, Masayuki KUZUYA, Yasunari MONGUCHI and Hironao SAJIKI*

A robust and quantitative gaseous hydrogen generation method has been developed in an effort to achieve efficient H_2 generation derived from H_2O. The present reaction could be achieved by a simple ball friction (milling) reaction of H_2O using a planetary ball mill machine with a stainless-steel vessel and balls. It was mediated by metals as an element of stainless steel of the ball mill and also promoted by mechanochemical processing.

[*Adv. Synth. Catal.* **357**, 1205-1210 (2015)] [Lab. of Organic Chemistry]

Palladium on Carbon-Catalyzed Aqueous Transformation of Primary Alcohols to Carboxylic Acids Based on Dehydrogenation under Mildly Reduced Pressure.

Yoshinari SAWAMA,* Kosuke MORITA, Shota ASAI, Masami KOZAWA, Shinsuke TADOKORO, Junichi NAKAJIMA, Yasunari MONGUCHI and Hironao SAJIKI*

The catalytic dehydrogenation of alcohols to carbonyl products is a green sustainable oxidation with no production of waste except for hydrogen, which can be an energy source. We have accomplished the palladium on carbon (Pd/C)-catalyzed dehydrogenation of primary alcohols to carboxylic acids in water under a mildly reduced pressure (800 hPa). The reduced pressure can be easily controlled by the vacuum controller of the rotary evaporator to remove the excess of generated hydrogen, which causes the reduction (reverse reaction) of aldehydes to alcohols (starting materials) and other undesirable side reactions.

[*Synlett* **26**, 700-704 (2015)] [Lab. of Organic Chemistry]

Osmium on Chelate Resin: Nonvolatile Catalyst for Synthesis of Diols from Alkenes.

Yasunari MONGUCHI,* Fumika WAKAYAMA, Hitoshi TAKADA, Yoshinari SAWAMA and Hironao SAJIKI*

Osmium tetraoxide (OsO_4) was immobilized on a commercially available chelate resin DIAION CR11 (CR11) just by simply immersing it in a methanol solution of OsO_4 at room temperature. The resulting purple solid, 5% Os/CR11, indicated no volatility, and effectively catalyzed the oxidation of various alkenes to the corresponding diols.

[*RSC Adv.* 13727-13732 (2015)] [Lab. of Organic Chemistry]

Multiple Deuteration of Alkanes Synergistically-Catalyzed by Platinum and Rhodium on Carbon as a Mixed Catalytic System.

Tsuyoshi YAMADA, Yoshinari SAWAMA,* Kyoshiro SHIBATA, Kosuke MORITA, Yasunari MONGUCHI and Hironao SAJIKI*

We have accomplished an efficient and mild multiple deuteration method for alkanes catalyzed by the combined use of heterogeneous platinum on carbon (Pt/C) and rhodium on carbon (Rh/C) catalysts in *i*-PrOD-d_8 and D_2O as a mixed solvent. The present multi-deuteration could be initiated by the transition metal-catalyzed dedeuteration of *i*-PrOD-d_8 to produce D_2 and the subsequent C–H bond activation of alkanes catalyzed by the Pt/C and/or Rh/C–D_2 complex. This method could be applied to the deuteration of wide variety of linear, branched and cyclic alkanes as useful deuterated materials under mild conditions.

[*Org. Lett.* **17**, 434-437 (2015)] [Lab. of Organic Chemistry]

$FeCl_3$-Catalyzed Self-Cleaving Deprotection of Methoxyphenylmethyl-Protected Alcohols.

Yoshinari SAWAMA,* Masahiro MASUDA, Shota ASAI, Ryota GOTO, Saori NAGATA, Shumma NISHIMURA, Yasunari MONGUCHI and Hironao SAJIKI*

4-Methoxyphenylmethyl ethers are widely utilized as alcohol protecting groups. $FeCl_3$ effectively catalyzes the deprotection of methoxyphenylmethyl-type ethers in a self-cleaving manner to produce oligomeric derivatives and alcohols. Remarkably, the highly pure mother alcohols can be obtained without silica gel column chromatography by using the 2,4-dimethoxyphenylmethyl group as a protective group.

[*Catalysts* **5**, 18-25 (2015)] [Lab. of Organic Chemistry]

Palladium on Carbon-Catalyzed Suzuki-Miyaura Coupling Reaction Using an Efficient and Continuous Flow System.

Tomohiro HATTORI, Aya TSUBONE, Yoshinari SAWAMA, Yasunari MONGUCHI,* Hironao SAJIKI*

The continuous flow Suzuki-Miyaura reaction between various haloarenes and arylboronic acids was successfully achieved within only *ca.* 20 s during the single-pass through a cartridge filled with palladium on carbon (Pd/C). No palladium leaching was observed in the collected reaction solution by atomic absorption spectrometry (detection limit: 1 ppm).

[*Heterocycles* **90**, 186-197 (2015)] [Lab. of Organic Chemistry]

Pd/C-catalyzed hydrodechlorination of dioxins from fly ash under ambient pressure and temperature.

Yasunari MONGUCHI,* Akiko IDO, Miki NIIKAWA, Nobuharu NAGATSU, Ryosuke MIZUKOSHI, Hisamitsu NAGASE and Hironao SAJIKI*

Dioxins, such as polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), which could be efficiently extracted from fly ash based on the method approved by the Japanese Industrial Standard, were degraded by the palladium on carbon (Pd/C)-catalyzed hydrodechlorination in the presence of triethylamine at room temperature under ordinary pressure with a greater than 97% efficiency. The distinct features of the present degradation method of dioxins are its mildness, simplicity, safety, and efficiency without any expensive facilities.

[*Chem. Eur. J.* **21**, 2222-2229 (2015)] [Lab. of Organic Chemistry]

Biaryl Synthesis via Ring-Opening Friedel-Crafts Arylation of 1,4-Epoxy-1,4-dihydronaphthalenes Catalyzed by Iron Trichloride.

Yoshinari SAWAMA,* Shota ASAI, Takahiro KAWAJIRI, Yasunari MONGUCHI and Hironao SAJIKI*

Biaryl and heterobiaryl compounds are important frameworks across a range of fields including pharmaceutical and functional material chemistries. We have accomplished the efficient synthesis of various naphthalene-linked arenes and heteroarenes as biaryls and heterobiaryls by the $FeCl_3$-catalyzed Friedel-Crafts reactions accompanied by the ring-opening of the 1,4-epoxy moiety of 1,4-epoxy-1,4-dihydronaphthalenes. Especially, it is noteworthy that 1-silylated substrates were regioselectively transformed to the 3-aryl-1-silylnaphthalenes and the double Friedel–Crafts reactions using thiophene derivatives could directly produce the corresponding bis-naphthlated thiophene derivatives.

[*Tetrahedron* **71**, 6499-6505 (2015)] [Lab. of Organic Chemistry]

Development of Chelate Resin-Supported Palladium Catalysts for Chemoselective Hydrogenation.

Yasunari MONGUCHI, Tomohiro ICHIKAWA, Kei NOZAKI, Kensuke KIHARA, Yuuko YAMADA, Yutaka MIYAKE, Yoshinari SAWAMA and Hironao SAJIKI*

Two kinds of palladium catalysts immobilized on a chelate resin bearing diiminoacetate or polyamine moieties on the polystyrene-divinylbenzene polymer were newly prepared by the adsorption of palladium (II) ions on these resins followed by the reduction to palladium (0) with hydrazine monohydrate. Both catalysts showed a similar activity for hydrogenation. A variety of reducible functionalities, except for benzylic alcohol, alkyl benzyl ether, silyl ether, and epoxide, could be reduced under the hydrogenation conditions using either catalyst. Since the palladium metal elution from the immobilized catalysts was never observed, the catalysts could be reused without any decrease in the catalyst activity for at least 5 runs.

[*Tetrahedron Lett.* **56**, 5886-5888 (2015)] [Lab. of Organic & Medicinal Chemistry]

Aerobic photooxidative bromination of aromatic compounds using carbon tetrabromide mediated by anthraquinone-2-carboxylic acid.

Masanori TANAKA, Yuji KAMITO, Cui LEI, Norihiro TADA, Akichika ITOH*

We developed the aerobic photooxidative bromination of aromatic compounds using carbon tetrabromide in the presence of anthraquinone-2-carboxylic acid under visible light irradiation.

[*Synlett* **26**, 1705-1709 (2015)] [Lab. of Organic & Medicinal Chemistry]

Aerobic photooxidative synthesis of secondary aldimines from benzylamines by using methylene blue.

Akifumi OKADA, Hiroki YUASA, Akitoshi FUJIYA, Norihiro TADA, Tsuyoshi MIURA, Akichika ITOH*

We have developed a concise oxidative coupling of primary benzylamines to yield secondary aldimines catalyzed by methylene blue by using molecular oxygen as the oxidant in the presence of visible-light irradiation from fluorescent lamps.

[*Adv. Synth. Catal*. **357**, 2017-2021 (2015)] [Lab. of Organic & Medicinal Chemistry]

Direct ortho-hydroxylation of 2-phenylpyridines using palladium(II) chloride and hydrogen peroxide.

Tomoaki YAMAGUCHI, Eiji YAMAGUCHI, Norihiro TADA, Akichika ITOH*

Direct functionalization of the ubiquitous C-H bond is receiving much attention because complex structures can be formed from simple precursors. This paper reports a useful method for the direct hydroxylation of 2-phenylpyridines using palladium(II) chloride and aq. hydrogen peroxide. In this method, hydrogen peroxide, which has high atom efficiency, is employed as the oxidant; and phenol derivs. are generated via C-H activation.

[*Tetrahedron Lett*. **56**, 1973-1975 (2015)] [Lab. of Organic & Medicinal Chemistry]

Facile and efficient synthesis of hydroxyalkyl esters from cyclic acetals through aerobic photo-oxidation using anthraquinone-2-carboxylic acid.

Tomoaki YAMAGUCHI, Yasuhisa KUDO, Shin-ichi HIRASHIMA, Eiji YAMAGUCHI, Norihiro TADA, Tyuyoshi Miura, Akichika ITOH*

A convenient metal-free oxidation protocol of various cyclic acetals with molecular oxygen and anthraquinone-2-carboxylic acid under visible light irradiation by a fluorescent lamp afforded their corresponding hydroxyalkyl esters.

[*Synlett* **26**, 412-415 (2015)] [Lab. of Organic & Medicinal Chemistry]

A study of aerobic photooxidation with a continuous-flow microreactor.

Yoshitomo NAGASAWA, Katyuya TANBA, Norihiro TADA, Eiji YAMAGUCHI, Akichika ITOH*

We report the development of an aerobic photooxidation process with a continuous-flow microreactor that can form a slug flow region on the chip. The approach solved several problems raised by using batch systems.

[*RSC Advances* **5**, 9591-9593 (2015)] [Lab. of Organic & Medicinal Chemistry]

Metal-free synthesis of imidazopyridine from nitroalkene and 2-aminopyridine in the presence of a catalytic amount of iodine and aqueous hydrogen peroxide.

Yuma TACHIKAWA, Yoshitomo NAGASAWA, Sohei FURUHASHI, Lei Cui, Eiji YAMAGUCHI, Norihiro TADA, Tsuyoshi MIURA, Akichika ITOH*

We have developed a metal-free synthetic method for 3-nitroimidazo[1,2-*a*]pyridines from nitroalkenes and 2-aminopyridines using catalytic amounts of iodine and aqueous hydrogen peroxide as a terminal oxidant.

[*Cancer Lett.* **360**, 28-38 (2015)] [Lab. of Pharmaceutical Analytical Chemistry]

Anti-cancer Fatty-acid Derivative Induces Autophagic Cell Death through Modulation of PKM Isoform Expression Profile Mediated by Bcr-abl in Chronic Myeloid Leukemia.

Haruka SHINOHARA, Kohei TANIGUCHI, Minami KUMAZAKI, Nami YAMADA, Yuko ITO, Yoshinori OTSUKI, Bunji UNO,* Tomoki NAOE, and Yukihiro AKAO

To develop a new strategy for the treatment of chronic myeloid leukemia (CML), we investigated the associations among bcr-abl, the cascade related to cancer energy metabolism, and autophagy induced by a fatty-acid derivative. c-Myc functioned as a transcriptional activator of bcr-abl, and regulated the hnRNP/PKM cascade. AIC-47, acting through the PPAR γ/β-catenin pathway, induced down-regulation of c-Myc, leading to the disruption of the bcr-abl/mTOR/hnRNP signaling pathway, and switching of the expression of PKM2 to PKM1. This switching caused autophagic cell death through an increase in the ROS level. Our findings suggest that AIC-47 induced autophagic cell death through the PPAR γ/β-catenin/bcr-abl/mTOR/hnRNP/PKM cascade.

[*Cancer Lett.* **363**, 17-27 (2015)] [Lab. of Pharmaceutical Analytical Chemistry]

MicroRNA-124 Inhibits Cancer Cell Growth through PTB1/PKM1/PKM2 Feedback Cascade in Colorectal Cancer.

Kohei TANITUCHI, Nobuhiko SUGITO, Minami KUMAZAKI, Haruka SHINOHARA, Nami YAMADA, Yoshihito NAKAGAWA, Yuko ITO, YoshinoriOTSUKI, Bunji UNO,* Kazuhisa UCHIYAMA, and Yukihiro AKAO

The role of microRNAs (miRs) in colorectal adenoma (CRA) and cancer (CRC) was investigated. The expression levels of miR-124 were decreased in CRA (81.8%) and CRC (57.6%) in 55 clinical samples. The ectopic expression of miR-124 induced apoptosis and autophagy in colon cancer cells. Also, miR-124 targeted polypyrimidine tract-binding protein 1 (*PTB1*), which is a splicer of pyruvate kinase muscles 1 and 2 (*PKM1*and *PKM2*) and induced the switching of PKM isoform expression from PKM2 to PKM1. siR-PTB1 induced drastic apoptosis in colon cancer cells. These findings suggest that miR-124 acts as a tumor-suppressor and a modulator of energy metabolism through a PTB1/PKM1/PKM2 feedback cascade in human colorectal tumor cells.

[*Anal. Sci.* **31**, 1189-1192 (2015)] [Lab. of Pharmaceutical Analytical Chemistry]

Simple Pretreatment and HILIC Separation for LC-ESI-MS/MS Determination of Adenosine in Human Plasma.

Hiroya MURAKAMI, Erina OHTANI, Tomoko IWATA, Yukihiro ESAKA, Takuma AOYAMA, Masanori KAWASAKI, Toshiki TANAKA, Shinya MINATOGUCHI, and Bunji UNO*

A simple pretreatment method and separation mode for the LC-ESI-MS/MS determination of adenosine in human plasma have been developed. Deproteinization by acetonitrile and ultrafiltration followed by chromatographic separation with a hydrophilic interaction chromatographic (HILIC) column give a highly sensitive MS/MS response without ionic suppression caused by the matrix compounds in human plasma. In addition, the presence of ammonium acetate in the mobile phase contributes to high sensitivity in MS/MS detection, facilitating the ionization of adenosine. This method seems to be amenable to the treatment of many samples in clinical practice.

[*J. Phys. Chem. A* **119**, 12990-12998 (2015)] [Lab. of Pharmaceutical Analytical Chemistry]

Spectroscopic Evidence for Through-Space Arene-Sulfur-Arene Bonding Interaction in *m*-Terphenyl Thioether Radical Cations.

Nicolas P.-A. MONNEY, Thomas BALLY, Takuhei YAMAMOTO,* and Richard S. GLASS

Electronic absorption spectra and quantum chemical calculations of the radical cations of *m*-terphenyl *tert*-butyl thioethers, where the S-*t*-Bu bond is forced to be perpendicular to the central phenyl ring, show the occurrence of through-space $[\pi^{\cdots}S^{\cdots}\pi]^{+}$ bonding interactions which lead to a stabilization of the thioether radical cations. Adding a second *m*-terphenyl *tert*-butyl thioether moiety does not lead to further delocalization; the spin and charge remain in one of the two halves of the radical cation. These findings have interesting implications with regard to the role of methionines as hopping stations in electron transfer through proteins.

[*Chem. Pharm. Bull.* **63**, 967-973(2015)] [Lab. of Pharmaceutical Analytical Chemistry]

Importance of Proton-Coupled Electron Transfer from Natural Phenolic Compounds in Superoxide Scavenging.

Tatsushi NAKAYAMA and Bunji UNO*

The superoxide $O_2^{\bullet-}$ scavenging reaction of (+)-catechin (Cat), quercetin (Que), rutin, and α-tocopherol (α-TOH) as natural phenolic compounds is investigated on the basis of electrochemical and ESR spectral measurements with the aid of density functional theory (DFT) calculations. The catechol moiety of Cat, Que, and rutin plays an essential role in concerted proton-coupled electron transfer (PCET) to $HO_2^{\bullet}$ derived from $O_2^{\bullet-}$ to give H_2O_2 and the corresponding *o*-benzoquinone radical anions. On the other hand, the presence of α-TOH causes sequential electron and proton transfers to $HO_2^{\bullet}$ to give H_2O_2 and the α-tocopheroxyl radical. The ESR spectral measurements and DFT calculation results suggest that the $O_2^{\bullet-}$ scavenging reaction of the natural phenolic compounds proceeds efficiently with the one-step concerted PCET or sequential PCET mechanism.

[*Powder Technology* **271**, 100-108 (2015)] [Lab. of Pharmaceutical Engineering]

Fabrication of spontaneous emulsifying powders for improved dissolution of poorly water-soluble drugs.

Y. WEERAPOL, S. LIMMATVAPIRAT, H. TAKEUCHI and P. SRIAMORNSAK

The aim of the present study was to fabricate spontaneous emulsifying powders (SEP) for improving dissolution of poorly water-soluble drugs for oral drug delivery. The effect of drugs with different lipophilicity (log. P), that is, nifedipine, felodipine, manidipine, and itraconazole on crystalline properties and dissolution profiles of SEP was also examined. The liquid spontaneous emulsifying formulation (SEF), composing of polyoxyl 35 castor oil, caprylic/capric glyceride and diethylene glycol monoethyl ether at a ratio of 1:1:8, was solidified with three different solid carriers, namely, fumed silica, porous silicon dioxide and porous calcium silicate (at 20%-50%). This was further confirmed by scanning electron microscopy.

[*Eur J Pharm Biopharm* **91**, 25-34 (2015)] [Lab. of Pharmaceutical Engineering]

Enhanced dissolution and oral bioavailability of nifedipine by spontaneous emulsifying powders: Effect of solid carriers and dietary state.

Y. WEERAPOL, S. LIMMATVAPIRAT, C. JANSAKUL, H. TAKEUCHI and P. SRIAMORNSAK

The objective of this study was to prepare spontaneous emulsifying powder (SEP) for improving dissolution and enhancing oral bioavailability of a poorly water-soluble drug, nifedipine (NDP). In order to investigate the effects of solid carrier properties, such as surface area and pore size, and a concurrent food intake on absorption of NDP in rats, different SEP formulations were prepared by adsorbing liquid spontaneous emulsifying formulation (SEF), composing of polyoxyl 35 castor oil, caprylic/capric glyceride and diethylene glycol monoethyl ether at a ratio of 1:1:8, onto various solid carriers (i.e.; silica (FS), porous calcium silicate (PCS) and porous silicon dioxide). The solid characterization by scanning electron microscopy, differential scanning calorimetry and powder X-ray diffraction revealed the absence of crystalline NDP in the formulations.

[*Powder Technology* **286**, 444-450 (2015)] [Lab. of Pharmaceutical Engineering]

Spray-dried composite particles of erythritol and porous silica for orally disintegrating tablets prepared by direct tableting.

S. TANIMURA, K. TAHARA and H. TAKEUCHI

This study investigated the preparation of orally disintegrating tablets (ODTs), which were prepared from spray-dried composite particles (CPs) of erythritol and porous silica by direct tableting. Although erythritol powder has poor compactability and caused problems during tableting, adding a small amount of CPs to erythritol improved tablet hardness. CPs containing an erythritol:porous silica ratio of 2:1 most effectively improved erythritol compactability. Erythritol powder containing CPs showed higher deformability than that of physical mixtures, and CPs inhibited elastic recovery after compression because of strong interparticulate bonding. Furthermore, CPs retained function as dry binders when stored under humid conditions. We confirmed that the use of CPs improved manufacturing of ODTs containing active pharmaceutical ingredients using an appropriate compression pressure.

[*Crystal Growth and Design* **15**, 5155-5156 (2015)] [Lab. of Pharmaceutical Engineering]

Continuous spherical crystallization of albuterol sulfate with solvent recycle system.

K. TAHARA, M. O'MAHONY and A. S. MYERSON

Spherical crystallization enables the direct preparation of crystal agglomerates of active pharmaceutical ingredients (APIs) with improved crystal handling properties. The continuous spherical crystallization of albuterol sulfate as a model API was developed using a mixed-suspension, mixed-product removal (MSMPR) crystallizer. Spherical agglomerates of albuterol sulfate were obtained via antisolvent crystallization using the MSMPR crystallizer with water as the solvent and an ethyl acetate/emulsifier (Pluronic L-121) mixture as the antisolvent. Steady-state continuous spherical crystallization was rapidly achieved after 30 min, and a yield of >95% was obtained. In the MSMPR crystallizer, the desired solvent to antisolvent ratio was maintained by controlling the flow rates of the feed, antisolvent, and recycle stream, and 90% of the mother liquor was recycled during the continuous spherical crystallization of albuterol sulfate by optimizing the rate of each stream.

[*J Vet Med Sci* **77**, 1379-1383 (2015)] [Lab. of Pharmaceutical Engineering]

Ligand-binding characteristics of feline insulin-binding immunoglobulin g.

T. SUZUKI, N. NISHII, S. TAKASHIMA, T. MATSUBARA, A. IWASAWA, H. TAKEUCHI, K. TAHARA, T. HACHISU and H. KITAGAWA

Polyclonal immunoglobulin (Ig) G autoantibodies against insulin have been identified in sera of healthy cats. We purified and fractionated insulin-binding IgGs from cat sera by affinity chromatography and analyzed affinity of insulin-binding IgGs for insulin and their epitopes. Following the passing of fraction A, which did not bind to insulin, insulin-binding IgGs were eluted into two fractions, B and C, by affinity chromatography using a column fixed with bovine insulin. Dissociation constant (KD) values between insulin-binding IgGs and insulin, determined by surface plasmon resonance analysis (Biacore™system), were 1.64e−4 M for fraction B (low affinity IgGs) and 2e−5 M for fraction C (high affinity IgGs). Epitope analysis was conducted using 16 peptide fragments synthesized in concord with the amino acid sequence of feline insulin by an enzyme-linked immunosorbent assay.

[*Int J Pharm* **479**, 302-305 (2015)] [Lab. of Pharmaceutical Engineering]

Characterization of insulin-loaded liposome using column-switching HPLC.

N. OHNISHI, S. TANAKA, K. TAHARA and H. TAKEUCHI

We evaluated the drug-encapsulation state of insulin (INS)-loaded liposome using a novel column-switching HPLC system that can automatically separate unloaded drug from encapsulated drug by hydrophobic interaction. When the INS-loaded liposome was dispersed in water (pH 7.4), the encapsulation efficiency (EE) obtained by the column-switching HPLC system was consistent with that obtained by a conventional ultracentrifugation method. However, the INS-loaded liposome dispersed in 0.1% acetic acid (pH 3.3) showed disagreement between the EEs obtained by both methods. Considering the results of particle size, zeta potential, and transmission electron microscope (TEM) observations, we hypothesized that the column-switching HPLC method was able to distinguish INS adsorbed onto the liposome surface from the encapsulated INS, although an ultracentrifugation method precipitated the adsorbed INS onto the liposome surface along with the encapsulated INS.

[*Biol Pharm Bull* **38**, 374-379 (2015)] [Lab. of Pharmaceutical Engineering]

Evaluation of antitumor effects of folate-conjugated methyl-β-cyclodextrin in melanoma.

K. MOTOYAMA, R. ONODERA, N. TANAKA, K. KAMEYAMA, T. HIGASHI, R. KARIYA, S. OKADA and H. ARIMA

Melanoma is a life-threatening disorder and its incidence is increasing gradually.Recently, we have developed folate-conjugated methyl-β-cyclodextrin (FA-M-β-CyD) and clarified its potential as a new antitumor agent involved in autophagic cell death. However, it remains uncertain whether FA-M-β-CyD exerts anticancer effects against melanomas. Therefore, in this study, we investigated the effects of FA-M-β-CyD on the folate receptor-α (FR-α)-expressing melanoma cell-selective cytotoxic effect. FA-M-β-CyD showed cytotoxic effects in Ihara cells, a human melanoma cell line expressing FR-α. In sharp contrast to methyl-β-cyclodextrin, FA-M-β-CyD entered Ihara cells [FR-α(+)] through FR-α-mediated endocytosis. Additionally, FA-M-β-CyD elicited the formation of autophagosomes in Ihara cells.

[*Chem. Pharm. Bull.* **63**, 489-494(2015)] [Lab. of Pharmaceutical Physical Chemistry]

Novel pH-Responsive Polymeric Micelles Prepared through Self-assembly of Amphiphilic Block Copolymer with Poly-4-vinylpyridine Block Synthesized by Mechanochemical Solid-State Polymerization.

Shin-ichi KONDO*, Yuna ASANO, Natsumi KOIZUMI, Kenjiro TATEMATSU, Yuka SAWAMA, Yasushi SASAI, , Yukinori YAMAUCHI, Masayuki KUZUYA and Shigeru KUROSAWA

We fabricated polymeric micelles containing 5-fluorouracil (5-FU) or fluorescein using the amphiphilic block copolymer, poly-4-vinylpyridine-*b*-6-O-methacryloyl galactopyranose. Although the polymeric micelles were stable at pH 7.4, they readily decomposed at pH 5, resulting in near complete release of 5-FU. Uptake of polymeric micelles containing fluorescein by HepG2 and HCT116 cells was also investigated. The cytotoxicity of polymeric micelles containing 5-FU was evaluated against HepG2 cells using a CCK-8 assay. The results suggest that polymeric micelles containing 5-FU are more cytotoxic to HepG2 cells than free 5-FU.

[*J. Photopolym. Sci. Thechnol.* **28**, 475-478 (2015)] [Lab. of Pharmaceutical Physical Chemistry]

Immobilization of Au Nano Particles Using the Durable Hydrophilic Polymer Surface Fabricated by Plasma-Assisted Method.

Shin-ichi KONDO*, Yasushi SASAI, Yukinori YAMAUCHI and Masayuki KUZUYA

We synthesized the polymer film immobilizing Au nano particles by the use of a durable hydrophilic surface fabricated by the plasma-assisted method. Two kinds of methods were used to immobilize Au nano particles. 2-Aminoethanethiol (AET) was introduced on the LDPE-VEMAC film (durable hydrophilic polymer surface), and then Au nano particles were immobilized on the film by the reaction of thiol group and Au.(Method A) VEMAC was immobilized on LDPE-VEMAC film introduced hexamethyl diamine, and then AET was reacted with VEMAC. Au nano particles were immobilized on this film to obtain LDPE-VEMAC-Au film. The LDPE-VEMAC-AU film (method B) could immobilize larger amount of Au nano particles than the film by Method A. It was also shown that the oxidation of benzyl alcohol proceeded in basic aqueous solution with LDPE-VEMAC-AU film.

[*Chem. Pharm. Bull.* **63**, 992-997(2015)] [Lab. of Pharmaceutical Physical Chemistry]

Development of Novel Polymeric Prodrugs Synthesized by Mechanochemical Solid-State Copolymerization of Hydroxyethylcellulose and Vinyl Monomers.

Naoki DOI, Yasushi SASAI, Yukinori YAMAUCHI, Tetsuo ADACHI, Masayuki KUZUYA and Shin-ichi KONDO*

Novel polymeric prodrugs were synthesized by mechanochemical solid-state copolymerization of hydroxyethylcellulose and the methacryloyloxy derivative of 5-fluorouracil (5-FU). The polymeric prodrug was quantitatively obtained after 14 h reaction. The number average molecular weight (Mn) and polydispersity (H) was 39,000 g/mol and 6.20, respectively. Stronger mechanical fracturing of the obtained polymer improved these properties (Mn = 16,000 g/mol and H = 1.94). 5-FU was sustainably released from the polymeric prodrugs and the rate was not affected by Mn or H of the prodrug. These results suggest that novel polymeric prodrugs composed of a polysaccharide and a synthetic polymer can be fabricated by mechanochemical solid-state polymerization.

[*Sci. Rep.* **5**, 8520 (2015)] [Lab. of Hygienic Chemistry & Molecular Toxicology]

Structural Basis for PPARγ Transactivation by Endocrine-Disrupting Organotin Compounds.

Shusaku HARADA, Youhei HIROMORI, Shota NAKAMURA, Kazuki KAWAHARA, Shunsuke FUKAKUSA, Takahiro MARUNO, Masanori NODA, Susumu UCHIYAMA Kiichi FUKUI, Jun-ichi NISHIKAWA, Hisamitsu NAGASE, Yuji KOBAYASHI, Takuya YOSHIDA, Tadayasu OHKUBO and Tsuyoshi NAKANISHI*

Organotins act as endocrine disruptors through the peroxisome proliferator–activated receptor γ (PPARγ) signaling pathway. To elucidate the mechanism underlying organotin-dependent PPARγ activation, we here analyzed the interactions of PPARγ ligand-binding domain (LBD) with triphenyltin (TPT) and tributylltin (TBT) by using X-ray crystallography, mass spectroscopy and reporter gene assays. Specific binding of organotins is achieved through non-covalent ionic interactions between the sulfur atom of Cys285 and the tin atom. Comparisons of the determined structures suggest that the strong activity of TPT arises through interactions with helix 12 of LBD primarily via π-π interactions. Our findings elucidate the structural basis of PPARγ activation by TPT.

[*Metallomics* **7**, 1180-1188 (2015)] [Lab. of Hygienic Chemistry & Molecular Toxicology]

Transactivation of the Human Retinoid X Recptor by Organotins: Use of Site-Directed Mutagenesis to Identify Critical Amino Acid Residues for Organotin-Induced Transactivation.

Youhei HIROMORI, Akira AOKI, Jun-ichi NISHIKAWA, Hisamitsu NAGASE and Tsuyoshi NAKANISHI*

Organotins act as endocrine disruptors through the retinoid X receptor (RXR) signaling pathway. To elucidate the mechanism underlying organotin-dependent RXR activation, we here used human RXRα mutants to investigate which amino acid residues of the receptor are critical for transactivation induced by organotins compared with that of rexinoids. We found that typical rexinoids failed to activate R316A and L326A RXRα mutants, but organotins activated the R316A mutant, the L326A mutant, or both but failed to activate a C432A mutant. These results suggest that the importance of L326, which is located in the β-strand, for rexinoid-induced transactivation of RXRα is comparable to that of R316; in contrast, C432 is critical for organotin-induced transactivation, whereas R316 and L326 are not required.

[*Chem. Res. Toxicol.* **28**, 1196-1204 (2015)] [Lab. of Hygienic Chemistry & Molecular Toxicology]

Structure-Dependent Activity of Phthalate Esters and Phthalate Monoesters Binding to Human Constitutive Androstane Receptor.

Hong ZHANG, Zhaobin ZHANG, Tsuyoshi NAKANISHI*, Yi WAN, Youhei HIROMORI, Hisamistu NAGASE and Jianying HU

The present study investigated the human constitutive androstane receptor (CAR) binding activities of 23 phthalate esters and 10 phthalate monoesters using a fast and sensitive human CAR yeast two-hybrid assay and a molecular docking method. Of 23 phthalate esters, 16 were evaluated as positive, whereas no obvious binding activities were found for the phthalate esters having alkyl chains more than six carbons in length. A molecular docking study suggested that the strong binding of phthalates to human CAR arises primarily from hydrophobic interactions, π–π interactions, and steric effects and that weak hydrogen bonds and weak halogen bonds greatly contribute to the high binding activity of mono-(2-ethyhexyl) tetrabromophthalate (TBMEHP).

[*J. Toxicol. Sci.* **40**, 383-387 (2015)] [Lab. of Hygienic Chemistry & Molecular Toxicology]

Chromium (VI)-induced transformation is enhanced by Zn deficiency in BALB/c 3T3 cells.

Tomoki KIMURA, Akira ONODERA, Fumika OKUMURA, Tsuyoshi NAKANISHI* and Norio ITOH

Metallothionein (MT), a heavy metal-binding protein, is induced by zinc and other heavy metals and protects cells from the toxic effects of these metals by sequestering them. MT cannot bind Cr, but by scavenging reactive oxygen species through its cysteine residues, it may act as a protective factor against Cr(VI)-induced DNA lesions. Here, we showed that Zn deficiency decreased MT expression in BALB/3T3 clone A31-1-1 cells and caused them to become highly susceptible to Cr(VI)-induced transformation. The increase in susceptibility to transformation was abolished by culturing the cells with supplemental Zn (50 μM). Previously, we reported that Cr(VI) inhibits MT transcription by preventing the zinc-dependent formation of a complex of metal response element-binding transcription factor-1 (MTF-1) and the co-activator p300. Our results suggest that the carcinogenicity of Cr(VI) is enhanced by MTF-1 dysfunction.

[*J. Environ. Health Sci. Eng.* **13**, 9 (2015)] [Lab. of Hygienic Chemistry & Molecular Toxicology]

Practical Remediation of the PCB-contaminated Soils.

Akiko IDO, Miki NIIKAWA, Shinji ISHIHARA, Yoshinari SAWAMA, Tsuyoshi NAKANISHI, Yasunari MONGUCHI, Hironao SAJIKI and Hisamitsu NAGASE*

A practical method for the elimination of PCBs from PCB-contaminated soil has been developed by the combination of Soxhlet extraction using a newly-developed modified Soxhlet extractor possessing an outlet valve on the extraction chamber with the chemical degradation. Various types of PCBs contaminated in soils could be completely extracted in refluxing hexane, and the subsequent hydrodechlorination could also be completed within 1 h in a hexane–MeOH (1 : 5) solution in the presence of Pd/C and Et_3N under ordinary hydrogen pressure and temperature without the transfer of the extracted PCBs to other reaction container (a complete one-pot procedure). The present system is quite useful as a simple, safe, mild and reliable remediation method of PCB-contaminated soil.

[*Pharmacol. Res. Perspect.* 3(2) e00132 (2015)] [Lab. of Molecular Biology]

A Novel 2-Decenoic Acid Thioester Ameliorates Corticosterone-induced Depression- and Anxiety-like Behaviors and Normalies Reduced Hippocampal Signal Transductin in Treated Mice.

Shoyo SHIBATA, Munekazu IINUMA, Hitomi SOUMIYA, Hidefumi FUKUMITSU* and Shoei FURUKAWA.

Daily administration of corticosterone (CORT) induced mice exibit mood disorder symtoms, such as depression- and anxiety-like behaviors. Using the CORT-induced mood disorder models, we investigated the protective effect of the ester, thioester, and amide compounds of 2-decenoic acid derivatives (termed compounds A, B, and C, respectively). The potency of the protective activity against the CORT-induced depression- or anxiety-like behaviors was found to be in the following order: compound B > C > A. In addition, therapeutic effect of compound B on depression- and anxiety-like behavior was observed after oral administration for 1 or 2 weeks, and for 3 weeks, respectively. Futher investigation revealed that the mode of compound B action is novel, potent and different from that of fluvoxamine, the most commonly prescribed drugs for mood disorders

[*Free Rad. Biol. Med.* **79**, 28-44 (2015)] [Lab. of Clinical Pharmaceutics]

Plasma-Activated Medium Induced A549 Cell Injury by a Spiral Apoptotic Cascade Involving the Mitochondrial-Nuclear Network.

Tetsuo ADACHI*, Hiromasa TANAKA, Saho NONOMURA, Hirokazu HARA, Shin-ichi KONDO and Masaru HORI

Plasma medicine is a rapidly expanding new field of interdisciplinary research that combines physics, chemistry, biology, and medicine. Non-thermal atmospheric pressure plasma can be applied to living cells and tissues and has emerged as a novel technology for cancer therapy. Plasma has recently been shown to affect cells not only directly, but also by the indirect treatment of cells with previously prepared plasma-activated medium (PAM). The objective of this study was to demonstrate the inhibitory effects of PAM on A549 cell survival and elucidate the signaling mechanisms responsible for cell death. The results demonstrated that H_2O_2 and/or other reactive species in PAM disturbed the mitochondrial-nuclear network in cancer cells through a caspase-independent apoptotic pathway.

[*Arch. Biochem. Biophys.* **575**, 54-60 (2015)] [Lab. of Clinical Pharmaceutics]

Oxidized Low-Density Lipoprotein Accelerates the Destabilization of Extracellular-Superoxide Dismutase mRNA during Foam Cell Formation.

Junya MAKINO, Miyuki NII, Tetsuro KAMIYA*, Hirokazu HARA and Tetsuo ADACHI

Extracellular-superoxide dismutase (EC-SOD) is one of the main anti-oxidative enzymes that protect cells against the damaging effects of superoxide. We investigated the regulation of EC-SOD expression during the oxidized low-density lipoprotein (oxLDL)-induced foam cell formation of THP-1-derived macrophages. EC-SOD expression was decreased by oxLDL, and its surpression was mediated by the binding to scavenger receptors, especially CD36. The stability of EC-SOD mRNA was decreased by oxLDL. Moreover, oxLDL promoted destabilization of ectopically expressed mRNA from EC-SOD gene with the sequence corresponding to 3'UTR of EC-SOD mRNA. These results suggested that oxLDL decreased the expression of EC-SOD, which, in turn, accelerated the destabilization of EC-SOD mRNA, leading to weaker protection against oxidative stress and atherosclerosis.

[*BioMetals* **28**, 891-902 (2015)] [Lab. of Clinical Pharmaceutics]

Zinc Regulates Expression of IL-23 p19 mRNA via Activation of eIF2α/ATF4 Axis in HAPI Cells.

Takuya DOI, Hirokazu HARA*, Miho KAJITA, Tetsuro KAMIYA and Tetsuo ADACHI

In this study, we examined the effect of zinc on IL-23 p19 mRNA expression using rat immortalized microglia HAPI cells. Exposure to zinc dose- and time-dependently induced the expression of IL-23 p19 mRNA in HAPI cells. Inhibitors of MAPK and NF-κB pathways failed to suppress this induction. Interestingly, we found that zinc stimulated the phosphorylation of eIF2α and promoted the nuclear accumulation of ATF4. Treatment with salubrinal, an eIF2α dephosphorylation inhibitor, enhanced zinc-induced ATF4 accumulation and IL-23 p19 mRNA expression. In addition, reporter assay using the IL-23 p19 promoter region revealed that ATF4 directly transactivated IL-23 p19 promoter and that dominant-negative ATF4 suppressed zinc-induced activation of IL-23 p19 promoter. Taken together, these findings suggest that zinc up-regulates expression of the IL-23 p19 gene via the eIF2α/ATF4 axis in HAPI cells.

[*Arch. Biochem. Biophys.* **584**, 51-60 (2015)] [Lab. of Clinical Pharmaceutics]

Plasma-Activated Medium-induced Intracellular Zinc Liberation Causes Death of SH-SY5Y Cells.

Hirokazu HARA*, Miko TANIGUCHI, Mari KOBAYASHI, Tetsuro KAMIYA and Tetsuo ADACHI

Plasma is an ionized gas consisting of ions, electrons, free radicals, neutral particles, and photons. Plasma-activated medium (PAM), which is prepared by the irradiation of cell-free medium with non-thermal atmospheric pressure plasma, induces cell death. In this study, we thus examined whether zinc is involved in PAM-induced cell death using human neuroblastoma SH-SY5Y cells. Exposure to PAM triggered cell death in SH-SY5Y cells. The zinc chelator TPEN protected against PAM-induced cell death. PAM elicited a rise of intracellular free zinc. In addition, PAM stimulated PARP-1 activation, mitochondrial ROS generation, and the depletion of intracellular NAD^+ and ATP. These findings suggest that PAM-induced PARP-1 activation causes energy supply exhaustion. Moreover, TPEN suppressed all of these events elicited by PAM. Taken together, we demonstrated here that zinc released from intracellular zinc stores serves as a key mediator of PAM-induced cell death in SH-SY5Y cells.

[*Sci. Rep.* **5**, 14780 (2015)] [Lab. of Clinical Pharmaceutics]

Copper Transport Protein Antioxidant-1 Promotes Inflammatory Neovascularization via Chaperone and Transcription Factor Function.

Gin-Fu CHEN, Varadarajan SUDHAHAR, Seock-Won YOUN, Archita DAS, Jaehyung CHO, Tetsuro KAMIYA*, Norifumi URAO, Ronald D. MCKINNEY, Bayasgalan SURENKHUU, Takao HAMAKUBO, Hiroko IWANARI, Senlin LI, John W. CHRISTMAN, Saran SHANTIKUMAR, Gianni D. ANGELINI, Costanza EMANUELI, Masuko-Ushio FUKAI and Tohru FUKAI

Copper (Cu) plays a fundamental role in inflammation and angiogenesis. Cu transport protein Antioxidant-1 (Atox1)-deficient mice show impaired limb perfusion recovery. Atox1 in endothelial cells (ECs) is essential for neovascularization and recruitment of inflammatory cells. Moreover, Atox1 functions as a Cu-dependent transcription factor for NADPH oxidase organizer p47phox, thereby increasing ROS-NFκB-VCAM-1/ICAM-1 expression and monocyte adhesion in ECs inflamed with TNFα.

[*Clin. Plasma Med.* **3**, 72-76 (2015)] [Lab. of Clinical Pharmaceutics]

Plasma with High Electron Density and Plasma-Activated Medium for Cancer Treatment.

Hiromasa TANAKA, Masaaki MIZUNO, Kenji ISHIKAWA, Hiroki KONDO, Keigo TAKEDA, Hiroshi HASHIZUME, Kae NAKAMURA, Fumi UTSUMI, Hiroaki KAJIYAMA, Hiroyuki KANO, Yasumasa OKAZAKI, Shinya TOYOKUNI, Shin'ichi AKIYAMA, Shoichi MARUYAMA, Suguru YAMADA, Yasuhiro KODERA, Hiroki KANEKO, Hiroko TERASAKI, Hirokazu HARA, Tetsuo ADACHI*, Machiko IIDA, Ichiro YAJIMA, Masashi KATO, Fumitaka KIKKAWA and Masaru HORI

Cancer treatment using non-thermal atmospheric pressure plasma is a brand new and challenging approach for cancer therapy. We have developed a plasma source with ultrahigh electron density, which we have applied to these cancer cells. In addition, we found that plasma-irradiated medium, termed PAM, itself can kill these cancer cells. *In vitro* and *in vivo* studies have suggested that PAM is an important tool for cancer therapy especially for disseminated cancers that are currently untreatable.

[*Int. J. Anal. Bio-Sci.* **3**, 63-72 (2015)] [Lab. of Clinical Pharmaceutics]

Foresight of Physical Development Indicated by the National Health and Nutrition Survey in Japan: An Approach in Terms of Biomedical Sciences.

Yojiro MAEHATA , Chihiro MIYAMOTO, Keiichi TSUKINOKI, Shun-suke TAKAHASHI, Fumihiko YOSHINO, Satoko WADA-TAKAHASHI, Ayaka YOSHIDA, Akira TANAKA, Tetsuo ADACHI*, Naoko IGOSHI, Teruo SHIBA, Naoya KISHIKAWA, Takahiro IMAZATO, Ikukatsu SUZUKI, Hiroshi IHARA, Hiroji SHIMOMURA, Hiroaki OKABE, Takaharu YANAGISAWA, Akira HOSHO and Eisuke MAEHATA

The present review of the data from The National Health and Nutrition Survey in Japan indicated the need for actions to ensure proper physical development. The first of the three stages of life (up to the age of 29 years old) was characterized as the key period for sound physical development. The review made us aware of many problems, such as the health state of economically disadvantaged schoolchildren and students and the deteriorated physical condition of young, new mothers eating less than 1,600 kcal.

[*Clin. Pharmacol. Biopharm.* **4**, 137 (2015)] [Lab. of Pharmaceutics]

Simple HPLC Method for the Determination of Caspofungin in Human Plasma.

Midori SODA*, Yuhei SHIBATA, Mika YASUE, Minami FUJIMURA, Hikari TAKAHASHI, Sakiko NAKAMURA, Akio SUZUKI, Takeshi HARA, Hisashi TSURUMI, Yoshinori ITOH and Kiyoyuki KITAICHI

Antifungal caspofungin (CPFG) was approved for the treatment of febrile neutropenia (FN). In this study, we tried to establish the simple and quantitative HPLC method to measure CPFG in human plasma with liquid-liquid extraction. CPFG and *p*-hydroxybenzoate ethyl ester, used as an internal standard (IS), were detected by a fluorescence detector and by UV-VIS, respectively. The calibration curves were linear from 1.0 to 20 μg/mL. The limit of detection and the lower limit of quantification were 0.53, and 1.0 μg/mL, respectively. The validation study of established method was within the acceptable range. These results suggest our established method would be applicable to measure plasma CPFG in patients with FN.

[*J. Neurosci. Res.* **93**, 370-379 (2015)] [Lab. of Medical Therapeutics & Molecular Therapeutics]

Zinc Transporters (ZnT3 and 6) Are Downregulated in the Spinal Cords of Patients with Sporadic Amyotrophic Lateral Sclerosis.

Masayuki KANEKO, Takao NOGUCHI, Saori IKEGAMI, Takeyuki SAKURAI, Akiyoshi KAKITA, Yasuko TOYOSHIMA, Taiho KAMBE, Mitsunori YAMADA, Masatoshi INDEN*, Hideaki HARA, Hitoshi TAKAHASHI, and Isao HOZUMI*

This study investigated the protein levels of ZnT in ALS patients and model mice. ZnT3 and ZnT6 protein levels were diminished in the spinal cords of sporadic ALS patients. Immunohistochemical staining demonstrated decreased ZnT3 and ZnT6 immunoreactivity in the ventral horn of the spinal cords in ALS patients. In addition, ZnT3 and ZnT6 protein levels were not altered in SOD1 (G93A) mutant transgenic mice before or after the onset of ALS symptoms compared with controls. These results suggest that ZnT3 and ZnT6 protein levels are decreased in the spinal cords of sporadic ALS patients.

[*Neurosci. Lett.* **589**, 92-97 (2015)] [Lab. of Medical Therapeutics & Molecular Therapeutics]

Conditioned Medium of Dental Pulp Cells Stimulated by Chinese Propolis Show Neuroprotection and Neurite Extension *in Vitro.*

Daichi KUDO, Masatoshi INDEN*, Shin-ichiro SEKINE, Naritaka TAMAOKI, Kazuki IIDA, Eiji NAITO, Kazuhiro WATANABE, Hiroaki KAMISHINA, Toshiyuki SHIBATA and Isao HOZUMI*

The purpose of this study was to clarify the effect of Chinese propolis on the expression level of neurotrophic factors in dental pulp cells (DPCs). As results, NGF, but not BDNF and NT-3, in DPCs was significantly elevated by the propolis in a concentration-dependent manner. The treatment with the propolis-stimulated CM of DPCs had a more protective effect than that with the CM of DPCs. The treatment with the propolis-stimulated CM of DPCs significantly induced neurite outgrowth from PC12 cells than that with the CM of DPCs. These results suggest that the CM of DPCs as well as DPCs will be an efficient source of new treatments for neurodegenerative diseases.

[*In Vitro Cell Dev. Biol. Anim.* **51**, 1012-1022 (2015)] [Lab. of Medical Therapeutics & Molecular Therapeutics]

Characterization of Canine Dental Pulp Cells and their Neuroregenerative Potential.

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The present study aimed to further characterize canine DPCs (cDPCs), particularly focusing on their neuroregenerative potentials. Canine DPCs constitutively expressed neural markers. Canine DPCs promoted neuritogenesis of PC12 cells, most likely through secretion of neurotrophic factors. Furthermore, SPIO nanoparticles could be effectively transported to cDPCs without significant cytotoxicity and unfavorable effects on neuritogenesis. SPIO-labeled cDPCs embedded in agarose spinal cord phantoms were successfully visualized with a magnetic resonance imaging arousing a hope for noninvasive cell tracking in transplantation studies.

[*Toxicol Sci.* **147**, 425-35 (2015)] [Lab. of Medical Therapeutics & Molecular Therapeutics]

Ah Receptor Signaling Controls the Expression of Cardiac Development and Homeostasis Genes.

Vinicius CARREIRA, Yunxia FAN, Qin WANG, Xiang ZHANG, Hisaka KURITA*, Chia-I KO, Mindi NATICHIONI, Min JIANG, Sheryl KOCH, Mario MEDVEDOVIC, Ying XIA, Jack RUBINSTEIN and Alvaro PUGA

Congenital heart disease (CHD) is the most common congenital abnormality. We show that the aryl hydrocarbon receptor (AHR) regulates the expression of crucial cardiogenesis genes and that interference with endogenous AHR functions, either by gene ablation or by agonist exposure during early development, causes overlapping structural and functional cardiac abnormalities. With striking similarity between AHR knockout and agonist-exposed wild type embryos, *in utero* disruption of endogenous AHR functions converge into dysregulation of molecular mechanisms needed for attainment and maintenance of cardiac differentiation. Our findings suggest that AHR signaling in the developing mammalian heart is central to the regulation of pathways crucial for cellular metabolism, cardiogenesis, and cardiac function, which are potential targets of environmental factors associated with CHD.

[*PloS One.* **10,** e0142440 (2015)] [Lab. of Medical Therapeutics & Molecular Therapeutics]

Disruption of Ah Receptor Signaling during Mouse Development Leads to Abnormal Cardiac Structure and Function in the Adult.

Vinicius CARREIRA, Yunxia FAN, Hisaka KURITA*, Qin WANG, Chia-I KO, Mindi NATICHIONI, Min JIANG, Sheryl KOCH, Xiang ZHANG, Jacek BIESIADA, Mario MEDVEDOVIC, Ying XIA, Jack RUBINSTEIN and Alvaro PUGA

The Developmental Origins of Health and Disease Theory propose that the environment encountered during fetal life and infancy permanently shapes tissue physiology and homeostasis may be at the heart of adult onset disease. Interference with endogenous developmental functions of the aryl hydrocarbon receptor (AHR), either by gene ablation or by exposure *in utero* to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, an AHR ligand, causes structural, molecular and functional cardiac abnormalities in embryos. The AHR signaling in the developing heart is one potential target of environmental factors associated with cardiovascular disease.

[*Infection* **43**, 353-359 (2015)] [Lab. of Microbiology & Immunology]

Thr72Ala Polymorphism in the NKG2D Gene is Associated with Early Symptomatic Congenital Cytomegalovirus Disease.

Rumi TANIGUCHI, Shin KOYANO, Tatsuo SUZUTANI, Keiji GOISHI, Yushi ITO, Ichiro MORIOKA, Hiroyuki NAKAMURA, Hideto YAMADA, Akira OKA and Naoki INOUE*

The potential risk factors for congenital cytomegalovirus (cCMV) infection or development of disease remain unclear. Here, we investigated the genetic polymorphisms in natural killer (NK) group 2, member D (NKG2D), an activating receptor expressed on NK cells, and in MHC class I-related chains A, the ligand of NKG2D, in 87 cCMV cases, and found that there was a significant association between cCMV disease and a single nucleotide polymorphism, Thr72Ala, in NKG2D.

[*J. Perinat. Med.***43**, 239-243 (2015)] [Lab. of Microbiology & Immunology]

Low Total IgM Values and High Cytomegalovirus Loads in the Blood of Newborns with Symptomatic Congenital Cytomegalovirus Infection.

Yoko KOBAYASHI, Ichiro MORIOKA, Tsubasa KODA, Yuji NAKAMACHI, Yoko OKAZAKI, Yoriko NOGUCHI, Miki OGI, Masatsugu CHIKAHIRA, Kenji TANIMURA, Yasuhiko EBINA, Toru FUNAKOSHI, Masanobu OHASHI, Kazumoto IIJIMA, Naoki INOUE*, Seiji KAWANO and Hideto YAMADA

We measured total IgM, CMV-IgM, CMV antigenemia, and CMV-DNA in blood and urine of 10 symptomatic and 13 asymptomatic newborns with congenital cytomegalovirus (CMV) infection to identify laboratory markers for symptomatic infection. Symptomatic newborns had significantly lower total IgM values and significantly more copies of CMV-DNA in blood (medians: total IgM 14 vs. 43 mg/dL, blood CMV-DNA 3.2×10^2 vs. 3.5×10^1 copies/10^6 white blood cells). CMV-IgM, CMV antigenemia, and urine CMV-DNA did not differ significantly.

[*Cell* **163**, 367-380 (2015)] [Lab. of Microbiology & Immunology]

Th17 Cell Induction by Adhesion of Microbes to Intestinal Epithelial Cells.

Koji ATARASHI, Takeshi TANOUE, Minoru ANDO, Nobuhiko KAMADA, Yuji NAGANO, Seiko NARUSHIMA, Wataru SUDA, Akemi IMAOKA, Hiromi SETOYAMA, Takashi NAGAMORI, Eiji ISHIKAWA, Tatsuichiro SHIMA, Taeko HARA, Shoichi KADO, Toshi JINNOHARA, Hiroshi OHNO, Takashi KONDO, Kiminori TOYOOKA, Eiichiro WATANABE, Shin-ichiro YOKOYAMA, Shunji TOKORO, Hiroshi MORI, Yurika NOGUCHI, Hidetoshi MORITA, Ivaylo I IVANOV, Tsuyoshi SUGIYAMA*, Gabriel NUNEZ, J Gray CAMP, Masahira HATTORI, Yoshinori UMESAKI and Kenya HONDA

We show that adhesion of microbes to intestinal epithelial cells is a critical cue for Th17 induction. Segmented filamentous bacteria, *Citrobacter rodentium* and *Escherichia coli* O157 showed adhesion to small intestinal epithelial cells, accompanied by induction of Th17 cells, whereas adhesion-defective mutants of these microbes failed to do so.

[*Naunyn-Schmiedebergs Arch. Pharmacol.* **388**, 1259-1269 (2015)] [Lab. of Microbiology & Immunology]

Ikarisoside A Inhibits Acetylcholine-induced Catecholamine Secretion and Synthesis by Suppressing Nicotinic Acetylcholine Receptor-ion Channels in Cultured Bovine Adrenal Medullary Cells.

Xiaojia LI, Yumiko TOYOHIRA, Takafumi HORISITA, Noriaki SATOH, Keita TAKAHASHI*, Han ZHANG, Munekazu IINUMA, Yukari YOSHINAGA, Susumu UENO, Masato TSUTSUI, Takeyoshi SATA and Nobuyuki YANAGIHARA

Ikarisoside A is a natural flavonol glycoside derived from plants of the genus *Epimedium*, which have been used in Traditional Chinese Medicine as tonics, antirheumatics, and aphrodisiacs. Here, we report the effects of ikarisoside A on catecholamine secretion and synthesis in cultured bovine adrenal medullary cells. We found that ikarisoside A inhibits acetylcholine-induced catecholamine secretion and synthesis by suppression of nicotinic acetylcholine receptor-ion channels in bovine adrenal medullary cells.

[*Am. J. Physiol. Renal. Physiol.*, **15**, F1386-97 (2015)] [Lab. of Biochemistry]

Downregulation of transient receptor potential M6 channels as a cause of hypermagnesiuric hypomagnesemia in obese type 2 diabetic rats.

Kaori TAKAYANAGI, Taisuke SHIMIZU, Yosuke TAYAMA, Akira IKARI*, Naohiko ANZAI, Takatsugu IWASHITA, Juko ASAKURA, Keitaro HAYASHI, Tetsuya MITARAI and Hajime HASEGAWA

We assessed the expression profile of Mg^{2+}-transporting molecules in obese diabetic rats as a cause of hypermagnesiuric hypomagnesemia, which is involved in the development of insulin resistance, hypertension, and coronary diseases. Urine Mg^{2+} excretion was increased in Otsuka Long-Evans Tokushima fatty (OLETF) rats and hypomagnesemia was apparent in OLETF rats but not in Long-Evans Tokushima Otsuka (LETO) rats. Gene expression of transient receptor potential (TRP)M6 was downregulated concomitant with Na^{+}-Cl^{-} cotransporter downregulation. TRPM6 appears to be a susceptible molecule that causes hypermagnesiuric hypomagnesemia as a tubulointerstitial nephropathy-independent altered tubular function in diabetic nephropathy.

[*Biochem. Pharmacol.*, **93**, 482-95 (2015)] [Lab. of Biochemistry]

A platelet-activating factor (PAF) receptor deficiency exacerbates diet-induced obesity but PAF/PAF receptor signaling does not contribute to the development of obesity-induced chronic inflammation.

Yuji TAKAHASHI, Takuto FUJII, Kyosuke FUJITA, Takahiro SHIMIZU, Taiga HIGUCHI, Yoshiaki TABUCHI, Masahiko YAMAGUCHI, Masakazu MATSUI, Ryoko HIGA, Yasuhiro YAMAZAKI, Akira IKARI*, Masaki MIYAKE, Masao MIWA, Satoshi ICHII, Junko SUGATANI and Takao SHIMIZU

Platelet-activating factor (PAF) is a well-known phospholipid that mediates acute inflammatory responses. In the present study, we investigated whether PAF/PAF receptor signaling contributed to chronic inflammation in the white adipose tissue (WAT) of PAF receptor-knockout (PAFR-KO) mice. We concluded that the marked accumulation of abdominal fat due to high-fat diet feeding led to more severe chronic inflammation in WAT, which is associated with glucose metabolism disorders, in PAFR-KO mice than in WT mice, and PAF/PAF receptor signaling may regulate energy expenditure and adiposity.

[*J. Cell. Physiol.*, **230**, 2776-2787 (2015)] [Lab. of Biochemistry]

Hyperosmolarity-induced down-regulation of claudin-2 mediated by decrease in PKCβ-dependent GATA-2 in MDCK cells.

Akira IKARI*, Naoko FUJII, Shinya HAHAKABE, Hisayoshi HAYASHI, Masahiko YAMAGUCHI, Yasuhiro YAMAZAKI, Satoshi ENDO, Toshiyuki MATSUNAGA and Junko SUGATANI.

Hyperosmolarity decreases claudin-2 expression in renal tubular epithelial cells, but the molecular mechanism remains undefined. Here, we found that the hyperosmolarity-induced decrease in claudin-2 expression is inhibited by Go6983, a non-selective protein kinase C (PKC) inhibitor, and PKCβ specific inhibitor in Madin-Darby canine kidney II cells. Claudin-2 has hyperosmolarity-sensitive region in its promoter, which includes GATA binding site. Our results suggest that hyperosmolarity decreases the expression level of claudin-2 via a decrease in PKCβ-dependent GATA-2 transcriptional activity in renal tubular epithelial cells.

[*Hepatology*, **62**, 1215-1226 (2015)] [Lab. of Biochemistry]

Involvement of a cyclic adenosine monophosphate-dependent signal in the diet-induced canalicular trafficking of adenosine triphosphate-binding cassette transporter g5/g8.

Yasuhiro YAMAZAKI, Kenta YASUI, Takahiro HASHIZUME, Arisa SUTO, Ayaka MORI, Yuzuki MURATA, Masahiko YAMAGUCHI, Akira IKARI* and Junko SUGATANI

The adenosine triphosphate-binding cassette (ABC) half-transporters Abcg5 and Abcg8 promote the secretion of neutral sterol into bile. Studies have demonstrated the diet-induced gene expression of these transporters, but the regulation of their trafficking when the nutritional status changes in the liver remains to be elucidated. Here, we generated a novel *in vivo* kinetic analysis that can monitor the intracellular trafficking of Abcg5/Abcg8 in living mouse liver by in vivo transfection of the genes of fluorescent protein-tagged transporters and investigated how hypernutrition affects the canalicular trafficking of these transporters. We found that canalicular trafficking of the fluorescent-tagged Abcg5/Abcg8 was enhanced by dibutyryl cAMP administration.

[*Nutrients*, **7**, 4578-4592 (2015)] [Lab. of Biochemistry]

Quercetin decreases claudin-2 expression mediated by up-regulation of microRNA miR-16 in lung adenocarcinoma A549 cells.

Hiroyuki SONOKI, Tomonari SATO, Satoshi ENDO, Toshiyuki MATSUNAGA, Masahiko YAMAGUCHI, Yasuhiro YAMAZAKI, Junko SUGATANI and Akira IKARI*

Claudin-2 is highly expressed in human lung adenocarcinoma tissues and cells. Knockdown of claudin-2 decreases cell proliferation and migration. Claudin-2 may be a novel target for lung adenocarcinoma. However, there are no physiologically active substances of foods which decrease claudin-2 expression. We here found that quercetin, a flavonoid present in fruits and vegetables, time- and concentration-dependently decreases claudin-2 expression in lung adenocarcinoma A549 cells. Our results suggest that quercetin decreases claudin-2 expression mediated by up-regulation of miR-16 expression and instability of claudin-2 mRNA in lung adenocarcinoma cells.

[*Biochim. Biophys. Acta.*, **1848**, 2326-2336 (2015)] [Lab. of Biochemistry]

Clathrin-dependent Endocytosis of claudin-2 by DFYSP peptide causes lysosomal damage in lung adenocarcinoma A549 cells.

Akira IKARI*, Saeko TAGA, Ryo WATANABE, Tomonari SATO, Shun SHIMOBABA, Hiroyuki SONOKI, Satoshi ENDO, Toshiyuki MATSUNAGA, Hideki SAKAI, Masahiko YAMAGUCHI, Yasuhiro YAMAZAKI and Junko SUGATANI

Claudins are tight junctional proteins and comprise a family of over 20 members. Abnormal expression of claudins is reported to be involved in tumor progression. Claudin-2 is highly expressed in lung adenocarcinoma tissues and increases cell proliferation, whereas it is not expressed in normal tissues. Claudin-2-targeting molecules such as peptides and small molecules may be novel anti-cancer drugs. We found that DFYSP, which mimics the second extracellular loop of claudin-2, increases the accumulation of the peptide and claudin-2 into the lysosome, resulting in lysosomal damage. Claudin-2 may be a new target for lung cancer therapy.

[*Chem. Biol. Interact.*, **250**, 30-39 (2015)] [Lab. of Biochemistry]

Acquisition of doxorubicin resistance facilitates migrating and invasive potentials of gastric cancer MKN45 cells through up-regulating aldo–keto reductase 1B10.

Yoshifumi MORIKAWA, Chihiro KEZUKA, Satoshi ENDO, Akira IKARI, Midori SODA, Keiko YAMAMURA, Naoki TOYOOKA, Ossama EL-KABBANI, Akira HARA and Toshiyuki MATSUNAGA*

In this study, we generated a doxorubicin (DOX)-resistant variant upon continuously treating human gastric cancer MKN45 cells with incremental concentrations of the drug. RT-PCR analysis revealed that aldo-keto reductases (AKR) member 1B10 is most highly up-regulated with the chemoresistance. In addition, the DOX sensitivity of MKN45 cells was reduced and elevated by overexpression and inhibition of AKR1B10, respectively. Moreover, the DOX-resistant cells had higher migrating and invasive abilities, which were significantly suppressed by addition of AKR1B10 inhibitors. These results suggest that AKR1B10 is a DOX-resistance gene in the gastric cancer cells, and is responsible for elevating the migrating and invasive potentials of the cells.

[*Biol. Pharm. Bull.*, **38**, 1309-1319 (2015)] [Lab. of Biochemistry]

Up-regulation of carbonyl reductase 1 renders development of doxorubicin resistance in human gastrointestinal cancers.

Toshiyuki MATSUNAGA*, Chihiro KEZUKA, Yoshifumi MORIKAWA, Ayaka SUZUKI, Satoshi ENDO, Kazuhiro IGUCHI, Takeshi MIURA, Toru NISHINAKA,Tomoyuki TERADA, Ossama EL-KABBANI, Akira HARA and Akira IKARI

Here, we established doxorubicin (DOX)-resistant phenotypes of human gastric MKN45 and colon LoVo cells by exposure to incremental concentrations of the drug. The gain of DOX resistance elevated the carbonyl reductase 1 (CBR1) expression. Although the CBR1 overexpression in the parental cells hardly shows significant reductase activity toward low concentration of DOX, the overexpression of CBR1 increased the reductase activity toward oxidative stress-derived cytotoxic aldehydes. Thus, CBR1 may promote development of DOX resistance through detoxification of cytotoxic aldehydes, rather than the drug's metabolism.

[*J. Biochem.*, **158**, 425-434 (2015)] [Lab. of Biochemistry]

Characterization of hamster NAD^+-dependent 3(17)β-hydroxysteroid dehydrogenase belonging to the aldo-keto reductase 1C subfamily.

Satoshi ENDO, Misato NODA, Akira IKARI, Ossama EL-KABBANI, Akira HARA and Toshiyuki MATSUNAGA*

The cDNAs for morphine 6-dehydrogenase (AKR1C34) and its homologous AKR1C35 were cloned from golden hamster liver, and their enzymatic properties and tissue distribution were compared. AKR1C34 and AKR1C35 oxidized various xenobiotic alicyclic alcohols using NAD^+, but differed in their substrate specificity for hydroxysteroids and inhibitor sensitivity. AKR1C35 also differed from AKR1C34 in its high sensitivity to flavonoids, which inhibited competitively with respect to 17β-estradiol. The mRNA for AKR1C35 was expressed liver-specific in male and ubiquitously in female. We also investigated the molecular determinants for the 3β-HSD activity by replacement of Val54 and Cys310 in AKR1C35 with the corresponding residues in AKR1C34. The mutation of Val54Ala significantly impaired this activity, suggesting that Val54 plays a critical role in recognition of the steroidal substrate.

[*Chem. Biol. Interact.*, **234**, 282-289 (2015)] [Lab. of Biochemistry]

Protective roles of aldo-keto reductase 1B10 and autophagy against toxicity induced by *p*-quinone metabolites of *tert*-butylhydroquinone in lung cancer A549 cells.

Satoshi ENDO*, Ayako NISHIYAMA, Miho SUYAMA, Mayuko TAKEMURA, Midori SODA, Huayue CHEN, Kazuo TAJIMA, Ossama EL-KABBANI, Yasuo BUNAI, Akira HARA, Toshiyuki MATSUNAGA and Akira IKARI

tert-Butylquinone (TBQ) and TBE are *p*-quinone metabolites of *tert*-butylhydroquinone (BHQ), an antioxidant used as a food additive. The *p*-quinones showed toxicity to A549 cells owing to their high electrophilicity reacting with biomolecules. The treatment with the *p*-quinones also induced autophagy. An autophagy inhibitor enhanced the cytotoxicity induced by TBQ and TBE, suggesting that autophagy contributes to alleviating the *p*-quinone-triggered cytotoxicity. In addition, the TBE-induced cytotoxicity and autophagy activation in the cells were significantly suppressed by overexpression AKR1B10. The data suggest autophagy and AKR1B10 contribute to the defense system against the cytotoxicity caused by the toxic *p*-quinone metabolites of BHQ.

[*Fitoterapia*, **101**, 51-56 (2015)] [Lab. of Biochemistry]

Structure-activity relationships of flavonoids for carbonyl reductase 1 (CBR1) inhibition.

Yuki ARAI, Satoshi ENDO*, Namiki MIYAGI, Naohito ABE, Takeshi MIURA, Toru NISHINAKA, Tomoyuki TERADA, Masayoshi OYAMA, Hiroaki GODA, Ossama EL-KABBANI, Akira HARA, Toshiyuki MATSUNAGA and Akira IKARI

CBR1 inhibitors are thought to be promising agents for adjuvant therapy with twofold beneficial effect in prolonging the anticancer efficacy of the anthracyclines while decreasing cardiotoxicity, a side effect of the drugs. In this study, we evaluated 27 flavonoids for their inhibitory activities of CBR1 in order to explore the structure-activity relationship (SAR). Among them, luteolin showed the most potent inhibition. The SAR of the flavonoids and the molecular docking indicated that a H-bond between the 7-hydroxy group and main-chain oxygen of Met234, in addition to H-bond interactions (of its 5-hydroxy and 4-carbonyl groups with catalytically important residues Tyr193 and/or Ser139) and a π-stacking interaction (between its phenyl ring and Trp229).

[*Arch. Biochem. Biophys.*, **569**, 19-25 (2015)] [Lab. of Biochemistry]

Phenylalanine 217 of rabbit aldo-keto reductase (AKR1C33) is a determinant for its strict NADP(H)-specificity and high sensitivity to a mixed-type inhibitor deoxycorticosterone.

Satoshi ENDO*, Toshiyuki MATSUNAGA, Akira IKARI, Ossama EL-KABBANI, Akira HARA and Yukio KITADE

In rabbit tissues, hydroxysteroid dehydrogenase belonging to the aldo-keto reductase (AKR) superfamily exists in six isoforms (AKRs: 1C5 and 1C29-1C33). AKR1C33 is strictly NADPH-specific, in contrast to dual NADPH/NADH specificity of the other isoforms. All coenzyme-binding residues of AKR1C5 are conserved in other isoforms, except that S217 and T273 are replaced with F217 and N272, respectively, in AKR1C33. To explore the determinants for the NADPH specificity of AKR1C33, we prepared its F217S and N272T mutant enzymes. The mutation of F217S, but not N272T, converted AKR1C33 into a dually coenzyme-specific form. The reverse mutation (S217F) in AKR1C32 produced a strictly NADPH-specific form. The results indicate the important role of F217 in the strict NADPH-dependency, as well as its involvement in the unique catalytic properties of AKR1C33.

[*Org. Biomol. Chem.*, **13**, 7487-7499 (2015)] [Lab. of Biochemistry]

Synthesis of 8-hydroxy-2-iminochromene derivatives as selective and potent inhibitors of human carbonyl reductase 1.

Dawei HU, Namiki MIYAGI, Yuki ARAI, Hiroaki OGURI, Takeshi MIURA, Toru NISHINAKA, Tomoyuki TERADA, Hiroaki GOUDA, Ossama EL-KABBANI, Shuang, XIA, Naoki TOYOOKA, Akira HARA, Toshiyuki MATSUNAGA, Akira IKARI and Satoshi ENDO*

CBR1 reduces anthracycline anticancer drugs to their less potent anticancer metabolites, which are linked with pathogenesis of cardiotoxicity. Then, CBR1 inhibitors are thought to be promising agents for adjuvant therapy with anthracyclines. In the present study, we succeeded in development of novel compound (**13h**) as the most potent competitive CBR1 inhibitor. Furthermore, **13h** inhibited the cellular metabolism by CBR1. The structure-activity relationship of the derivatives, mutational analysis and molecular docking of **13h** in CBR1 revealed that the interactions of **13h** with the substrate-binding residues are important for the tight binding.

[*J. Exp. Integr. Med.* **5**, 183-192 (2015)] [Lab. of Pharmacology]

Immunomodulatory Effects of Lovastatin on Ovalbumin-induced Bronchial Asthma in Mice.

Mohamed BALAHA, Samah KANDEEL, Hiroyuki TANAKA*, Hirotaka YAMASHITA, Mohamed N. ABDEL-RAHMAN and Naoki INAGAKI

Lovastatin (LOV) is used for lowering cholesterol in hypercholesterolemia to reduce risk of cardiovascular disease. It is reported that LOV has immunomodulatory effects for autoimmune disorder and graft-versus-host disease. Because the effects of LOV in allergic airway inflammation were still unclear, the present study aimed to investigate the immunomodulatory and anti-inflammatory effects of LOV in a mouse model of allergic asthma. BALB/c mice were sensitized by OVA with alum intraperitoneally, and exposed to 1% OVA to induce bronchial asthma. Oral administration of LOV decreased in the number of inflammatory cells and levels of Th2-cytokines in bronchoalveolar lavage fluid, and serum levels of OVA-specific IgE and IgG1. Additionally, LOV improved goblet cell hyperplasia, collagen deposition, and E-cadherin expression in bronchial epithelial cells.

[*J. Neurochem.* **132**, 583-594 (2015)] [Lab. of Molecular Pharmacology]

The extracellular fragment of GPNMB improves memory and increases hippocampal GluA1 levels in mice.

Kenta MURATA, Yuta YOSHINO, Kazuhiro TSURUMA, Shigeki MORIGUCHI, Atsushi OYAGI, Hirotaka TANAKA, Mitsue ISHISAKA, Masamitsu SHIMAZAWA, Kohji FUKUNAGA and Hideaki HARA*

Glycoprotein nonmelanoma protein B (GPNMB, alias osteoactivin), a type I transmembrane glycoprotein, is cleaved by extracellular proteases, resulting in release of an extracellular fragment (ECF). Here, we investigated the role of GPNMB in memory and learning by using transgenic (Tg) mice over-expressing GPNMB (Tg mice on a BDF-1 background) and ECF-treated mice. In the hippocampus of both wild-type and Tg mice, GPNMB was highly expressed in neurons and astrocytes. Tg mice exhibited memory improvements in two types of learning tasks but were impaired in a passive-avoidance test. These findings suggest that GPNMB might become a novel target for research on higher order brain functions.

[*Brain Res.* **1594**, 36-45 (2015)] [Lab. of Molecular Pharmacology]

Involvement of diacylglycerol kinase β in the spine formation at distal dendrites of striatal medium spiny neurons.

Yasukazu HOZUMI, Kenichi KAKEFUDA, Miwako YAMASAKI, Masahiko WATANABE, Hideaki HARA* and Kaoru GOTO

Spine formation, a salient feature underlying neuronal plasticity to adapt to a changing environment, is regulated by complex machinery involving membrane signal transduction. The diacylglycerol kinase (DGK) family, which is involved in membrane lipid metabolism, catalyzes the phosphorylation of a lipid second messenger, diacylglycerol (DG). We performed Golgi–Cox staining to examine morphological aspects of MSNs in the striatum of DGKβ-knockout (KO) mice. Results show that striatal MSNs of DGKβ-KO mice exhibited lower dendritic spine density at distal dendrites than wild-type mice did. These findings suggest that DGKβ regulates the spine formation at distal dendrites in medium spiny neurons.

[*J. Neurosci. Res.* **93**, 1552-1566 (2015)] [Lab. of Molecular Pharmacology]

Glycoprotein Nonmetastatic Melanoma Protein B ameliorates skeletal muscle lesions in a SOD1^{G93A} mouse model of amyotrophic lateral sclerosis.

Yuki NAGAHARA, Masamitsu SHIMAZAWA, Hirotaka TANAKA, Yoko ONO, Yasuhiro NODA, Kazuki OHUCHI, Kazuhiro TSURUMA, Masahisa KATSUNO, Gen SOBUE and Hideaki HARA*

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive loss of motor neurons and subsequent muscular atrophy. In the present study, superoxide dismutase 1/glycine residue 93 changed to alanine (SOD1(G93A)) transgenic mice were used as a model of ALS. Glycoprotein nonmetastatic melanoma protein B directly affects skeletal muscle and prevents muscular pathology in SOD1(G93A) mice and may therefore serve as a target for therapy of ALS.

[*Eur. J. Pharmacol.* **741**, 301-307 (2015)] [Lab. of Molecular Pharmacology]

Zonisamide suppresses endoplasmic reticulum stress-induced neuronal cell damage *in vitro* and *in vivo*.

Saori TSUJII, Mitsue ISHISAKA, Masamitsu SHIMAZAWA, Takanori HASHIZUME and Hideaki HARA*

Zonisamide has been reported to have protective effects on epilepsy and Parkinson′s disease and to work via various mechanisms of action, such as inhibition of monoamine oxidase-B and enhancement of tyrosine hydroxylase. Recently, it has been suggested that zonisamide itself shows neuroprotective actions. Therefore, in the present study we investigated the neuroprotective effects of zonisamide against endoplasmic reticulum (ER) stress. Zonisamide affected ER stress via caspase-3. We think that ER stress, particularly the mechanism via caspase-3, is involved in part of the neuroprotective effect of zonisamide against the experimental models of Parkinson′s disease.

[*Pharmacol. Res. Perspect.* **3**, e00140 (2015)] [Lab. of Molecular Pharmacology]

VGF and striatal cell damage in *in vitro* and *in vivo* models of Huntington's disease.

Yasuhiro NODA, Masamitsu SHIMAZAWA, Hirotaka TANAKA, Shigeki TAMURA, Teruyoshi INOUE, Kazuhiro TSURUMA and Hideaki HARA*

Huntington's disease (HD) is an inherited genetic disorder, characterized by cognitive dysfunction and abnormal body movements, and at present there is no effective treatment for HD. Therapeutic options for HD are limited to symptomatic treatment approaches and there is no cure for this devastating disease. Here, we examined whether SUN N8075, (2S)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{4-[4-(4-fluorobenzyl)phenyl]-1-piperazinyl}-2-propanol dime-thanesulfonate, which exerts neuroprotective effects by antioxidant effects and induction of VGF nerve growth factor inducible (VGF), has beneficial effects in STHdh cells derived from striatum of knock-in HD mice and R6/2 HD mice. SUN N8075 may be an effective candidate for HD treatments.

[*Pharmacol. Rep.* **67**, 275-280 (2015)] [Lab. of Molecular Pharmacology]

The effects of valproate and olanzapine on the abnormal behavior of diacylglycerol kinase β knockout mice.

Mitsue ISHISAKA, Saori TSUJII, Takahiro MIZOGUCHI, Kazuhiro TSURUMA, Masamitsu SHIMAZAWA and Hideaki HARA*

Diacylglycerol kinase (DGK) is an enzyme that converts diacylglycerol to phosphatidic acid. Previously, we reported that DGKβ knockout (KO) mice showed mania-like behaviors such as hyperactivity, reduced anxiety, and cognitive impairment. Furthermore, lithium ameliorated the hyperactivity and reduced anxiety of DGKβ KO mice. In this study, we investigated the effects of the clinically active antimanic drugs valproate and olanzapine on the abnormal behaviors of DGKβ KO mice. These drugs attenuated the abnormal behaviors of DGKβ KO mice.

[*Biochem. Biophys. Res. Commun.* **458**, 274-279 (2015)] [Lab. of Molecular Pharmacology]

Glucagon-like peptide-1 protects the murine hippocampus against stressors *via* Akt and ERK1/2 signaling.

Yuta YOSHINO, Mitsue ISHISAKA, Saori TSUJII, Masamitsu SHIMAZAWA and Hideaki HARA*

Alzheimer's disease (AD) is a common neurodegenerative disease characterized by cognitive dysfunction and neuronal cell death in the hippocampus and cerebral cortex. Glucagon-like peptide-1 (GLP-1) is an insulinotropic peptides. GLP-1-associated medicines are widely used as treatments for type 2 diabetes. In addition, they have been shown to ameliorate pathology in AD mouse models. Here, we investigated the effects of GLP-1 on different stressors in murine hippocampal HT22 cells. GLP-1 (7–36) is protective against these stressors via activation of survival signaling molecules, such as Akt and ERK1/2 in HT22 cells. In conclusion, GLP-1 and activators of the GLP-1 receptor might be useful targets for the treatment of AD.

[*Sci. Rep.* **5**: 9898 (2015)] [Lab. of Molecular Pharmacology]

The effect of triamcinolone acetonide on laser-induced choroidal neovascularization in mice using a hypoxia visualization bio-imaging probe.

Shinsuke TAKATA, Tomomi MASUDA, Shinsuke NAKAMURA, Takahiro KUCHIMARU, Kazuhiro TSURUMA, Masamitsu SHIMAZAWA, Hideko NAGASAWA, Shinae KIZAKA-KONDOH and Hideaki HARA*

Hypoxic stress is a risk factor of ocular neovascularization. Hypoxia visualization may provide clues regarding the underlying cause of angiogenesis. Recently, we developed a hypoxia-specific probe, protein transduction domain-oxygen-dependent degradation domain-HaloTag-Rhodamine (POH-Rhodamine). In this study, we observed the localization of HIF-1α proteins by immunohistochemistry and the fluorescence of POH-Rhodamine on RPE-choroid flat mounts. POH-Rhodamine is useful for evaluating tissue hypoxia in a laser-induced CNV model, suggesting that TAAC suppressed CNV through tissue hypoxia improvement.

[*Invest. Ophthalmol. Vis. Sci.* **56**, 6914-6924 (2015)] [Lab. of Molecular Pharmacology]

Protective effects of antiplacental growth factor antibody against light-induced retinal damage in mice.

Hiroshi IZAWA, Yuki INOUE, Yuta OHNO, Kazuki OJINO, Kazuhiro TSURUMA, Masamitsu SHIMAZAWA and Hideaki HARA*

Placental growth factor (PlGF) is part of the VEGF family and is known to be involved in angiogenesis, vasopermeability, and neuroprotection. Recently, PlGF has been reported as a novel therapeutic target for wet AMD. However, there are few reports about the effect of PlGF against dry AMD. We investigated the effects of PlGF against photoreceptor degeneration. Anti-PlGF antibody has protective effects against light-induced retinal degeneration in the murine retina through inhibition of RPE breakdown after light exposure. Thus, anti-PlGF antibody may be useful therapeutic agents in dry AMD.

[*Invest. Ophthalmol. Vis. Sci.* **56**, 2511-2518 (2015)] [Lab. of Molecular Pharmacology]

TUDCA promotes phagocytosis by retinal pigment epithelium via MerTK activation.

Hiromi MURASE, Kazuhiro TSURUMA, Masamitsu SHIMAZAWA and Hideaki HARA*

Renewal and elimination of the aged photoreceptor outer segment (POS) by RPE cells is a daily rhythmic process that is important for long-term vision. Phagocytic dysfunction results in photoreceptor cell death. Tauroursodeoxycholic acid (TUDCA), an endogenous bile acid, is known to show neuroprotective effects in stroke, neurological diseases, and retinal degeneration models. In this study, we investigated the effects of TUDCA on retinal phagocytosis. TUDCA enhanced phagocytosis of POS and protected against H2O2-induced phagocytic dysfunction. It also promoted phagocytic function via activation of Mer tyrosine kinase receptor (MerTK), which is known to have a key role in the physiological renewal of POS. These results suggest that TUDCA activates MerTK, which is important for phagocytosis of POS. Tauroursodeoxycholic acid may represent a new therapeutic option for the treatment of retinal diseases.

[*Exp. Eye Res.* **132**, 64-72 (2015)] [Lab. of Molecular Pharmacology]

Effect of a sigma-1 receptor agonist, cutamesine dihydrochloride (SA4503), on photoreceptor cell death against light-induced damage.

Masamitsu SHIMAZAWA, Sou SUGITANI, Yuki INOUE, Kazuhiro TSURUMA and Hideaki HARA*

Cutamesine dihydrochloride is an agonist of sigma-1 receptor, which is a ligand-operated receptor chaperone at the mitochondrion-associated endoplasmic reticulum (ER) membrane. ER stress plays a pivotal role in light irradiation-induced retinal damage. In the present study, we examined whether cutamesine is effective against experimental degenerative retinal damages in vitro and in vivo. Cutamesine protects against retinal cell death in vitro and in vivo by the agonistic effect of sigma-1 receptor. Therefore, sigma-1 receptor may have a potential as a therapeutic target in retinal diseases mediated by photoreceptor degeneration.

[*Curr. Neurovasc. Res.* **12**, 128-134 (2015)] [Lab. of Molecular Pharmacology]

An experimental model for exudative age-related macular degeneration with choroidal neovascularization using the common marmoset.

Masamitsu SHIMAZAWA, Tomomi MASUDA, Shinsuke NAKAMURA, Miki MIWA, Katsuki NAKAMURA and Hideaki HARA*

This study aimed to establish an experimental exudative age-related macular degeneration (AMD) model in the common marmoset (Callithrix jacchus), which is a small New World monkey. Choroidal neovascularization (CNV) was induced by laser irradiation on the left eye of each animal under anesthesia. In conclusion, we succeeded in producing an experimental exudative type of AMD model in the common marmoset. This model may be useful in elucidating the pathophysiological mechanism and screening of new candidates for exudative AMD.

[*J. Neurosci. Res.* **93**, 1675-1683 (2015)] [Lab. of Molecular Pharmacology]

Involvement of endoplasmic reticulum stress in optic nerve degeneration after chronic high intraocular pressure in DBA/2J mice.

Kazuki OJINO, Masamitsu SHIMAZAWA, Hiroshi IZAWA, Yukimichi NAKANO, Kazuhiro TSURUMA and Hideaki HARA*

DBA/2J mice are one of several animal strains used for experimental models of both intraocular hypertension and glaucoma. This study investigates the relationship between endoplasmic reticulum (ER) stress and optic nerve degeneration in DBA/2J mice. Our findings suggest that ER stress plays a role in optic nerve degeneration during chronic ocular hypertension. Furthermore, ER stress may be related in some way to astrocyte activation.

[*Mol. Vis.* **21**, 883-892 (2015)] [Lab. of Molecular Pharmacology]

Photobiomodulation of 670 nm light increased the phagocytosis in the human retinal pigment epithelial cells.

Shinichiro FUMA, Hiromi MURASE, Yoshiki KUSE, Kazuhiro TSURUMA, Masamitsu SHIMAZAWA and Hideaki HARA*

Photobiomodulation is the treatment with light in the far-red to near-infrared region of the spectrum and has been reported to have beneficial effects in various animal models of disease, including an age-related macular degeneration (AMD) mouse model. Previous reports have suggested that phagocytosis is reduced by age-related increased oxidative stress in AMD. Therefore, we investigated whether photobiomodulation improves phagocytosis caused by oxidative stress in a human retinal pigment epithelial, ARPE-19 cell line. Near-infrared light photobiomodulation (670 nm) may be a noninvasive, inexpensive, and easy adjunctive therapy to help inhibit the development of ocular diseases induced by the activation of phagocytosis.

[*BMC Complement. Altern. Med.* **15**: 421 (2015)] [Lab. of Molecular Pharmacology]

Brazilian green propolis water extract up-regulates the early expression level of HO-1 and accelerates Nrf2 after UVA irradiation.

Yuichi SAITO, Kazuhiro TSURUMA, Kenji ICHIHARA, Masamitsu SHIMAZAWA and Hideaki HARA*

Exposure to ultraviolet A (UVA) irradiation is the major cause of human skin aging. Suppression of UVA irradiation-induced skin fibroblast cell damage protects the skin against aging. An oxidative stress response transcription factor nuclear factor-(erythroid-derived 2)-related factor 2 (Nrf2) has an important role as a cytoprotective system against oxidative stress in the human skin and other organs. Propolis has been commonly used as a traditional medicine since ancient times. In this study, we examined the mechanism of WEP-mediated skin protection and the possible involvement of Nrf2/antioxidant response element (ARE) pathways. WEP acts as an early inducer of HO-1 and rapid activator of Nrf2 to protect against UVA-induced oxidative stress.

[*Biosci. Biotechnol. Biochem.* **79**, 1838-1844 (2015)] [Lab. of Molecular Pharmacology]

Japanese *Huperzia serrata* extract and the constituent, huperzine A, ameliorate the scopolamine-induced cognitive impairment in mice..

Takuya OHBA, Yuta YOSHINO, Mitsue ISHISAKA, Naohito ABE, Kazuhiro TSURUMA, Masamitsu SHIMAZAWA, Masayoshi OYAMA, Takeshi TABIRA and Hideaki HARA*

Huperzia serrata has been used as a Chinese folk medicine for many years. It contains huperzine A, which has a protective effect against memory deficits in animal models; however, it is unclear if *H. serrata* extract exerts any effects in Alzheimer's disease (AD) models. We used *H. serrata* collected in Japan and determined its huperzine A content using HPLC. We determined its inhibitory effects on acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) activity. Japanese *H. serrata* extract ameliorates cognitive function deficits by inhibiting AChE. Therefore, *H. serrata* extract may be valuable for the prevention or treatment of dementia in AD.

[*Food Function* **14**, 25-31 (2015)] [Lab. of Molecular Pharmacology]

Investigation of preventive effects of propolis and its constituents against age-related macular degeneration.

Kazuhiro TSURUMA, Norihito TAKANO, Shunsuke IMAI, Yuichi SAITO, Tetsuro ITO and Hideaki HARA*

Propolis and bee pollen are products made by honey bee, and have many functions such as an antioxidant effect. They have been confirmed their functions various in vitro and in vivo models. Age-related macular degeneration (AMD) is known one of the retinal degeneration diseases, leading to visual field defect. Hypertension, aging, exposure to light and oxidative stress are known as risk factors of AMD. In this study, we investigated the protective effect of propolis and bee pollen against in vitro and in vivo light-induced retinal damage models. Ethanol extracted propolis exert the protective effects on these models, and ethanol extracted bee pollen had the protective effect on retinal damage in vitro.

[*Jpn. Pharmacol. Ther*. **43**, 209-229 (2015)] [Lab. of Molecular Pharmacology]

A double-blinded, placebo-controlled, crossover trial and open-label safety trials of extract of *Aquilaria* sp (Thymelaeaceae) leaves.

Mamoru KAKINO, Shigemi TAZAWA, Hiroe MARUYAMA, Yoko ARAKI, Kenji ICHIHARA, Hiroyuki KONO, Munekazu IINUMA and Hideaki HARA*

We investigated whether or not intake of an extract of *Aquilaria crassna*（agarwood）leaves ameliorates constipation—related symptoms in healthy volunteers with mild constipation, and then we also assessed clinical events produced by subchronic oral administration or an overdose of the agarwood leave extract in healthy volunteers. We prepared a tablet containing a mixed powder of 100 mg agarwood leave extract and 100 mg dextrin for carrying out these clinical experiments. Present results indicate that the adequate ingestion of the *Aquilaria* crassna leaves extract possibly serves to relieve constipation without critical adverse reaction.

[*Cancer Med.* **4**, 1344-1355 (2015)] [Lab. of Molecular Pharmacology]

Clinical significance of glycoprotein nonmetastatic B and its association with HER2 in breast cancer.

Masako KANEMATSU, Manabu FUTAMURA, Masafumi TAKATA, Siqin GAOWA, Atsuko YAMADA, Kasumi MORIMITSU, Akemi MORIKAWA, Ryutaro MORI, Hideaki HARA* and Kazuhiro YOSHIDA

Glycoprotein nonmetastatic B (*GPNMB*) is a potential oncogene that is particularly expressed in melanoma and breast cancer (BC). To clarify its clinical significance in BC, we measured serum GPNMB *in vivo* and investigated its cross talk with human epidermal growth factor 2 (HER2). GPNMB might be a surrogate marker for BC and may cross talk with the HER2 signal pathway. GPNMB may therefore emerge as an important player in anti-HER2 therapy.

[*Jpn. J. Pharm. Health Care Sci.* **41**, 44-49 (2015)] [Lab.of Pharmacy Practice & Social Science]

Problems Related to the Online Distribution of Over-The-Counter Drugs: Provision of Drug Information and Quality Control.

Kazushi GODA, Hideki HAYASHI, Yu KATOH, Rina KAMIMURA, Yutaro KITA, Rio IWAMOTO, Yoshihiro KONDOH and Tadashi SUGIYAMA*

In this study, we investigated the method to identify health conditions of customers and the delivery channels of OTC drugs from the distributors to consumers, using 130 online stores as our sample. First-class OTC drugs were sold at 29 stores. All the stores set up a column on which consumers could select their health conditions on a computer screen. However, in 25 of the stores, “no problem” had been inserted in the column beforehand. All the stores delivered OTC drugs through home delivery services, which did not store in cool conditions. These findings suggest a need for online distribution of OTC drugs to incorporate an improved method of providing drug information to consumers and ensuring quality control.

[*Int. Canc. Conf. J.*, **4**, 35-40 (2015)] [Lab.of Pharmacy Practice & Social Science]

A Patient with Malignant Pleural Mesothelioma Complicated with Dubin-Johnson Syndrome Treated with Cisplatin/Pemetrexed Combination Therapy: The Need to Consider Mutation to the ATP-Binding Cassette-C2 Gene and the Pharmacokinetics of Pemetrexed..

Makoto NAKASHIMA, Tatsuo KATO, Katsuhiko MATSUURA, Yoshinori IMANISHI, Takeshi UCHIUMI, Takuji FUJINAGA and Tadashi SUGIYAMA*

We recently treated a patient with malignant pleural mesothelioma complicated with Dubin-Johnson syndrome with cisplatin/pemetrexed combination therapy. The excretion of pemetrexed was found to be good, and no delay of excretion was observed compared to that in normal patients. It appears that ABCC2 might not be related to the excretion of pemetrexed. These results suggest that standard dose cisplatin/pemetrexed combination therapy from the first course could be conducted for patient with malignant pleural mesothelioma complicated with Dubin-Johnson syndrome.

[*Jpn. J. Pharm. Health Care Sci.* **41**, 198-204 (2015)] [Lab.of Pharmacy Practice & Social Science]

Color Change of Various Medicines under LED Lighting and Fluorescent Lighting.

Shuji YAMASHITA, Yoshihiro NOGUCHI, Masafumi KUBOTA, Kazuhiro IGUCHI, Shinya AOKI, Shigeharu TANEI, Mitsuhiro NAKAMURA, Hitomi TERAMACHI and Tadashi SUGIYAMA*

LED is widely used in lighting applications. For example, LED lighting is used in the backlight of the liquid crystal display of a cell-phone and the smartphone, a signal and the source of light of the endoscope. In this study, we examined the differences in color change degree of various medicines between LED lighting and fluorescent lighting. We evaluated color change degree of various medicines by subjective sight of evaluator and objective colorimeter. Noticeable color changes were observed in Lasix® 20 mg Tab., Fluitran® 2 mg Tab. and Phenobal® powder after exposure of either LED lighting or fluorescent lighting. Interestingly, the color change of Lasix® 20 mg Tab. was less in the LED lighting compared to the fluorescent lighting. The evaluation of LED lighting may be necessary to be taken into consideration in the stability test for medicine.

[*Drug Metab Pharmacokinet.* **30**, 149-153 (2015)] [Lab. of Pharmacy Practice & Social Science]

Relationship between *ABCB1* gene polymorphisms and severe neutropenia in patients with breast cancer treated with doxorubicin/cyclophosphamide chemotherapy.

Midori IKEDA, Daiki TSUJI, Keisuke YAMAMOTO, Yong-Il KIM, Takashi DAIMON, Yutaro IWABE, Masahiro HATORI, Ryo MAKUTA, Hideki HAYASHI*, Kazuyuki INOUE, Hidenori NAKAMICHI, Mitsuru SHIOKAWA and Kunihiko ITOH

Chemotherapy-induced neutropenia is one of the major adverse events which results in the reduction of chemotherapy. Doxorubicin is a substrate of the adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) transporter; reportedly, ABCB1 polymorphisms influence doxorubicin pharmacokinetics. We evaluated the association between chemotherapy-induced neutropenia and ABCB1 polymorphisms in patients with breast cancer. *ABCB1* polymorphisms may influence the extent of chemotherapy-induced neutropenia in doxorubicin and cyclophosphamide combination-treated patients with breast cancer.

[*J. Jpn. Soc. Hosp. Pharm.*, **51**, 434-438 (2015)] [Lab.of Pharmacy Practice and Social Science]

Evaluation of Satisfaction Level of Supplementary Tool about Cancer Pain Medication Therapy.

Yumi GOTO, Norio SUZUKI, Michio KIMURA, Tomoko NISHIKAWA, Eiseki USAMI, Tomoaki YOSHIMURA, Tadashi SUGIYAMA*, Hiromi MORI

We prepared supplementary tool about cancer pain medication therapy for medical stuffs and onducted a questionnaire survey for its satisfaction. The supplementary tool has handiness and included available opioid list at our hospital, opioid titer conversion table, flow rate, opioid rotation, non-opioid analgesics, side effects measures, dermatome, adjuvant analgesics. From the results of the questionnaire, the supplementary tool was often used by doctors and pharmacists. The frequency used nformations were opioid titer conversion table and flow rate. The informations that should be improved were adjuvant analgesics, non-opioid analgesics and side effects measures. In the future, we want to offer continuous support to medical stuffs at the cancer pain drug therapy.

[*J. Clin. Pharm. Ther.*, **40**, 279-284 (2015)] [Lab.of Pharmacy Practice & Social Science]

The Association between Risk Factors and Time of Onset for tThrombocytopenia in Japanese Patients Subjected to Linezolid Therapy: A Retrospective Analysis.

Toshikazu ICHIE, Daisuke SUZUKI, Kazumasa YASUI, Hiroyasu TAKAHASHI, Masamitsu MATSUDA, Hideki HAYASHI, Yoji SUGIURA and Tadashi SUGIYAMA*

This study was conducted retrospectively to identify risk factors that might contribute toward the development thrombocytopenia resulting from the intravenous administration of Linezolid (LZD). A total of 47 patients were included for this study. These patients were divided into 2 groups: 22 patients were assigned to a non-thrombocytopenia group and 25 patients were assigned to a thrombocytopenia group. The results of the multivariate logistic regression analysis revealed a significant difference related to the duration of LZD treatment and white blood cell (WBC) count between the 2 groups. This finding shows that duration of LZD treatments and WBC count are risk factors associated with thrombocytopenia resulting from the LZD administration.

[*J. Jpn. Soc. Hosp. Pharm.*, **51**, 545-548 (2015)] [Lab.of Pharmacy Practice and Social Science]

Analysis of Factors Influencing Thrombocytopenia Associated with Concomitant Temozolomide and Radiotherapy.

Toshikazu ICHIE, Hiroyasu TAKAHASHI, Chie YAMAZEKI, Daisuke SUZUKI, Takeshi OKADA, Nozomi KOBAYASHI, Hideki HAYASHI, Yoji SUGIURA and Tadashi SUGIYAMA*

This study was conducted retrospectively to identify risk factors that might contribute to the development of thrombocytopenia consequent to TMZ and concomitant radiotherapy. A total of 15 patients who received TMZ and concomitant radiotherapy were selected. The patients were divided into 2 groups according to the thrombocytopenia grade: Grade <2 (n = 10) or Grade ≥2 (n = 5). In a univariate analysis, the Grade ≥2 group was significantly older, and the proportion of elderly people (≥65 years) was significantly higher in the Grade ≥2 group. This finding suggests the possibility that an increase in age, especially among elderly people (≥65 years), is a risk factor associated with thrombocytopenia consequent to concomitant TMZ and radiotherapy.

[*Thromb. Res.* **135**, 861-866 (2015)] [Lab. of Pharmacy Practice & Social Science]

Plasma vitamin K concentrations depend on *CYP4F2* polymorphism and influence on anticoagulation in Japanese patients with warfarin therapy.

Keita HIRAI, Yuto YAMADA, Hideki HAYASHI*, Masaki TANAKA, Kohei IZUMIYA, Masayuki SUZUKI, Misa YOSHIZAWA, Hideaki MORIWAKI, Takehide AKIMOTO, Daiki TSUJI, Kazuyuki INOUE and Kunihiko ITOH.

Warfarin is characterized by a large inter-individual variability in dosage requirement. This study aimed to analyze the contribution of the CYP4F2 genetic polymorphism and plasma vitamin K concentration on the warfarin pharmacodynamics in patients and to clarify the plasma vitamin K concentration affecting warfarin sensitivity index in rats. The plasma vitamin K1 (VK1) and menaquinone-4 (MK-4) concentrations are significantly influenced by *CYP4F2* genetic polymorphism but not associated with warfarin therapy at the observed concentration in Japanese patients.

[*Drug Metab Pharmacokinet.* **30**, 227-230 (2015)] [Lab. of Pharmacy Practice & Social Science]

Reduced folate carrier 1 gene expression levels are correlated with methotrexate efficacy in Japanese patients with rheumatoid arthritis.

Yui TAZOE, Hideki HAYASHI*, Seiji TSUBOI, Tomone SHIOURA, Taiji MATSUYAMA, Hiroshi YAMADA, Keita HIRAI, Daiki TSUJI, Kazuyuki INOUE, Tadashi SUGIYAMA and Kunihiko ITOH

Responsiveness to methotrexate (MTX) for treating rheumatoid arthritis (RA) varies among individual patients. We investigated the effects of folate transporter gene expression levels on disease activity among 56 Japanese patients with RA who were undergoing MTX therapy. *Reduced folate carrier 1* (*RFC1*) mRNA expression levels and RA disease activity scores were significantly negatively correlated, as disease activity scores were lower for patients with higher *RFC1* mRNA expression levels. Thus, the clinical efficacy of MTX was associated with the expression level of a folate transporter gene. Increased RFC1 expression may increase MTX uptake by immune cells, such as lymphocytes, and as a result, RA disease activity would be reduced.

[*Pharmazie*, **70**, 404-409 (2015)] [Lab.of Pharmacy Practice & Social Science]

Influence of Serebral Fluid Drainage on the Pharmacokinetics of Vancomycin in Neurosurgical Patients.

Toshikazu ICHIE, Kimihiko URANO, Daisuke SUZUKI, Takeshi OKADA, Nozomi KOBAYASHI, Hideki HAYASHI, Yoji SUGIURA, Keiko YAMAMURA and Tadashi SUGIYAMA*

Our objective was to retrospectively investigate the influence of cerebral fluid drainage on the serum concentrations and pharmacokinetic parameters of Vancomycin (VCM). We compared the daily doses of VCM, serum VCM concentrations, serum concentration/dose ratio (C/D ratio), and pharmacokinetics parameters between patients who underwent cerebral fluid drainage (drainage group) and controls. The patients in drainage group showed a significantly lower trough concentration of VCM. Further, the patients in the drainage group showed a significantly lower trough C/D ratio. Our findings suggest that a high dose of VCM is required to maintain optimal serum concentrations of VCM in patients managed with cerebral fluid drainage.

[*Jpn. J. Pharm. Palliat. Care Sci.*, **8**, 59-63 (2015)] [Lab.of Pharmacy Practice & Social Science]

Survey of Implementation Status of Continuous Morphine Dosing in Ppatients with Terminal-phase Lung Cancer.

Makoto NAKASHIMA, Tatsuo KATO and Tadashi SUGIYAMA*

In this study, we surveyed the implementation status of continuous morphine dosing to understand the clinical condition of patients with terminal-phase lung cancer and to consider the palliative care required. Among 103 patients who died of lung cancer, 34 (33.0 %) were continuously administered morphine. Twenty-three patients were administered morphine to alleviate respiratory discomfort; the efficacy rate was 39.1 %. Fifteen patients were administered morphine to alleviate cancer-related pain; the efficacy rate was 46.7 %. The time to die from initiating morphine administration was tended to longer than that in whome the patients whose effect of morphine was ambiguous. These results suggest that continuous morphine dosing alleviates respiratory discomfort and cancer-related pain in patients with terminal-phase lung cancer.

[*Pharmazie*, **70**, 522–526 (2015)] [Lab.of Pharmacy Practice & Social Science]

Gastrointestinal Symptoms after the Substitution of Sevelamer Hydrochloride with Lanthanum Carbonate in Japanese Patients Undergoing Hemodialysis.

Daisuke SUZUKI, Toshikazu ICHIE, Hideki HAYASHI, Yoji SUGIURA and Tadashi SUGIYAMA*

In this study, we investigated the short and long-term changes in digestive symptoms in these patients after substituting sevelamer hydrochloride with lanthanum carbonate. We studied 16 patients (4 men, 12 women) and evaluated their gastrointestinal symptoms before administration, at the time of administration, and 2, 4, 8, and 12 weeks after administration, using the Gastrointestinal Symptom Rating Scale. In addition, we conducted repeat evaluations 52 weeks after administration for the patients in whom lanthanum carbonate was administered continuously for 52 weeks. This study shows that substituting sevelamer hydrochloride with lanthanum carbonate improves constipation symptoms in hemodialysis patients from an early stage, which indicates its usefulness in improving constipation symptoms caused by sevelamer hydrochloride.

[*J. Jpn. Soc. Hosp. Pharm.*, **51**, 1009-1013 (2015)] [Lab.of Pharmacy Practice and Social Science]

Does Reduction of Metronidazole Affect Outcome Against Clostridium Difficile Associated Diarrhea in Severe Renal Impairment Patients?.

Daisuke SUZUKI, Toshikazu ICHIE, Hideki HAYASHI, Yoji SUGIURA and Tadashi SUGIYAMA*

Metronidazole (MNZ) is the therapeutic drug for Clostridium difficile-associated diarrhea. MNZ is not clear whether to adjust the dose depending on renal function. In this study, we considered whether it was useful to reduce a dose of MNZ depending on renal function. Patients were devided into normal renal function group (eGFR>= 10mL / min) and low renal function group (eGFR <0mL / min). The difference was not observed between two groups at efficiency, relapse rate, use duration. C-reactive protein after administration of MNZ were reduced significantly compared with before administration in the both groups. These findings suggest adjust the dose of MNZ depending on renal function will not affect the efficacy against Clostridium difficile-associated diarrhea.

[*Jpn. J. Pharm. Health Care Sci.* **41**, 799-810 (2015)] [Lab.of Pharmacy Practice & Social Science]

Survey of Patients Taking Drugs that Influence Car Driving with Received Cancer Chemotherapy and Approach for Proposition of Drug Selection.

Makoto NAKASHIMA, Hitomi MIURA, Yoko UENO, Tomoko OKA, Mari OKU, Ayako FUKUSHIMA, Morihiko TERASHI, Masahiko OSAKO, Hideki HAYASHI and Tadashi SUGIYAMA*

The package insert of notandum, a narcotic drug, states that patients who take this drug must not drive a car, or should drive a car carefully. Many drugs used in supportive cancer chemotherapy and palliative therapy contain warnings regarding driving a car. Twenty-one of 127 outpatients in our hospital who received cancer chemotherapy were prescribed drugs that affect car driving. Sixteen patients drove a car on a daily basis. When selecting drugs, the necessity of driving should be checked to maintain quality-of-life. In contrast, because all patients who take opioid analgesics must refrain from driving, and because opioid analgesics cannot be replaced with other drugs, accessing validity of descriptions in the package insert are necessary in the future.

[*Anticancer Res.* **35**, 6671-6677 (2015)] [Lab. of Pharmacy Practice & Social Science]

Effects of Cabazitaxel in Renal Cell Carcinoma Cell Lines.

Kosuke MIZUTANI, Masashi TOMODA, Yuta OHNO, Hideki HAYASHI*, Yasunori FUJITA, Kyojiro KAWAKAMI, Koji KAMEYAMA, Taku KATO, Tadashi SUGIYAMA, Yoshinori ITOH, Masafumi ITO and Takashi DEGUCHI

Advanced renal cell carcinoma is treated with mammalian target of rapamycin (mTOR) inhibitors or tyrosine kinase inhibitors (TKIs). The effects of these drugs are, however, limited and novel treatment strategies are required. Clear-cell type renal cell carcinoma (ccRCC) is chemo-resistant, in part, due to expression of multidrug resistance proteins such as p-glycoprotein. Cabazitaxel, a tubulin-binding taxane drug used for castration-resistant prostate cancer, has less affinity for p-glycoprotein compared to docetaxel. Cabazitaxel inhibited cell growth and induced tubulin polymerization more potently than docetaxel. The intracellular concentration of cabazitaxel was much higher than docetaxel in all cell lines. Cabazitaxel inhibits growth of ccRCC cells expressing p-glycoprotein and could thus be possibly used for advanced ccRCC patients in combination with targeted-therapy enhancing their effects.

[*Jpn. J. Drug Inform.* **17**, 155-163 (2015)] [Lab.of Pharmacy Practice & Social Science]

Invention of Check Points Used in Pharmaceutical Management in Hospital Ward Utilizing PREAVOID.

Makoto NAKASHIMA, Yoshihiro YAMAMOTO, Akira TAKAHASHI, Takuya GOTO, Mie KOMINAMI, Tomomi KONISHI, Yukiko SHIBATA, Hideki HAYASHI and Tadashi SUGIYAMA*

PREAVOID is pharmaceutical intervention that is utilized to illustrate pharmacists' contributions to medical care. We determined 16 pharmaceutical-management items based on PREAVOID that was conducted at Nagara Medical Center. Moreover, we conducted a pre-questionnaire survey assessing whether pharmacists who had worked in the ward for fewer than 4 years attended to these 16 check items in their daily work prior to our introducing the list to them. The results indicate that the 16 check items are a useful educational tool for enabling pharmacists to conduct high quality pharmaceutical management from the initial stage and that using the 16 check items is superior to pharmacists only gaining this ability via prolonged experience working in the ward.

[*Eur. J. Clin. Nutr.* **69**, 198-204 (2015)] [Lab. of Clinical Pharmacy]

Hyponatremia and Hypokalemia as Risk Factors for Falls.

Tomoya TACHI*, Takafumi YOKOI, Chitoshi GOTO, Michi UMEDA, Yoshihiro NOGUCHI, Masahiro YASUDA, Miake MINAMITANI, Takashi MIZUI, Teruo TSUCHIYA and Hitomi TERAMACHI

Although hyponatremia and hypokalemia have been reported to increase the rate of falls, how they affect falls is not fully understood. We retrospectively examined 2948 patients, ≥18 years old who had been hospitalized for ≥3 days at Gifu (Japan) Municipal Hospital between May 2012 and April 2013 to determine the effects of hyponatremia and hypokalemia on the risk of falls. After the patients had been divided into fall and non-fall groups, their data were subjected to multiple regression analysis to identify significant differences. The multivariate analysis results revealed significant differences between the groups in terms of the presence of hyponatremia, hypokalemia, central nervous system disease and/or age ≥65 years. The results indicated that the presence of hyponatremia or hypokalemia increases the risk of falls.

[*Jpn. J. Pharm. Health Care Sci.* **41**, 113-120 (2015)] [Lab. of Clinical Pharmacy]

Effect of Group Instructions for Improving Awareness about Medication-notebook Use on the Purchase of Over-the-counter Drugs and Dietary Supplements.

Tomoya TACHI, Shoko ASANO, Chitoshi GOTO, Tatsuhiko YOSHIDA, Kazumasa USUI, Misa KATO, Takafumi YOKOI, Yoshihiro NOGUCHI, Kazuhide TANAKA, Masahiro YASUDA, Takashi MIZUI and Hitomi TERAMACHI*

To understand the consciousness and situation of medication-notebook use and clarify effect of group instruction for improvement of the consciousness, we gave lecture about medication-notebook use and investigated items such as consciousness about a medication notebook before and after the lecture. Regarding the consciousness about medication-notebook use for OTC drugs and dietary supplements, the rates of evaluations 4 and 5 before the lecture were low regardless of ways to purchase them, but the evaluations increased significantly. Our study clarified that consciousness about medication-notebook for OTC drugs and dietary supplements is not enough at present and suggested that group instruction about medication-notebook use improve the consciousness.

[*Healthy Aging Res.* 4:23. doi:10.12715/har.2015.4.23 (2015)] [Lab. of Clinical Pharmacy]

Analysis of Potential Cost Reductions Related to Falls in Hospitalized Elderly Patients by Correcting High-dose Prescriptions of Sedative Hypnotics.

Tomoya TACHI, Takafumi YOKOI, Chitoshi GOTO, Michi UMEDA, Masahiro YASUDA, Takashi MIZUI, Yoshihiro NOGUCHI and Hitomi TERAMACHI*

High-dose sedative hypnotics may increase fall risk in elderly patients. The association between falls and high-dose usage of sedative hypnotics was retrospectively investigated in hospitalized elderly patients to evaluate the potential cost reductions associated with fall prevention by changing high-dose prescriptions. Analysis revealed a significantly higher rate of falls in the group using high-dose sedative hypnotics compared to the non-high-dose group. Assessment of cost demonstrated potential savings of ¥589 per case if falls could be prevented by correcting high-dose prescriptions. This study indicates that high-dose prescriptions of sedative hypnotics may be associated with fall risk in the elderly. Correcting the prescriptions would be beneficial for the medical economy.

[*Jpn. J. Cancer Chemother.* **42**, 477-479 (2015)] [Lab. of Clinical Pharmacy]

A Female Chronic Myeloid Leukemia Patient who Gave Birth after Stopping Imatinib Intentionally but who Maintained a Major Molecular Response with Interferon.

Tomohiro OSAWA, Takeshi TAKAHASHI, Masahiro YASUDA, Michi UMEDA, Katsuhiro NAGAYA, Tomoya TACHI, Hideko GOTO, Senji KASAHARA, Hitomi TERAMACHI* and Chitoshi GOTO

Imatinib was administrated to a 38-year-old woman with chronic myeloid leukemia(CML). A major molecular response (MMR)(≤5 copies/0.5 μgRNA in Amp-CML detected using the transcription mediated amplification/hybridization protection assay(TMA/HPA)method) was achieved in 18 months. She maintained MMR for 10 months, and wished to become pregnant. Imatinib was stopped intentionally because she wished to plan a pregnancy, but we prescribed interferon alpha (IFN-a) due to the likelihood of the CML recurring after pregnancy. The nausea caused by IFN-a was improved by administrating it during the night, and she gave birth to a healthy baby by a normal delivery, whilst maintaining MMR.

[*Plos One.* **10,** e0124169. doi:10.1371/journal.pone.0124169 (2015)] [Lab. of Clinical Pharmacy]

The Impact of Outpatient Chemotherapy-Related Adverse Events on the Quality of Life of Breast Cancer Patients.

Tomoya TACHI, Hitomi TERAMACHI*, Kazuhide TANAKA, Shoko ASANO, Tomohiro OSAWA, Azusa KAWASHIMA, Masahiro YASUDA, Takashi MIZUI, Takumi NAKADA, Yoshihiro NOGUCHI, Teruo TSUCHIYA and Chitoshi GOTO

To clarify the impact of adverse events associated with the initial course of outpatient chemotherapy on the quality of life of breast cancer patients, we conducted a survey to assess the quality of life in 48 breast cancer patients before and after receiving their first course of outpatient chemotherapy at Gifu Municipal Hospital. The decrease in quality of life after chemotherapy was greater in anorexic patients than in non-anorexic patients. Our findings reveal that anticancer drug-related adverse events, particularly anorexia, reduce overall quality of life following the first course of outpatient chemotherapy in current breast cancer patients.

[*Jpn. J. Pharm. Health Care Sci.* **41**, 347-354 (2015)] [Lab. of Clinical Pharmacy]

The Analysis of Adverse Events Associated with Angiotensin Receptor Blockers and Hydrochlorothiazide Fixed-dose combination: Data Mining of the Japanese Adverse Drug Event Report database, JADER.

Yoshihiro NOGUCHI, Hiroki ESAKI, Shoko ASANO, Takafumi YOKOI, Kazumasa USUI, Misa KATO, Kosuke SAITO, Tomoya TACHI and Hitomi TERAMACHI*

We analyzed adverse events using data from the Japanese Adverse Drug Event Report database from April 2004 to September 2013. The adverse events surveyed were hypokalemia, hyperkalemia, hyponatremia and hyperuricemia. We calculated the Reporting Odds Ratio (ROR) from the number of reports that were extracted from the database and evaluated. A signal was detected for all the adverse events that were included in this study. Therefore, it is considered that there is a need to monitor the clinical laboratory values, such as electrolyte levels, for patients taking angiotensin receptor blocker/hydrochlorothiazide fixed-dose combination.

[*Anticancer Res.* **35**, 2063-2069 (2015)] [Lab. of Clinical Pharmacy]

Structural Changes in Albumin Are a Possible Mechanism for Fluctuation of Cefazorin and Ibuprofen Plasma Protein Binding in Rats with Carcinogen-induced Osteosarcoma.

Yukari ITAKURA, Shino TAGA, Chieko IWATA, Hitomi TERAMACHI*, Ken-ichi MIYAMOTO, Hiroyuki TSUCHIYA, Takashi WADA and Ryo MATSUSHITA

To elucidate variations in the protein-binding rate of specific drugs in the presence of cancer, as well as the mechanisms involved, experiments were performed using Fisher 344 model rats. A single i.v. injection of cefazolin (CEZ) or ibuprofen (IB) was administered to both tumor-bearing and control groups. The protein-unbound fraction (fp) of CEZ in plasma from the tumor-bearing group increased approximately 2.9-fold and the fp of IB also increased about 2.7-fold. For that reason, we purified albumin from plasma and examined its spectroscopic signature. We showed that conformational changes had occurred in albumin in the tumor-bearing group.

[*Jpn. J. Pharm. Health Care Sci.* **41**, 488-496 (2015)] [Lab. of Clinical Pharmacy]

The Analysis of Effects of the Diuretics on Levels of Blood Potassium and Blood Sodium with Angiotensin Receptor Blockers and Thiazide Diuretics Combination therapy: Data Mining of the Japanese Adverse Drug Event Report Database, JADER.

Yoshihiro NOGUCHI, Hiroki ESAKI, Shoko ASANO, Takafumi YOKOI, Kazumasa USUI, Misa KATO, Kosuke SAITO, Tomoya TACHI and Hitomi TERAMACHI*

In this study, using Japanese Adverse Drug Event Report database (JADER), we calculated proportional reporting ratio (PRR), one of the safety signals of hypokalemia, hyperkalemia, hyponatremia and hypernatremia, to determine the effects of thiazide diuretic (TD) on blood potassium and blood sodium levels when used in combination therapy with an angiotensin receptor blocker (ARB). While using a fixed-dose combination therapy, it is necessary to note that both drugs could increase the risk of adverse events mentioned in this study.

[*Jpn. J. Pharm. Health Care Sci.* **41**, 515-526 (2015)] [Lab. of Clinical Pharmacy]

Impact of Outpatient Chemotherapy-related Adverse Effect on Daily Life and Work Productivity in Breast Cancer Patients.

Kazuhide TANAKA, Tomoya TACHI, Shoko ASANO, Tomohiro OSAWA, Azusa KAWASHIMA, Akiyo HORI, Masahiro YASUDA, Takashi MIZUI, Takumi NAKADA, Teruo TSUCHIYA, Hitomi TERAMACHI* and Chitoshi GOTO

To investigate the impact of outpatient chemotherapy-related adverse effects on patient's daily life and work productivity, we performed a questionnaire survey on quality of life (EQ-5D and QOL-ACD), adverse effects and time loss before the first and the second course in 48 breast cancer patients receiving first outpatient chemotherapy in Gifu Municipal Hospital. No significant decrease in EQ-5D utility was observed, but a significant decrease in QOL-ACD score was observed. The average hour when an aderse effect influenced patient's daily life was 3.63 hours/day, and the average work productivity was 2,359 yen/day.

[*Oncol. Lett.* **9**, 2341-2346 (2015)] [Lab. of Clinical Pharmacy]

Adherence and Awareness of the Therapeutic Intent of Oral Anticancer Agents in an Outpatient Setting.

Michio KIMURA, Kenji NAKASHIMA, Eiseki USAMI, Mina IWAI, Toshiya NAKAO, Tomoaki YOSHIMURA, Hiromi MORI and Hitomi TERAMACHI*

To clarify the adherence and awareness of oral anticancer agents by type and therapeutic purpose in outpatients prescribed with tegafur/gimeracil/oteracil potassium (S-1) or capecitabine oral agents, outpatients undergoing the treatment at Ogaki Municipal Hospital in June 2013 completed a questionnaire survey. No significant differences in medication adherence were identified between the patients administered S-1 and the patients administered capecitabine. In addition, no significant differences were identified in therapeutic purpose between adjuvant therapy, and advanced and recurrent therapies. In conclusion, for patients treated with S-1 or capecitabine, the type and therapeutic purpose of oral anticancer agents did not affect medication adherence.

[*Pharmazie* **70**, 489-493 (2015)] [Lab. of Clinical Pharmacy]

Effects of Antidiabetes Drugs on Functional Independence Measure on a Subacute Rehabilitation Ward for Stroke Patients.

Eiji KOSE, Manabu TOYOSHIMA, Tomoya TACHI, Hitomi TERAMACHI*, Takashi KAWAKUBO and Hiroyuki HAYASHI

To confirm antidiabetes drugs as factors affecting the outcomes of rehabilitation, we investigated the effects of antidiabetes drugs on functional independence measure (FIM) in stroke patients with diabetes who were discharged from the subacute rehabilitation ward. We chose the frequently used antidiabetes drugs [sulfonylurea (SU), dipeptidyl peptidase-IV inhibitors (DPP-IVIs), and α-glycosidase inhibitors (α-GIs)] as the basis for categorizing the patients. We compared the patients' background features and laboratory data among the three groups. As a result, when SU was used in stroke patients with diabetes, it is difficult to obtain significant FIM-M gain, FIM-C gain, FIM-M efficiency, and FIM-C efficiency compared with of-GIs.

[*Jpn. J. Pharm. Health Care Sci.* **41**, 667-675 (2015)] [Lab. of Clinical Pharmacy]

Analysis of Adverse Events Associated with the Anti-Allergic Agents Rx-to-OTC-Switched Using Data Mining of the Japanese Adverse Drug Event Report (JADER) Database.

Yoshihiro NOGUCHI, Hiroki ESAKI, Shoko ASANO, Takafumi YOKOI, Kazumasa USUI, Misa KATO, Kosuke SAITO, Tomoya TACHI and Hitomi TERAMACHI*

We assessed safety signals by detecting of adverse events caused by anti-allergic Rx-to-OTC-switched agents. We analyzed data from the Japanese Adverse Drug Event Report for April 2004 to September 2013. We surveyed 10 types of adverse events, including hepatic disorders, severe cutaneous adverse reactions, and anaphylactic reactions. Signals were detected in hepatic disorders with all medicines, except for emedastine and diphenhydramine. These results showed that using anti-allergic Rx-to-OTC-switched agents potentially lead to severe adverse events, indicating that it is essential to provide drug information regardless of risk classification for the proper use of the drugs.

[*Gifu byoyaku*. **58**, 29-31 (2015)] [Lab. of Clinical Pharmacy]

Differences in the Instruction Contents between Practical Training in Hospital and Education in Universtiy.

Tomoya TACHI, Chitoshi GOTO, Masahiro FUKUTA, Masahiro YASUDA, Takashi MIZUI, Kenji KOBAYASHI, Makoto SAHASHI, Yoshihiro NOGUCHI, Teruo TSUCHIYA and Hitomi TERAMACHI*

To clarify the differences in the instruction contents between practical training in hospital and education in university, we performed a questionnaire survey on the differences in curricurum of pharmaceutical education. The subjects were students in practical training at the pharmacy in Gifu Municipal Hospital. Many students answered “diiferent in the instruction contents between practical training in hospital and education in university especially in “Dispensing” and “pharmaceutical care”, respectively 64.3% and 57.1%.

[*Pharmazie* **70**, 674-677 (2015)] [Lab. of Clinical Pharmacy]

Risk Factors for Developing Infusion Reaction after Rituximab Administration in Patients with B-cell Non-Hodgkin's Lymphoma.

Tomoya TACHI, Masahiro YASUDA, Kazumasa USUI, Katsuhiro NAGAYA, Tomohiro OSAWA, Atsuhi ICHIHASHI, Yoshihiro NOGUCHI, Hideko GOTO, Senji KASAHARA, Takeshi TAKAHASHI, Chitoshi GOTO and Hitomi TERAMACHI*

To identify risk factors based on clinical test values for developing infusion reaction after rituximab (RTX) administration, we retrospectively investigated patients with B-cell non-Hodgkin's lymphoma who had received RTX for the first time at the Gifu Municipal Hospital. Multivariate analysis showed significant differences with respect to a soluble interleukin-2 receptor (sIL-2R) level > 2,000 U/L, hemoglobin (Hb) < lower standard limit (LSL), and steroid administration, indicating that sIL-2R > 2,000 U/L, Hb < LSL, and a lack of steroid premedication are risk factors for developing infusion reaction following RTX treatment.

[*J. Jpn. Soc. Hosp. Pharm.* **51**, 1455-1461 (2015)] [Lab. of Clinical Pharmacy]

The Practice of Education Program of Outpatient Chemotherapy in Pharmaceutical Practical Training and the Evaluation of Proficiency Level Focused on Communication with Patients.

Tomoya TACHI, Hitomi TERAMACHI*, Kazuhide TANAKA, Tomohiro OSAWA, Yoshihiro NOGUCHI, Azusa KAWASHIMA, Katsuhiro NAGAYA, Akihide KODA, Akiyo HORI, Masahiro YASUDA, Takashi MIZUI and Chitoshi GOTO

In this study, we constructed a novel education program of outpatient chemotherapy in pharmaceutical practical training and evaluated proficiency level focused on communication with patients. We performed this program to students in practical training at the pharmacy of Gifu Municipal Hospital. The students in practical training could learn "communication with patients" and "attainable goals" by the practice of this program.

[*Jpn. J. Pharm. Health Care Sci.* **41**, 870-879 (2015)] [Lab. of Clinical Pharmacy]

Questionnaire Survey of Implementation Status of "Education for Medicines" at Junior High School in Japan.

Hitomi TERAMACHI*, Kosuke SAITO, Hiroki ESAKI, Misa KATO, Kazumasa USUI, Yoshihiro NOGUCHI, Tomoya TACHI and Shingo KATSUNO

To clarify the status of the implementation of medical education in schools, we conducted a questionnaire survey that targeted junior high school teachers in Japan via mail. Health and physical education (HPE) teachers were in charge of Education of Medicines in 91.8%. But 1.1% of schools did not offer Education of Medicines classes. The results of the survey indicate that HPE teachers provided Education of Medicines classes in accordance with the revision of school curriculum guidelines at many junior high schools. However, some schools did not offer the classes. In Japan, it is necessary to enhance Education of Medicines activities in the pharmaceutical field by involving specialists from different areas.

[*Jpn. J. Cancer Chemother*. **42**, 2447-2450 (2015)] [Lab. of Clinical Pharmacy]

The Establishment of Indicators of Thrombocytopenia in Patients Receiving Lenalidomide Therapy.

Masahiro YASUDA, Tomoya TACHI, Michi UMEDA, Katsuhiro NAGAYA, Tomohiro OSAWA, Atsushi ICHIHASHI, Hideko GOTO, Senji KASAHARA, Takeshi TAKAHASHI, Chitoshi GOTO and Hitomi TERAMACHI*

The onset of thrombocytopenia and related factors was analyzed in patients with multiple myeloma (MM) receiving lenalidomide (Len) therapy, Gifu Municipal Hospital between July 2010 and March 2014. The patients were examined from the start of Len therapy until treatment discontinuation, prolongation, or dose reduction. A significant correlation was observed between platelet (Plt) count prior to the start of Len therapy (pre-treatment Plt) and the difference between pre-treatment Plt and the minimum Plt up to the point in time of treatment discontinuation, prolongation, or dosage reduction ($r = 0.674$). Multivariate analysis showed that a Plt count below the lower limit of the normal value was identified as a factor, suggesting that a Plt count below the lower limit of the normal value prior to the start of Len therapy is a prognostic factor for thrombocytopenia as a side-effect of Len therapy.

[*Clin. Exp. Nephrol.* **19**, 1107-1113 (2015)] [Lab. of Clinical Pharmacy]

Renal Function Evaluation in Patients with Cancer who were Scheduled to Receive Carboplatin or S-1.

Kanako SHIBATA, Yoshinari YASUDA, Ryo KOBAYASHI, Yuichi ANDO, Tomoya SHIMOKATA, Hideki KAMIYA, Mutsuharu HAYASHI, Shoichi MARUYAMA, Seiichi MATSUO, Makoto NAKAO, Teruo TSUCHIYA and Hitomi TERAMACHI*

We analyzed the performance of glomerular filtration rate (GFR) equations among patients with cancer whose GFR values were measured by inulin clearance (Cin) using a cross-sectional study. Subjects were 41 patients with cancer whose GFR values were measured by Cin for drug dosing studies of carboplatin or S-1 in Nagoya University Hospital and 29 non-cancer patients. Body mass index and urinary creatinine excretion were significantly associated with eGFRcreat/Cin, and cancer was only associating factor with eGFRcys/Cin. eGFRcys should not be used for evaluation of renal function in patients with cancer because it underestimates GFR.

[*Industrial Health.* **53**, 100-108 (2015)] [Lab. of Drug Informatics]

Prevalence of Subjective Symptons among Hospital Pharmacists and Association with Drug Compounding Practices.

Ryoichi INABA, Atsuhi HIOKI, Yoshihiro KONDO, Hiroki NAKAMURA and Mitsuhiro NAKAMURA*

In Japan, the principal role of hospital pharmacists has changed from that of dispensing medicines for outpatients to provision of clinical pharmacy services for inpatients. A self-administered questionnaire about subjective symptoms, working patterns, work environments and job satisfaction was administered to 495 hospital pharmacists and 84 prefectural office-based pharmacists (control group). The prevalence of subjective symptoms that pharmacists noticed after starting drug compounding was lower in hospital pharmacists than in community pharmacists. Job satisfaction was lower in hospital pharmacists than in office-based pharmacists; however, there was no clear association between the subjective symptoms reported and job satisfaction. Further studies on removal effect of drug dust in a dispensary and symptoms in individual pharmacy facilities are needed.

[*Allergol. Int.* **64**, 277-279 (2015)] [Lab. of Drug Informatics]

Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: The Food and Drug Administration Adverse Event Reporting System, 2004–2013.

Junko ABE, Kanako MATAKI, Ryogo UMETSU, Natsumi UEDA, Yamato KATO, Yoko NAKAYAMA, Yasutomi KINOSADA, Hideaki HARA, Naoki INAGAKI and Mitsuhiro NAKAMURA*

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which are severe cutaneous adverse reactions, are associated with fatal disorders. The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is the largest and most well-known database worldwide, and it reflects the realities of clinical practice. Valdecoxib, lamotrigine, phenytoin, and furosemide showed high values for the adjusted RORs in the ≤17-year-old group. We considered that mycoplasma infection could partially explain the high value of the adjusted RORs of SJS/TEN in the ≤17-year-old patients. This study was the first to evaluate the relationship between SJS/TEN and aging by using the FAERS database.

[*Biol. Pharm. Bull.* **38**, 680-686 (2015)] [Lab. of Drug Informatics]

Analysis of the Interaction between Clopidogrel, Aspirin and Proton Pump Inhibitors using the FDA Adverse Event Reporting System Database.

Yukiya SUZUKI, Honami SUZUKI, Ryogo UMETSU, Hiroaki URANISHI, Junko ABE, Yuri NISHIBATA, Yasuaki SEKIYA, Nobuteru MIYAMURA, Hideaki HARA, Teruo TSUCHIYA, Yasutomi KINOSADA and Mitsuhiro NAKAMURA*

Clopidogrel is an antiplatelet agent widely used in combination with aspirin to limit the occurrence of cardiovascular (embolic/thrombotic) events. The objective of this study was to analyze the effect of the simultaneous use of clopidogrel, aspirin, and PPIs on hemorrhagic and embolic/thrombotic events using the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database. Among patients included in the FAERS database, the concurrent use of aspirin and clopidogrel with PPIs reduced the adjusted ROR of GI hemorrhagic events. PPIs had little influence on the adjusted ROR of embolic/thrombotic events.

[*J. Cell Biochem.* **116**, 2227-2238 (2015)] [Lab. of Drug Informatics]

Increased SPHK2 Transcription of Human Colon Cancer Cells in Serum-Depleted Culture: The Involvement of CREB Transcription Factor.

Naoki MIZUTANI, Yukari OMORI, Koji TANAKA, Hiromi ITO, Akira TAKAGI, Tetsuhito KOJIMA, Masahiro NAKATOCHI, Hideo OGISO, Yoshiyuki KAWAMOTO, Mitsuhiro NAKAMURA*, Motoshi SUZUKI, Mamoru KYOGASHIMA, Keiko TAMIYA-KOIZUMI, Yoshinori NOZAWA, Takashi MURATE.

Sphingosine kinases (SPHK) are important to determine cells' fate by producing sphingosine 1-phosphate. Colon cancer cells examined continued to grow in FCS(−) culture, although mildly, while hypoxia and glucose depletion suppressed cell proliferation or induced cell death, suggesting the different role of SPHK2 in different stress conditions. Because of the unique relationship observed after serum depletion, we examined effects of siRNA for SPHK2, and found the role of SPHK2 as a growth or survival factor but not a cell proliferation inhibitor in FCS(−) culture.

[*Int. J. Med. Sci.* **12**, 312-321 (2015)] [Lab. of Drug Informatics]

Evaluation of Dabigatran- and Warfarin- Associated Hemorrhagic Events Using the FDA-Adverse Event Reporting System Database Stratifed by Age.

Junko ABE, Ryogo UMETSU, Yamato KATO, Natsumi UEDA, Yoko NAKAYAMA, Yukiya SUZUKI, Toshiyuki SUZUKI, Hideko NAGASAWA, Yasutomi KINOSADA and Mitsuhiro NAKAMURA*

The objective of this study was to evaluate the interaction between aging and dabigatran- and warfarin-induced gastrointestinal (GI) and nervous system hemorrhage using data available in the FDA Adverse Event Reporting System database. We demonstrated that dabigatran-associated GI hemorrhage was significantly increased in patients over the age of 80 years. The reporting odds ratios (RORs) of dabigatran increased with increasing age, although aging had little effect on warfarin-associated GI hemorrhage. The ROR for anticoagulant-associated nervous system hemorrhage was not significantly affected by aging. Our results indicate that the excretion of dabigatran may be affected by aging, as compared to warfarin, likely due to renal function decline.

[*J. Pharm. Health Care Sci.* **1**, 15 (2015)] [Lab. of Drug Informatics]

Hyperglycemic Adverse Events Following Antipsychotic Drug Administration in Spontaneous Adverse Event Reports.

Yamato KATO, Ryogo UMETSU, Junko ABE, Natsumi UEDA, Yoko NAKAYAMA, Yasutomi KINOSADA and Mitsuhiro NAKAMURA*

The aim of this study was to evaluate the relationship between antipsychotic drugs and adverse hyperglycemic events using the FDA Adverse Event Reporting System (FAERS) database. In particular, we focused on adverse hyperglycemic events associated with atypical antipsychotic use, which are major concerns. The reporting ratio increased with co-administration of multiple antipsychotic drugs. For example, adverse hyperglycemic events represented 21.6% of reports for quetiapine monotherapy, 39.9% for two-drug polypharmacy, and 66.3% for three-drug polypharmacy. Antipsychotic drug polypharmacy may influence signal strength, and may be associated with hyperglycemia.

[*YAKUGAKU ZASSHI.* **135**, 991-1000 (2015)] [Lab. of Drug Informatics]

Adeverse Event Trends Associated with Over-the-counter Drugs: Data Mining of the Japanese Adverse Drug Event Report Database.

Ryogo UMETSU, Junko ABE, Natsumi UEDA, Yamato KATO, Yoko NAKAYAMA, Yasutomi KINOSADA and Mitsuhiro NAKAMURA*

The aims of the present study were as follows: (1) to assess the tendency of AEs to occur with over-the-counter (OTC) drug use in Japan; (2) to detect a safety signal for OTC drugs using the reporting odds ratio (ROR); and (3) to evaluate clustery features, which include suspected drugs and therapeutic classifications, and safety signal indices (number of reports and the ROR), using cluster analysis. The same medicinal ingredient may demonstrate similar tendencies of the occurrence of AEs and similar clustery features in the Japanese Adverse Drug Event Report database. Our analysis of AEs associated with OTC drugs may be useful for pharmacists and patients alike. Further studies are required to draw better-informed conclusions.

[*J. Biochem.* **158**, 309-319 (2015)] [Lab. of Drug Informatics]

Increased acid ceramidase expression depends on upregulation of androgen-dependent deubiquitinases, USP2, in a human prostate cancer cell line, LNCaP.

Naoki MIZUTANI, Minami INOUE, Yukari OMORI, Hiromi ITO, Keiko TAMIYA-KOIZUMI, Akira TAKAGI, Tetsuhito KOJIMA, Mitsuhiro NAKAMURA*, Soichiro IWAKI, Masahiro NAKATOCHI, Motoshi SUZUKI, Yoshinori NOZAWA, Takashi MURATE.

Acid ceramidase (ACDase) metabolizes ceramide to sphingosine, leading to sphingosine 1-phosphate production. LNCaP but not PC3 and DU-145, exhibited the highest ACDase protein. Among three cell lines, ASAH1 mRNA level was not correlated with ACDase protein expression, and the 5′-promoter activity did not show androgen dependency, suggesting the post-transcriptional regulation of ACDase in LNCaP cells. ACDase regulation by androgen in androgen-sensitive LNCaP cells is mainly due to its prolonged protein half-life by androgen-stimulated USP2 expression.

[*Jpn. J. Pharm. Health Care Sci.* **41**, 556-565 (2015)] [Lab. of Drug Informatics]

Analysis of the Association between Renin-Angiotensin System Blockers and Angioedema.

Yuuki HANE, Ryogo UMETSU, Natsumi UEDA, Yamato KATO, Yoko NAKAYAMA, Toshinobu MATSUI, Junko ABE, Yasutomi KINOSADA and Mitsuhiro NAKAMURA*

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II-receptor blockers (ARBs) are classified as renin-angiotensin system blockers. Angioedema is serious adverse event caused by ACEIs. Generally, there were fewer reports of angioedema associated with ARBs than with ACEIs. We analyzed the association of renin-angiotensin system blockers and angioedema in reports of FAERS and JADER database, and classified type of ACEIs and ARBs in Weibull distribution. We evaluated the association between each drug and adverse event using the number of relevant reports, reporting ratio, and reporting odds ratio (ROR). The RORs indicate that angioedema is positively associated with both ACEIs and ARBs. ACEIs and ARBs are classified as early failure type in Weibull distribution. ACEIs and ARBs should be administered carefully with regard to angioedema.

[*Biol. Pharm. Bull.* **38**, 1638-1644 (2015)] [Lab. of Drug Informatics]

Analysis of Neuropsychiatric Adverse Events in Patients Treated with Oseltamivir in Spontanenous Adverse Event Reports.

Natsumi UEDA, Ryogo UMETSU, Junko ABE, Yamato KATO, Yoko NAKAYAMA, Zenichiro KATO, Yasutomi KINOSADA and Mitsuhiro NAKAMURA*

There have been concerns that oseltamivir (OS) causes neuropsychiatric adverse events (NPAEs). We analyzed the association of age and gender with NPAEs in patients treated with OS using a logistic regression model. NPAE data were obtained from the U.S. Food and Drug Administration Adverse Event Reporting System (2004 to 2013). The lower limit of the reporting odds ratio (ROR) 95% confidence interval (CI) of “abnormal behavior” in Japan, Singapore, and Taiwan was ≥1. The effects of the interaction terms for OS in male patients aged 10–19 years were statistically significant. The adjusted NPAE RORs were increased in male and female patients under the age of 20 years. OS use could be associated with “abnormal behavior” in males aged 10–19 years.

[*Jpn. J. Drug Infom.* **17**, 145-154 (2015)] [Lab. of Drug Informatics]

Adverse Event Signals of Interstitial Lung Disease in the FDA Adverse Event Reporting System (FAERS) Database and the Japanese Adverse Drug Event Report (JADER) Database.

Toshinobu MATSUI, Ryogo UMETSU, Yamato KATO, Natsumi UEDA, Junko ABE, Yoko NAKAYAMA, Yuuki HANE, Yasutomi KINOSADA and Mitsuhiro NAKAMURA*

The Japanese Ministry of Health, Labor, and Welfare lists interstitial lung disease as an serious adverse drug event. The Food and Drug Administration Adverse Event Reporting System (FAERS) and the Japanese Adverse Drug Event Report (JADER) databases are available to detect adverse events signals. We analyzed reports of interstitial lung disease in FAERS and JADER and calculated the reporting fraction and reporting odds ratio (ROR) of drugs potentially associated with interstitial lung disease. We applied weibull shape parameter to time-to-event data in JADER. With the time-to-event analysis using Weibull shape parameter, time-dependency of adverse events in each drug was different. Therefore, these drugs should be used carefully in clinical practice.

[*Trad. Kampo. Med.* **2**, 2 SEP (2015)] [Lab. of Drug Informatics]

Analysis of Licorice-induced Pseudoaldosteronism in the Japanese Adverse Drug Event Report Database.

Yamato KATO, Ryogo UMETSU, Naoki HOSOYA, Natsumi UEDA, Junko ABE, Yoko NAKAYAMA, Yumi MOTOOKA, Yasutomi KINOSADA, Masayoshi OYAMA and Mitsuhiro NAKAMURA*.

We analyzed the association of age, sex, and dosage with licorice-associated pseudoaldosteronism using spontaneous adverse event reports. Pseudoaldosteronism was reported frequently in female patients aged >50 years. ROR of pseudoaldosteronism were calculated and stratified by licorice dosage. ROR (95%CI) for doses <2.5, 2.5–4.9, and ≥5.0 g were 20.9 (15.1–28.8), 26.1 (15.1–45.0), and 147.3 (150.3–206.0), respectively. Despite the limitations of spontaneous reporting, licorice dosage may be associated with pseudoaldosteronism. Considering the causality restraint of the current analysis, further epidemiological studies are recommended.

[*Biol. Pharm. Bull.* **38**, 1689-1699 (2015)] [Lab. of Drug Informatics]

Association between Selective Serotonin Reuptake Inhibitor Therapy and Suicidality: Analysis of U.S. Food and Drug Administration Adverse Event Reporting System Data.

Ryogo UMETSU, Junko ABE, Natsumi UEDA, Yamato KATO, Toshinobu MATSUI, Yoko NAKAYAMA, Yasutomi KINOSADA and Mitsuhiro NAKAMURA*

Selective serotonin reuptake inhibitors (SSRIs) are prescribed for the treatment of depression worldwide. SSRIs are suspected to increase the risk of suicidal ideation and behavior (suicidality) in children, adolescents, and young adults. We examined the association between SSRI therapy and suicidality by applying a logistic regression model to age-stratified data from the Food and Drug Administration (FDA) Adverse Event Reporting System database. Although the adjusted RORs were lower in the subset analyses than in the whole data analyses, both analyses indicated associations between SSRI treatment and suicidal and self-harm events. In both analyses these associations were stronger in the <18 y.o. group than other age groups.

[*J. Jpn. Pharm. Assoc.* **67**, 1629-1633 (2015)] [Lab. of Drug Informatics]

Survey of Inquiries about Prescriptions at the Pharmacy in Gifu Prefecture.

Hirokazu IBUKA, Miyuki YOKOYAMA, Hajime TANI, Eiji TAKASHIMA, Tatsuhiko YOSHIDA, Yutaka KANAMORI, Akiko KAWASE, Yoshihiro KONDO, Tokumitsu KATO, Eiichi ENDO, Yasushi HIBINO, Seijiro SUGINO, Shigeyoshi YAMAUCHI, Masataka ITO, Mitsuhiro NAKAMURA* , Futoshi YAMASAKI.

The Ministry of Health, Labour and Welfare explains the objectives of promotion of separation of the pharmacy and clinics. We analyzed the number of inquries concerning doubts in prescriptions and the nature of the doubts for prescriptions issued in the community pharmacies in Gifu prefecture (215 pharmacies). The total number of prescriptions was 55854. The inquires were frequently about “duplicated prescription.” About 6% of the “duplicated prescription have led to changes in the prescriptions and have been added NHI point. Proper and positive execution of these operations in routine pharmacy work is considered to lead to contribute to the proper use of drugs.

[*J. Pharm. Health Care Sci.* **1**, 34 (2015)] [Lab. of Drug Informatics]

Analysis of the time-to-onset of osteonecrosis of jaw with bisphosphonate treatment using the data from a spontaneous reporting system of adverse drug events.

Mitsuhiro NAKAMURA*, Ryogo UMETSU, Junko ABE, Toshinobu MATSUI, Natsumi UEDA, Yamato KATO, Sayaka SASAOKA, Kouhei TAHARA, Hirofumi TAKEUCHI, Yasutomi KINOSADA.

Bisphosphonates (BPs) are potent antiresorptive agents used to treat osteoporosis and the complications associated with malignant bone metastasis. The aim of this study was to evaluate the incidence of bisphosphonate-related osteonecrosis of the jaw (BRONJ) using the Japanese Adverse Drug Event Report (JADER) database. In particular, we focused on the time-to-onset profile of BRONJ. We calculated the reporting odds ratio (ROR) of BPs potentially associated with BRONJ. The lower 95 % confidence interval of the Weibull-shape parameter β for I.V. BPs (pamidronate and zoledronate) exceeded 1. The risk of BRONJ with I.V. BPs increased over time. The incidence of BRONJ with BP treatment should be closely monitored for a 3-year period.

[*J. Community Pharm. Pharm. Sci.* **7**, 105-111 (2015)] [Lab. of Community Pharmacy]

Effect of Automated Blood Pressure Device Cuff Position on Blood Pressure Measurement.

Kazuhiro IGUCHI*, Rio IWAMOTO, Chihiro SAKAI, Shuji YAMASHITA, Yoshihiro NOGUCHI, Toshiyuki MATSUNAGA, Mitsuhiro NAKAMURA, Tadashi SUGIYAMA and Hitomi TERAMACHI

We tested the effect of cuff position—one of the main factors responsible for blood pressure measurement reliability—on blood pressure reading. When the measurement was performed with the wrist-cuff device in the low position, the most elevated readings were observed; systolic and diastolic blood pressure readings in the low position, as compared with those in the correct position, significantly increased by 15.8 ± 8.6 mmHg and 15.1 ± 5.5 mmHg, respectively. When the measurement was performed with the arm-cuff device in the low position, systolic and diastolic blood pressure readings were increased by 4.5 ± 5.7 mmHg and 3.3 ± 4.9 mmHg, respectively as compared with those in the correct position. This result indicates the significance of the correct cuff position for handling an automated blood pressure device.

[*Cutan. Ocul. Toxicol.* **11**, 1-10 (2015)] [Lab. of Community Pharmacy]

Chronic Liver Injury in Mice Promotes Impairment of Skin Barrier Function via Tumor Necrosis Factor-alpha.

Satoshi YOKOYAMA*, Keiichi HIRAMOTO, Mayu KOYAMA and Kazuya OOI

Alcohol causes oxidative stress in the liver and increases the expression of inflammatory mediators that cause hepatocellular damage. However, during chronic liver injury, it is unclear if/how these liver-derived factors affect distal tissues such as the skin. The purpose of this study was to evaluate skin barrier function during chronic liver injury. In mice with alcohol-induced liver injury, transepidermal water loss was significantly increased, and skin hydration decreased. TNF receptor (TNFR) 2 expression was upregulated in the skin of alcohol-administered mice, while TNFR1 levels remained constant. Interestingly, the impairment of skin barrier function was ameliorated by administering an anti-TNF-α antibody.We propose a novel mechanism whereby plasma TNF-α, via TNFR2 alone or with TNFR1, plays an important role in skin barrier function during chronic liver disease in these mouse models.

[*Exp. Dermatol.* **24**, 779-784 (2015)] [Lab. of Community Pharmacy]

Impairment of Skin Barrier Function via Cholinergic Signal Transduction in a DSS-induced Colitis Mouse Model.

Satoshi YOKOYAMA*, Keiichi HIRAMOTO, Mayu KOYAMA and Kazuya OOI

Dry skin has been clinically associated with visceral diseases. To clarify this disease-induced skin disruption, we used a dextran sulfate sodium (DSS)-induced colitis mouse model. Following treatment with DSS, transepidermal water loss was higher and skin hydration was lower in DSS-treated mice compared to controls. Interestingly, the number of tryptase-expressing mast cells was elevated in skin. To evaluate the function of cholinergic signaling in mast cells, atropine was administered to DSS-treated mice. Our data indicate that muscarinic acetylcholine receptors (mAChRs) are the primary receptors functioning in colon-to-skin signal transduction, as DSS-induced skin disruption was suppressed by atropine. Thus, skin disruption is likely associated with DSS-induced colitis, and the activation of mast cells via mAChRs is critical to this association.

[*Biol. Pharm. Bull.* **38**, 947-950 (2015)] [Lab. of Community Pharmacy]

Impaired Skin Barrier Function in Mice with Colon Carcinoma Induced by Azoxymethane and Dextran Sodium Sulfate.

Satoshi YOKOYAMA*, Keiichi HIRAMOTO, Mayu KOYAMA and Kazuya OOI

We have previously reported that impaired skin barrier function was induced by small intestinal injury in mice. Therefore, we postulated that other intestinal diseases might also influence skin barrier function. In this study, we evaluated the skin barrier function of hairless mice with colon carcinoma that was induced by azoxymethane and dextran sodium sulfate. In mice treated with these drugs, we observed elevated transepidermal water loss and reduced skin hydration levels, compared to those in the control mice. In addition, plasma NO_2^-/NO_3^- levels were significantly elevated, and expression of type I collagen was significantly reduced in the treated mice, compared to those in control. These results suggest that impaired skin barrier function occurs in mice when colon carcinoma is present.

[*Pharm. Biol.* **53**, 913-920 (2015)] [Lab. of Community Pharmacy]

Immunological Changes in the Intestines and Skin after Senna Administration.

Yurika YAMATE, Keiichi HIRAMOTO, Satoshi YOKOYAMA* and Kazuya OOI

It has been reported that chronic sennoside use is associated with the development of melanosis coli, colonic adenoma, and/or carcinomas. We investigated the immunological changes in the colon and skin after the administration of senna. We investigated the colon and epidermis of mice after a single administration of senna and after repeated once per week administrations. We demonstrated that the DOPA-positive cells in the colon increased at 12 h after single administration and were further increased from at 5–28 d after repeated administration. We also studied the physiological changes of the small intestine using the charcoal meal test. We found that there was a tendency for peristalsis to be inhibited after repeated senna administration. In the epidermis, the number of Langerhans cells decreased, especially after repeated administration. The present findings suggested that it is necessary to pay attention to not only the intestine but also the skin, during long-term senna treatment.

[生薬学雑誌 **69**, 48-52 (2015)] [Lab. of Herbal Garden]

Description of a European Herbal Drug, Chasteberry

Eiji SAKAI, Osamu IIDA, Nobuo KAWAHARA, Jin MURATA and Takahiro SASAKI*

Chasteberry, the fruit of *Vitex agnus-castus*, has been used in Europe from ancient times for medicinal purposes, and is described in De Materia Medica by an ancient Greece physician, Pedanius Dioscorides. Currently, chasteberry is listed in European pharmacopoeia and its medicinal products are widely distributed in the European market. Since there are several crude drugs derived from the plants belonging to the same genus as chasteberry, the morphological investigation of chasteberry has been performed in order to differentiate it from other crude drugs of the same genus.

[*Phytochemistry Letters* **11**, 32-36 (2015)] [Lab. of Herbal Garden]

Two new butanolides from the roots of *Litsea aucminata*

Hitoshi TANAKA*, Yoshiaki TAKAYA, Junya TOYODA, Tadashi YASUDA, Masaru SATO,Jin MURATA, Hiroko MURATA, Koichi KABURAGI Osamu IIDA, Koji SUGIMURA and Eiji SAKAI, Osamu IIDA, Nobuo KAWAHARA, Jin MURATA and Takahiro SASAKI

Litsea is a genus belonging to the family Lauraceae with ca. 622 species, which are distributed in tropical and subtropical Australia, New Zealand, North America, South America and Asia. Two new butanolides, licunolides A (1) and B (2). Were isolated from the roots of *Litsea acuminata*, together with three known compounds: isolancifolide, longifolin and sesquirose furan. The structures of compounds 1 and 2 were determined by spectroscopic studies (IR, MS, 1D and 2D NMR) and chemical evidence.

[*Jpn. J. Health Rec.* **11**, 13-20 (2015)] [Lab. of Health and Sport Science]

Characteristics of the Relationship between Differences in Attachment Style and Dependence on Love in University Students.

Hiroko SUGIURA, Chiharu TAMAI and Haruo SUGIURA*

This study examined the relationship between love addiction, which is a form of codependency, and attachment style, which is said to affect romantic relationships. The ECR–GO, and the Love Addiction Tendency Scale were used as measurement scales. The students were divided into one of four types of styles based on whether they had higher or lower than the average score on each of the two dimensions of the ECR–GO, and their scores on the Love Addiction Tendency Scale were compared. Students identified as “preoccupied” had strong anxiety about being left or abandoned by their sweethearts, and acceptance by others led to their happiness; those identified as “fearful” had strong anxiety about being abandoned and were distrustful of others; and those identified as “secure” had a positive image about love and a low tendency to depend heavily on their sweethearts.

[*Jpn. J. Health Rec.* **11**, 21-28 (2015)] [Lab. of Health and Sport Science]

Effects of Exercise and Nutrition Management on Body Weight and Percent of Body Fat in the Small Group of Obesity Population

Haruo SUGIURA*, Setsuko UEYA, Maki OKADA, Taiei NODA, Hiromi MIYANO, Mari NARITA and Etsuo UEYA

The purpose of the present study was to investigate the effects of exercise and nutrition management (health diet for one month) on body weight and percent of body fat in the small group of obesity population (4 females and 1 male, 55.4±8.6 years of age). As the result, body weight, BMI, percent of body fat, body fat mass and abdominal circumference in the post-health diet class were significantly lower than those in the pre-health diet class. The one month health diet class scarcely affected the lean body mass in the all subjects. These results suggest that the health diet for one month effectively decreased body weight and percent body fat in the small group of obesity population, and that it contributes to the prevention of the lifestyle-related diseases.

[*Jpn. J. Health Rec.* **11**, 29-37 (2015)] [Lab. of Health and Sport Science]

Relationship between Assertiveness and Interpersonal Stress in Present-day University Students

Haruo SUGIURA*, Mika HATORI and Hiroko SUGIURA

Popular opinion says that university students nowadays tend to be afraid of active interpersonal relationships, avoid revealing their inner selves, and seek seemingly smooth relationships. It can be speculated that this type of personality places them under huge stress. This study examined the relationship between assertiveness and interpersonal stress in university students. From 253 sophomores to seniors of “A” University, 139 valid responses were obtained. The Assertiveness Scale for Adolescents and the Interpersonal Stress Event Scale were used as measurement scales. The students were divided into three groups based on their scores on the Assertiveness Scale, and their scores on the Interpersonal Stress Event Scale were compared. The results showed not only that a student with weak assertiveness would end up with more interpersonal stress events, but also that a student with adequate assertiveness had few interpersonal stress events.

[*Clin Ther*. **37**, 1652-1660 (2015)] [Lab. of Global Regulatory Science]

Development of Novel Pharmaceutical Agents for Alzheimer's Disease: The Impact of Regulatory Initiatives in Japan and the United States.

Katsura TSUKAMOTO

The goal of the present article was to analyze the status, clarify the problems, and discuss the scientific and political challenges of disease-modifying drug development for Alzheimer's disease (AD). Compared with diabetes mellitus drugs, there is a lack of quantitative surrogate end points among AD drugs. The development of quantitative surrogate end points remains necessary to improve the development of AD drugs. Therefore, collaboration among industry, government, and academia should be encouraged. Following the principles of regulatory science, strategies to develop drugs for illnesses with unmet needs can be framed by investigating the effects of past, current, and future AD drug development initiatives.

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